ELSEVIER

Progress in Neurobiology 79 (2006) 247–340

progress in Neurobiology

www.elsevier.com/locate/pneurobio

From Malthus to motive: How th e HPA axis engineers the phenotype, yoking needs to wants☆

Norman Pecoraro [a,1,*], Mary F. Dallman [a], James P. Warne [a], Abigail B. Ginsberg [a], Kevin D. Laugero [b], Susanne E. la Fleur [c], Hani Houshyar [d], Francisca Gomez [e], Aditi Bhargava [f], Susan F. Akana [a]

[a] *University of California, Department of Physiology, San Francisco, United States*
[b] *Amylin Pharmaceuticals, United States*
[c] *Rudolph Magnus Institute for Neuroscience, Department of Pharmacology and Anatomy, University Medical Center, University of Utrecht, Netherlands*
[d] *Merck Frosst, Montreal, Canada*
[e] *Universidad Complutense, Madrid, Spain*
[f] *University of California, Department of Surgery, San Francisco, United States*

Received 11 January 2006; received in revised form 17 July 2006; accepted 24 July 2006

Abstract

The hypothalamo–pituitary–adrenal (HPA) axis is the critical mediator of the vertebrate stress response system, responding to environmental stressors by maintaining internal homeostasis and coupling the needs of the body to the wants of the mind. The HPA axis has numerous complex drivers and highly flexible operating characterisitics. Major drivers include two circadian drivers, two extra-hypothalamic networks controlling top-down (psychogenic) and bottom-up (systemic) threats, and two intra-hypothalamic networks coordinating behavioral, autonomic, and neuroendocrine outflows. These various networks jointly and flexibly control HPA axis output of periodic (oscillatory) functions and a range of adventitious systemic or psychological threats, including predictable daily cycles of energy flow, actual metabolic deficits over many time scales,

Abbreviations: 2DG, 2-deoxyglucose; 11-βHSD1, 11-β-hydroxysteroid-dehydrogenase-1; 11-βHSD2, 11-β-hydroxysteroid-dehydrogenase-2; ACh, acetylcholine; ACTH, adrenocorticotropin hormone; ADP, anterodorsal preoptic nucleus; ADX, adrenalectomy; AgRP, agouti-related peptide; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole; AVP, arginine vasopressin; AVPO, anteroventral preoptic nucleus; AVPV, anteroventral periventricular preoptic nucleus; B, corticosterone; BLA, basolateral amygdala; BMI, body mass index; BNST, bed nucleus of the stria terminalis; CAD, coronary artery disease; CART, cocaine–amphetamine related transcript; CeA, central nucleus of the amygdala; CNS, central nervous system; CREB, cAMP response element binding protein; CRF, corticotropin releasing factor; CS, conditioned stimulus; CVD, cardiovascular disease; CVO, circumventricular organs; DA, dopamine; DAMGO, μ opiate receptor agonist; DAT, dopamine transporter; DBH, dopamine-β hydroxylase; DEX, dexamethasone; DIO, diet-induced obesity; DMH, dorsomedial hypothalamic nucleus; DR, resistant to diet-induced obesity; E, epinephrine; ENK, enkephalin; EOP, endogenous opioid peptides; eWAT, epididymal white adipose tissue; FAS, fatty acid synthase; FFA, free fatty acids; GABA, gamma-aminobutyric acid; GC, glucocorticoid; GR, glucocorticoid receptor; GRE, glucocorticoid response elements; HPA, hypothalamo–pituitary–adrenal axis; hRNA, heteronuclear RNA; HVPG, hypothalamic visceromotor pattern generator; ICSS, intracranial self-stimulation; i.c.v., intracerebroventricular; IEG, immediate early gene; IL-6, interleukin 6; IML, intermediolateral column; LA, lateral amygdala; LEO, light-entrainable oscillator; LH, lateral hypothalamus; LTP, lont-term potentiation; mPFC, medial prefrontal cortex; MPO, medial preoptic nucleus; MR, mineralocorticoid; mRNA, messenger RNA; αMSH, α-melanocyte stimulating hormone; mWAT, mesenteric white adipose tissue; NACC, nucleus accumbens; NE, norepinephrine; NMDA, *n*-methyl-D-aspartic acid; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; PAG, periaquaductal gray; PEPCK, phosphoenolpyruvate carboxykinase; PNMT, pehnolethanolamine *N*-methyltransferase; POMC, pro-opiomelanocortin; PS, parastrial nucleus; PSTN, parasubthalamic nucleus; PTSD, post-traumatic stress disorder; PVN, paraventricular hypothalamic nucleus; PVT, paraventricular thalamus; PWAT, perirenal white adipose tissue; RET, reticular nucleus; RVLM, rostroventral lateral medulla; SCN, suprachiasmatic nuclei; scWAT, subcutaneous white adipose tissue; SIP, schedule-induced polydipsia; sPVZ, sub-paraventricular zone; TH, tyrosine hydroxylase; TNFα, tumor necrosis factor α; UR, unconditioned response; US, unconditioned stimulus; VMH, ventromedial hypothalamus; VNAB, ventral noradrenergic bundle; VTA, ventral tegmental area; WAT, white adipose tissue

☆ Supported in part by NIH grants DA 016944 and DK 28172.

* Correspondence to: Department of Physiology, University of California, 513 Parnassus Ave., San Francisco, CA 94143-0444, United States. Tel.: +1 415 486 3861.

E-mail address: norman.pecoraro@ucsf.edu (N. Pecoraro).

[1] Wrote the majority of this review based on years of collaboration with the co-authors who have variously provided sections of the manuscript, data, suggestions and expertise.

doi:10.1016/j.pneurobio.2006.07.004

predicted metabolic deficits, and the state-dependent management of post-prandial responses to feeding. Evidence is provided that reparation of metabolic derangement by either food or glucocorticoids results in a metabolic signal that inhibits HPA activity. In short, the HPA axis is intimately involved in managing and remodeling peripheral energy fluxes, which appear to provide an unidentified metabolic inhibitory feedback signal to the HPA axis via glucocorticoids. In a complementary and perhaps a less appreciated role, adrenocortical hormones also act on brain to provide not only feedback, but feedforward control over the HPA axis itself and its various drivers, as well as coordinating behavioral and autonomic outflows, and mounting central incentive and memorial networks that are adaptive in both appetitive and aversive motivational modes. By centrally remodeling the phenotype, the HPA axis provides ballistic and predictive control over motor outflows relevant to the type of stressor. Evidence is examined concerning the global hypothesis that the HPA axis comprehensively induces integrative phenotypic plasticity, thus remodeling the body and its governor, the brain, to yoke the needs of the body to the wants of the mind. Adverse side effects of this yoking under conditions of glucocorticoid excess are discussed.

Keywords: Hypothalamo–pituitary–adrenal axis; Stress; Phenotypic plasticity; Energy balance; Motivation

Contents

1. Introduction

> The cause to which I allude, is the constant tendency in all animated life to increase beyond the nourishment prepared for it. . .upon the whole, that the population is in general so nearly on a level with the average supply of food, that every little deficiency from unfavourable weather or other causes, occasions distress. . .

Robert Malthus, (Of the Checks to Population; An Essay on the Principle of Population: A View of its Past and Present Effects on Human Happiness; with an Inquiry into Our Prospects Respecting the Future Removal or Mitigation of the Evils which It Occasions Published: London: John Murray, 1826. Sixth edition. First published: 1798.)

Stress that accompanies population growth is the ultimate ancestral concern, remains palpable in the problems of contemporary society, and is highly relevant to theoretical issues of the proximate and ultimate causes of stress. To summarize from Malthus: population growth first leaps exponentially, only to be hampered by self-induced resource scarcity and environmental toxication, before finally crushing itself at the limits of carrying capacity. In the perpetual struggle for resources, relatively minor events routinely threaten homeostasis. Darwin appreciated variation and heritability, but failed to understand the pressures driving adaptation until reading Malthus, which led him to the inescapable conclusion of natural selection. Heritable variation and logistic growth are as common in yeast, bacteria, and flowering plants as they are in humans, and therefore, it follows that natural selection demands a fundamental yoking of stress and energetics.

The key vertebrate mechanism that guards against metabolic inadequacy in times of resource shortages and its attendant stressors is the hypothalamo–pituitary–adrenal (HPA) axis. Stress hormones secreted from the adrenal cortex, i.e., glucocorticoids (GCs), were aptly named for their roles in

peripheral glucose mobilization, but their accepted importance to peripheral energy balance generally ignores the key coherence of their functions in both the periphery and the central nervous system. This review examines a scheme of HPA axis function in which GCs yoke needs to wants, where they frequently have largely inverse functions in the periphery and brain—peripherally they are catabolic and remodel energy toward adiposity and greater caloric efficiency, whereas centrally they remodel motivational structure, mounting appetitive and aversive networks that amplify the value of both positive and negative incentives for a variety of outcomes. Below we examine the complexity of the central HPA axis drivers and flexibility of the operating characteristics, evidence suggesting that GCs provide indirect metabolic feedback regulation of the HPA axis which can be mimicked by food, evidence that chronically elevated GCs feedforward in brain to activate specific central incentive networks, evidence suggesting an influential role of GCs in brain plasticity, including learning, neuronal remodeling, natural and supernormal forms of incentive relativity, and, finally we discuss the adverse consequences of sustained elevations of GCs. Thus, we hope to provide an overview of how GCs remodel the phenotype to yoke the needs of the body to the wants of the mind in ways that are typically, but not necessarily adaptive.

2. HPA axis anatomy and operationing characteristics

2.1. The HPA axis itself

The essential components that lead to increased adrenocortical secretion are known as the hypothalamo–pituitary–adrenal axis (Fig. 1). The final common output pathway from brain begins with the paraventricular nucleus (PVN) of the hypothalamus, which contains small-bodied, corticotropin-releasing factor (CRF) synthesizing motor neurons that also synthesize arginine vasopressin (AVP). Axons from CRF cells project to the median eminence where they release their contents into the primary portal vasculature via diffusion into leaky capillaries. After vascular transport to and diffusion from the secondary plexus in the anterior pituitary, CRF and AVP stimulate glandular corticotrope cells to synthesize pro-opiomelanocortin (POMC), a large molecule that is processed by convertases in the cell to adrenocorticotropic hormone (ACTH) and stored in secretory vesicles. Also, in immediate response to CRF/AVP, stored ACTH is released into the systemic circulation. Elevated plasma ACTH then stimulates the adrenal cortex (zona fasciculata) to synthesize on demand and secrete GCs into the circulation where they then act on peripheral and central brain cells containing glucocorticoid receptors (GR). Thus, the GCs not only act at the periphery but also cross the blood brain barrier to cause wide-ranging changes in brain function. The PVN also contains magnocellular cells containing oxytocin (OXY) or vasopressin (AVP) that reside laterally to CRF neurons and project to the neural lobe of the pituitary. Non-neuroendocrine, descending PVN cell divisions control behavioral and autonomic outflows.

The scheme of neuroendocrine motor output is deceptively simple given the manifold stimuli that regulate activity in the HPA axis. Summary statements often suggest that activation of the CRF motorneuron in the PVN is subject to regulation by both ‘‘bottom-up’’ or ‘‘systemic’’ stimuli and ‘‘top-down’’ or cognitive stimuli, also referred to as actual or predicted threats, respectively,[2] but even these broad strokes underestimate the types of stimuli controlling HPA output, which include periodic, recurring stimuli (e.g., seasonal, circadian, ultradian) and systemic events (e.g., hunger, food, exercise, injury, infection, hypoxia, temperature, volume and osmotic stimuli, drugs, sleep deprivation, aversive stimuli, and positive and negative expectancies).

Fig. 2 shows the major drivers of the HPA axis in schematic form. The PVN and its neighboring sub-paraventricular zone (sPVZ) integrate widely ranging anatomical and neurochemical inputs from both hypothalamic and extra-hypothalamic sites. Local inputs from the sPVZ to PVN include a complex microcircuitry for both GABAergic and glutamatergic fast transmission. Much of this input is from cortical and limbic inputs (for reviews see Herman et al., 2003, 2002). Inputs to the HPA axis may be thought of as consisting of two main types: periodic pattern-generators characterized by an endogenous oscillatory capacity and non-periodic pattern generators that are driven by adventitious, exogenous stimuli, or in the case of hunger, interoceptive stimulation when food is unavailable. At least four pattern generators are known or predicted to have critical influences on the HPA axis. Two with clearly circadian periods include the light-entrainable oscillator (LEO), also known as the suprachiasmatic nuclei (SCN), and the food-entrainable oscillator (FEO), which is of uncertain anatomical origin, although the dorsomedial hypothalamic nuclei (DMN) are critical for its expression (Gooley et al., 2006). Another periodic oscillator is ultradian (not shown) that drives secretory bursts on the order of minutes to hours (Iranmanesh et al., 1990; Sarnyai et al., 1995; Veldhuis et al., 2001). A recently identified

[2] The distinction between systemic and psychological stress has face validity, and may have construct validity insofar knife cuts of ascending catecholaminergic pathways can prevent fos activation in upstream stress networks following a systemic stressor (e.g., electric shock; Li et al., 1996). Distinct mechanisms underlie activation of hypothalamic neurosecretory neurons and their medullary catecholaminergic afferents in categorically different stress paradigms but do not prevent activation in the same nodes following a psychological stressor, such as restraint. However, the distinction is not clear-cut. Most systemic stressors probably have psychological components, as well, e.g., malaise and sickness behavior, and the experience of pain. In addition, one might also imagine that increased HPA activity following endotoxin administration or a broken leg serves multiple functions beyond anti-inflammatory actions, such as preserving energetic functions in an animal that cannot forage efficiently or safely. Likewise, social stress could also act as a predictor for metabolic stress, as in the case of subordinate animals being thwarted from feeding opportunities by dominants. Some stimuli, such as those reflecting circadian processes, are even more difficult to categorize as ‘‘top-down’’ or ‘‘bottom-up.’’ In addition, sometimes the term ‘‘neurogenic’’ is used to describe predicted threats, but finally, there is likely a great deal of intrinsic coordination between neuroendocrine motor systems, and other motor systems. With these caveats, it can be a useful distinction when trying to parse the necessary and sufficient inputs to the HPA axis.

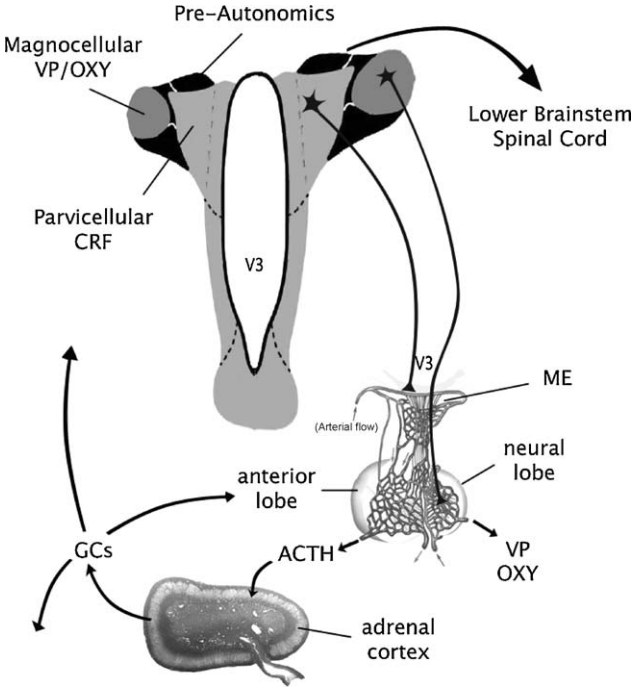

Fig. 1. The hypothalamo–pituitary–adrenal (HPA) axis. The paraventricular nucleus (PVN) of the hypothalamus is depicted as a bilateral coronal section in an oblique view with the third ventricle (V3) indicating midline. The periventricular region (light gray) contains parvicellular neuroendocrine cells with CRF/AVP-containing neurons in the dorsolateral region that project to the median eminence and portal vasculature of the anterior pituitary. The magnocellular neuronal division (medium gray) consists of cell containing oxytocin and vasopressin the project directly to the posterior, neural lobe of the pituitary. The descending division of the PVN (black) contains pre-autonomic neurons projecting to lower brainstem areas and spinal cord that are involved in both behavioral and autonomic regulation. CRF/AVP release into the portal vasculature of the anterior pituitary stimulates glandular corticotropes to release adrenocorticotropin hormone (ACTH) into systemic circulation. Plasma ACTH then stimulates adrenalcortical cells to synthesize and release glucocorticoids (GC) into systemic circulation to act on peripheral tissues and organs and feedback to the pituitary corticotropes and the central nervous system.

network, the hypothalamic viscermotor pattern generator (HVPG) (Thompson and Swanson, 2003) is a putative pattern generator predicted from anatomical considerations. This is the least functionally characterized network, but is in a position to mediate both periodic and aperiodic signals, as it receives prominent input from circadian drivers and cortico-striato-pallidal networks mediating top-down, psychogenic stimuli. Finally, an array of networks mediating bottom-up, largely aperiodic stimulation of HPA axis output, such as those controlling actual systemic threats, include the ascending ventral noradrenergic bundle (VNAB) originating in the lower brainstem, and the melanocortin system involving neuropeptide Y (NPY) and POMC neurons within the arcuate nucleus of the hypothalamus and lower brainstem. This latter melanocortin system has some overlapping anatomical distribution with the HVPG and the VNAB. Finally, HPA axis sensitivity to immune challenges is mediated through the circumventricular organs and leptomeningeal systems. Thus, the variety of pathways driving HPA axis output is as diverse as potential challenges to homeostasis.

2.2. Periodic pattern generators

2.2.1. The light-entrainable oscillator

The HPA axis exhibits a prominent daily (≈24 h) rhythm that is normally under the control of the suprachiasmatic nuclei of the hypothalamus (SCN), also known as the light-entrainable oscillator, as lesions of the SCN block daily light-entrained rhythmicity (Moore and Eichler, 1972). In most diurnal and nocturnal animals under laboratory circumstances of a regular light/dark cycle and ad libitum food, the peak (acrophase) of HPA rhythms occurs just before the onset of the activity phase, whereas the nadir occurs during sleep. The SCN sit atop the optic chiasm in the basal hypothalamus and receive transduced light stimuli via the retinohypothalamic tract that entrains the endogenous pacemaker activities in the SCN to a precise 24 h period. Activity in the SCN then drives the HPA axis and PVN pre-autonomic neurons.

There are multiple pathways by which the SCN may control adrenal cortical output. The SCN project directly to PVN CRF neurons (Buijs et al., 1998; Vrang et al., 1997), where they can directly affect CRF motorneuron output, in both neuroendocrine and descending pre-autonomic divisions of PVN. The SCN indirectly influence PVN CRF neurons via substantial projections to the sub-paraventricular zone, which targets the PVN with GABAergic inputs. The SCN substantially project to the dorsomedial hypothalamus (DMH) and preoptic nuclei, which also project strongly to neuroendocrine and pre-autonomic divisions and are of great relevance to coordination of visceromotor outflows. AVP levels in and around the PVN vary on a circadian basis, being highest at rest, during basal HPA activity. AVP infusions into brain cause rapid decreases in GC, and lesser decreases in ACTH. The DMH are the most effective infusion-site, and provide substantial, presumably inhibitory, GABAergic fibers to CRF neurons. Disinhibition of HPA activity by AVP antagonists occurs only in SCN-intact animals, suggesting origination of the inhibitory AVP in the SCN. Other hypothalamic recipients of SCN input that in turn influence PVN output include the arcuate and supraoptic nuclei (Kalsbeek and Buijs, 2002; Saeb-Parsy et al., 2000). Outside the hypothalamus, the SCN project to paraventricular thalamus (PVT), a common target of both acute and chronic stress networks.

There also appears to be an additional neuronal route by which the SCN control adrenal activation. Whereas ACTH output is associated with rhythmic output from SCN (Cascio et al., 1987), adrenal sensitivity to ACTH appears to involve a neural, non-rhythmic component that reveals itself as a masking effect due to SCN activity controlled by light. Pseudo-rabies virus injected into the adrenals is retrogradely propagated trans-synaptically via the intermediolateral column to PVN pre-autonomics and the SCN, showing that the SCN project multi-synaptically to innervate the adrenal (Buijs et al., 1998). In rats, adrenal sensitivity to ACTH appears to increase about 2.5-fold at the acrophase compared to the nadir of the rhythm (Dallman et al., 1978; Jasper and Engeland, 1994; Kaneko et al., 1980; Sage et al., 2002), and this shift in sensitivity requires intact splanchnic neural innervation of the adrenals (Ulrich-Lai et al.,

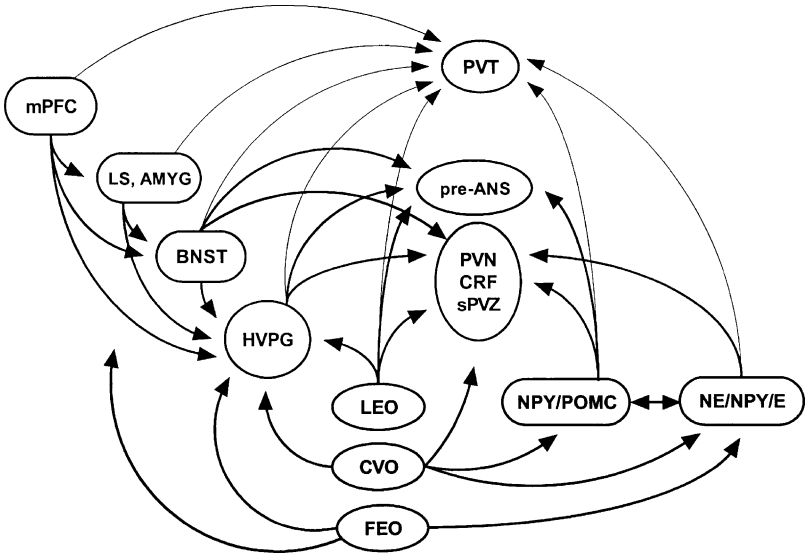

Fig. 2. Major drivers of the HPA axis. This highly simplified schematic depicts the major drivers of the HPA axis, with some indications of their coordinated drive on autonomics (pre-ANS) and one another. For simplicity, paraventricular (PVN) corticotropin releasing factor-containing (CRF)-containing cells are grouped with the heavily interconnected sub-paraventricular zone (sPVZ). The suprachiasmatic nuclei, the master, light-entrainable oscillator (LEO) provides endogenous circadian drive to the paraventricular nucleus (PVN) corticotropin-releasing factor-containing cells, PVN pre-autonomics, and the hypothalamic visceromotor pattern generator (HVPG). During restricted, scheduled feedings a second food-entrainable oscillator (FEO) swings into motion to track mealtimes and entrain food anticipatory rhythms. Systemic threats to homeostasis are signaled through circumventricular organs (CVO), the melanocortin (neuropeptide Y/pro-opiomelanocortin; NPY/POMC) system in the arcuate nucleus of the hypothalamus, and ascending medullary catecholaminergic (norepinephrine, epinephrine, NPY; NE, E) neurons. Psychogenic drive on the HPA axis is represented by multi-layered cortico-striato-pallido-hypothalamic networks, in this case showing the visceromotor medial prefrontal cortex (mPFC) projecting to the lateral septum (LS) and amygdala (AMY), bed nucleus of the stria terminalis (BNST), and HVPG. Virtually all HPA axis drivers also project the ''neuroendocrine'' paraventricular thalamus (PVT).

2005). Furthermore, Buijs et al. (1999) showed that presenting light during the dark phase rapidly reduces plasma corticosterone concentrations without reducing ACTH, but this occurs only in animals with intact SCN (Buijs et al., 1999). Thus, the SCN influence HPA output through direct innervation of the CRF motor neurons, as well as indirect access through secondary hypothalamic pattern generators (see below), and by neuronally controlling adrenal sensitivity to ACTH.

It remains further possible that the SCN could influence hypothalamically driven GC secretion by humoral signals, insofar as SCN ''islands'' isolated in permeable membranes can restore some types of rhythmicity (Hakim et al., 1991), although the case for GC secretion has yet to be demonstrated. Sub-components of the HPA axis, such as the pituitary and adrenals themselves, display intrinsic rhythms in vitro, but the light-entrainable SCN appear to function as a master to these other slave oscillators (for reviews see Buijs and Kalsbeek, 2001; Moore-Ede et al., 1982; Perreau-Lenz et al., 2004; Silver and Moore, 1998).

Light-entrained rhythms of the HPA axis appear to be related to the demands of waking activity, insofar as they accompany or just precede waking in all known species. As has been pointed out by others, our own intuition tells us that waking is not necessarily stressful (Day, 2005). However, it should be added that these same rhythms can be stress-related since humans can show elevated peaks in cortisol during the work week compared to weekends (Schlotz et al., 2004), and the rhythm's nadir can be increased during hunger (Dallman et al., 1999), fasting (Samuels and McDaniel, 1997) or life-time food restriction (Masoro, 2005). The perceived non-stressfulness of normal daily rhythms of activity and energy fluxes in the freely feeding condition simply reflects an ancient solution, gracefully perfected over geological time. The importance of circadian synchronization is evident, as obliteration of the clockwork reduces lifespan (Moore-Ede et al., 1982).

2.2.2. *The food-entrainable oscillator*

A second circadian oscillatory system provides for non-photic, food-entrainable rhythms of GC, and is referred to as the food-entrainable oscillator (for a review see Hiroshige et al., 1991; Mistlberger, 1994; Stephan, 2001; Stephan, 2002). Although circadian rhythms are normally entrained to the LEO, and hence light schedules, when food availability schedules are pitted against the light/dark cycle, the GC rhythm shifts, becomes entrained to the time of food availability, and peaks just before a once-daily meal.

Food-entrainment entails the readjustment, in addition to GC secretion, of an entire suite of rhythms that are related to activity, procurement and ingestion of food, body temperature, activity, drinking, feeding (Moore-Ede et al., 1982), as well as many digestive and hepatic rhythms (Balsalobre et al., 2000, 1998; Diaz-Munoz et al., 2000; Saito et al., 1975, 1976). In a large variety of species tested, once-daily access to food results in the development of food-anticipatory activity in these rhythms. The key conditions for food entrainment appear to be food deprivation and periodic eating of threshold-sized meals. Even a prior history of scheduled meals is sufficient for entrainment, since anticipatory activity can occur at a

remembered time relative to the light cycle (phase angle) if food deprivation alone is reinstituted without providing meals (Stephan, 2002).

Food-anticipatory rhythms are considered truly endogenous circadian rhythms because they are phase-adjustable to any phase of the light dark cycle, they have a range of entrainment, they can free-run, and they persist for at least 2 days in the absence of exogenous stimulation. Although circadian clock mechanisms are considered non-associative processes (Mistlberger, 1994), for some of the reasons just mentioned, there must be some type of memorial consultation in at least one of the cases mentioned above, namely, the case of deprivation alone calling forth anticipatory activity at the former time of scheduled meals, which appears to require a ''consulted clock'' (Gallistel, 1990).

The independence of the FEO from the LEO is assured, in that food anticipatory activity, including adrenal activity (Krieger, 1972), remains robust in SCN-lesioned animals (Krieger et al., 1977). Although many brain lesion studies, including those involving bilateral destruction of PVN, have attempted to discern a nuclear locus of the putative food-entrainable oscillator, only lesions of the DMH and the parabrachial nuclei have eliminated or markedly damped temperature, GC, and food anticipatory activity (FAA) rhythms (Davidson et al., 2000; Gooley et al., 2006). However, residual time-keeping was noted, and replicated (Landry et al., 2006). Subordinate levels of the HPA axis have been ruled out as the source oscillator, as both hypophysectomized (Davidson and Stephan, 1999) and adrenalectomized rats (Mistlberger, 1994) still show behavioral anticipation of meals (Stephan et al., 1979). It is worth adding, however, that adrenalectomy (ADX) also results in the normally robust locomotor activity rhythm becoming severely ''uninspired.'' Although lesions of the ventromedial hypothalamus (VMH) did not eliminate behavioral FAA (Mistlberger and Rechtschaffen, 1984), the amplitude of the food-entrainment signal may also depend to some extent on activity in the ventromedial hypothalamus (Choi et al., 1998; Honma et al., 1987). Because clock genes are located in many tissues throughout the brain and periphery, the FEO may consist of distributed central and peripheral oscillator systems that couple under appropriate circumstances.

Ascending noradrenergic (NE)/neuropeptide Y (NPY) neurons originating in the nucleus of the tractus solitarius (NTS) may be involved in transducing a food-entrained circadian signal from the NTS to the PVN, resulting in the pre-feeding elevations of corticosterone. NPY increases in the PVN prior to meals on restricted food schedules (Kalra et al., 1991; Yoshihara et al., 1996a,b), and is known to stimulate both feeding (Kalra et al., 1991) and corticosterone (Leibowitz et al., 1988). 6-Hydroxydopamine (6OHDA) lesions of the ventral noradrenergic bundle eliminate the pre-feeding peak of corticosterone in rats with intact SCN (Hiroshige et al., 1991). Elevations in NPY can be dissociated from elevations in corticosterone, as corticosterone concentrations diminish immediately post-prandially in food-retricted rats, whereas NPY secretion does not (Yoshihara et al., 1996c). In addition, although the arcuate nuclei supply NPY efferents to CRF neurons in the PVN (Liposits et al., 1988), arcuate NPY mRNA increases under both food deprivation without entrainment and under restricted feeding, whereas NPY mRNA in NTS increases only under restricted feeding, suggesting that the arcuate nuclei are sensitive to caloric deprivation, whereas the NTS conveys signals about meal schedules (Ishizaki et al., 2003). However, the view that the ascending NE/NPY neurons are not responsive to food deprivation appears to be at odds with results showing that there is ascending NE/NPY control over acute glucoprivation (Ishizaki et al., 2003; and see below).

Although it is typically reported to take anywhere from 3 to 13 days to obtain reliable food-anticipatory activity, White and Timberlake have provided unique evidence using 31 h (i.e., long T) schedules of food presentation that the FEO, or parts of it, can be reset by a single meal (White and Timberlake, 1999). Because this particular long T schedule is outside of the range of entrainment of the rhythm, and mealtimes never repeat a local time of day for the first 24 presentations, with each meal advancing 7 h in local time on subsequent presentations, the behavioral activation seen 24–26 h after the last large meal, cannot and does not anticipate the next meal, but rather ''ensues from'' the previous meal, a phenomenon that has been referred to as ''circadian ensuing activity.'' This is noteworthy not only because it demonstrates a novel resetting mechanism for the FEO, but also because the behavioral activation seen during 31 h schedules of food availability strongly resembles the profile of corticosterone secretion seen under long T schedules found by Honma et al. (1984).

Food entrainment involves the induction of clock genes in stress-sensitive brain networks. Recently, measurement of the expression of a clock gene, period2, has shown per2 rhythms in both the oval subnuclei in the bed nuclei of the stria terminalis (BNST-ov) and in the central nucleus of the amygdala (CeA) that are in phase with the per2 rhythm in the SCN; all of these rhythms peak at ZT13, the time of day when the onset of daily activity occurs in rats (Amir et al., 2004; Lamont et al., 2005b). The per2 rhythms in the limbic system cell groups can be forced out of phase with that in the SCN by placing rats on a restricted feeding paradigm (Lamont et al., 2005a). However, neither salt depletion, nor rhythmic presentation of highly palatable foods entrain per2 rhythms in the absence of co-existing negative energy balance (restriction of body weight gain) (Lamont et al., 2005a). Moreover, in rats housed in a L–L cycle, which develop per2 arrhythmicity in both BNST-ov and SCN with time, a restricted feeding regimen re-establishes a per2 rhythm that is 12 h out of phase with feeding. Of considerable interest, the rhythms in per2 in the BNST-ov and CeA, but not the SCN, disappear when rats are adrenalectomized (Amir et al., 2004; Lamont et al., 2005b), and are restored by corticosterone supplied in a phasic, but not tonic pattern (Segall et al., 2005). Thus, per2 expression in these two sites in limbic brain is highly sensitive to food entrainment under conditions of lower-than-normal energy status and also to phasic corticosterone concentrations. It is still unknown whether, or how, the rhythm in per2 in these sites is coupled to physiological consequences.

Unlike the situation of light entrainment, the food-entrained HPA rhythm may reflect a condition of stress, as hunger appears

to be required, the rhythms must be shifted away from their preferred angle to light in order to be detected as ''food-entrained'' in the intact animal, and because clock gene expression in stress-sensitive brain networks is dependent on both hunger and GCs. The LEO and FEO circadian drivers are flexible insofar as they each allow independent phase shifting, and great flexibility in their coupling with each other. They are constrained, insofar as each adheres to a preferred free-running period within the circadian range, a range of entrainment, and a more-or-less specific phase-response curve. Together, these two major oscillators allow an animal to anticipate and mobilize resources for at least two separate major events, such as light–dark transitions and meals, or even two separate meals. An example of coordination between light- and food-entrainable rhythms is provided below.

In a study on motivation (Pecoraro et al., 2002), we asked whether very brief sessions (5–6 min) of daily access to a 32% sucrose solution was a sufficient stimulus for food entrainment, and whether this entrainment might depend on the food restriction status of the animal. Rats living in a light/dark cycle were presented with a brief sucrose meal for 12 days during the light phase, at or near the nadir of activity, hormone, and temperature rhythms. Chow was provided near the beginning of the 12-h dark/12-h light cycle throughout the study, 180° out of phase with the sucrose meal to avoid contamination from the caloric input of chow. Some animals were restricted to 85% of their free-feeding weights, whereas the others were fed ad libitum. Fig. 3 shows the average waveforms of temperature rhythms in both freely feeding (Fig. 3A) and food-restricted animals (Fig. 3B). Prior to providing sucrose, both ad libitum and food-restricted animals showed normal entrainment to dark onset. However, once daily 32% sucrose was available 4 h into the light cycle, only the food-restricted animals showed anticipatory increases in core body temperature.

Fig. 4A–D show various measures, including core temperature, wheel running, plasma corticosterone, and insulin before and after the time of sucrose drinking. Fig. 4A and B show the difference scores between baseline and sucrose drinking phases for the 3-h time window before the receipt of sucrose that were derived from average waveforms for temperature (Fig. 3A) and wheel running (Fig. 3B) At about 1.5 h before sucrose, only food-restricted animals had anticipatory increases in temperature and wheel running. Fig. 4 (panels C and D) shows plasma corticosterone and insulin concentrations, respectively, just before and after the rats drank sucrose. Although we did not collect 24 h data for corticosterone secretion, the results shown in Fig. 4C are entirely consistent with an entrainment interpretation, since corticosterone was elevated only in food-restricted animals prior to sucrose, and fell immediately after. It was not clear whether food-restriction was necessary for this, because of the confounding factor of differences in sucrose intake. Food-deprived rats drank about 30% of their daily calories in the brief sessions, which is within the range of previously reported thresholds for food-entrainment (Mistlberger and Rusak, 1987; Stephan, 1997; White et al., 1999), whereas the ad libitum fed animals drank about half as much, which is believed to be sub-threshold.

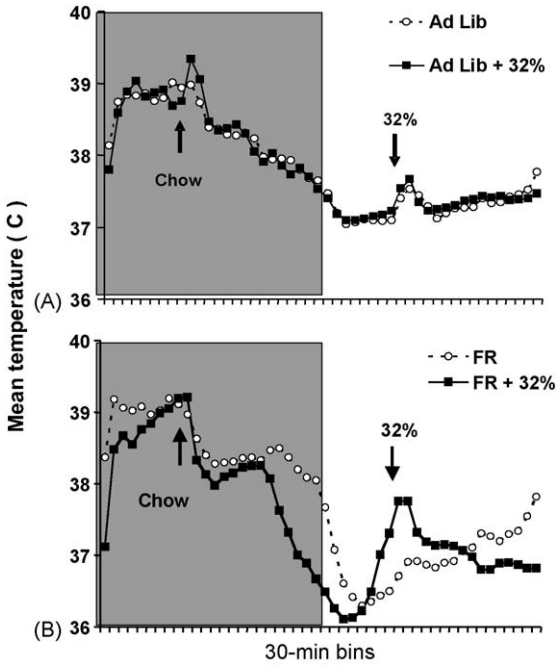

Fig. 3. Examples of daily body temperature rhythms simultaneously controlled by both the LEO and the FEO under conditions of ad libitum feeding (panel A) and in animals restricted to 85% free-feeding weights (panel B). The data are shown as 4-day average waveforms folded at 24 h and averaged into 30 min bins. The dark/light cycle (12/12) is shown in gray and white shading, respectively. Arrows indicate when chow and sucrose were provided. Sucrose was available for 5–6 min. Open circles indicate the 24-h rhythm in animals before providing sucrose, whereas black-filled squares show the rhythm when both chow and 32% sucrose solutions were provided. Under ad libitum feeding conditions, the rhythm is controlled solely by the light/dark cycle whether or not sucrose is available. In food-restricted (FR) animals, the rhythm is entrained by the light/dark cycle (and perhaps chow) during chow-only food restriction, but later core temperature excursions also anticipate the sucrose meal when it is regularly provided. In all likelihood, the LEO controls light/dark entrainment, whereas the FEO controls the sucrose meal presented 4 h into the light cycle a time when core temperature is normally at its nadir. Data adapted from Pecoraro et al. (2002).

Thus, during normal light and ad libitum feeding cycles, activity in the HPA axis regulates the normal flow of energy, shifting from glycogenolysis to lipolysis as the animal shifts from the resting state to activity. When energy availability changes, as in the case of food restriction, the HPA axis changes as well, matching its activity to both the current state of energy balance and the availability of food. It does so in conjunction with a whole suite of energy preparatory rhythms that are coordinated with the light–dark cycle as well. For now, the main points are that very brief periods of access to food are sufficient for food entrainment, even when pitted against the light/dark cycle and a larger, supplemental chow meal provided 12 h later. The suites of circadian anticipatory activation strongly suggest that animals are spending energy, e.g., increasing core temperature, activity, and hepatic glucose output via HPA axis activation, in order to acquire energy. These two circadian systems appear to provide automatic control over predictable daily cycles of food availability. Understanding that the default function of the HPA axis is controlling daily cycles of energy acquisition is of key importance to understanding stressor-related GC secretion.

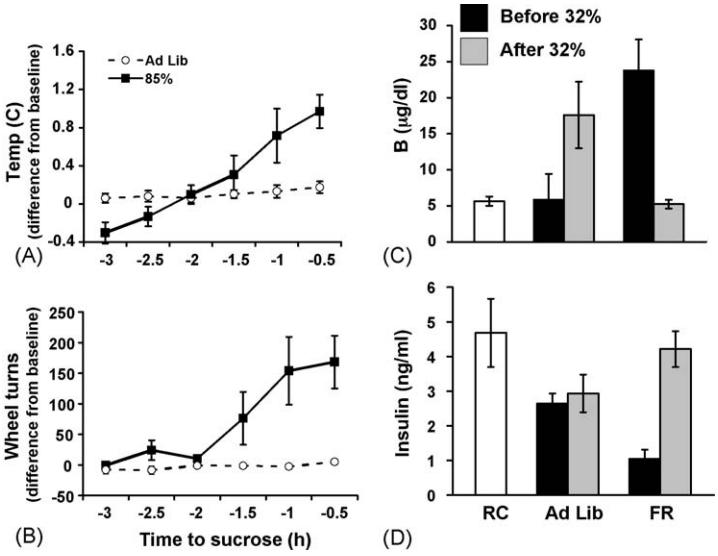

Fig. 4. Food-entrainable rhythms. Demonstrations of food anticipatory activity in body temperature (panel A) and wheel running (panel B) in the hours prior to the receipt of an expected sucrose meal in rats food-restricted to 85% free-feeding weights (black-filled squares). The rats were given chow at night and sucrose during the light phase for 5–6 min (see Fig. 3). The average waveform and corresponding data points from the baseline period prior to sucrose presentation were subtracted from the temperature waveform during sucrose availability. Clearly, both temperature and wheel running difference scores indicate anticipation of the meal in the food-restricted rats, but not in those fed ad libitum (open circles). Mean (±S.E.M.) plasma concentrations of corticosterone (B; panel C) and insulin (panel D) for room controls (RC), ad libitum fed (ad lib) and food-restricted (FR) rats before and after receiving a 32% sucrose meal. Four animals from each experimental group were killed before, and four were killed after drinking sucrose. Freely feeding room controls are shown to indicate normal basal values and procedure quality. In ad libitum feeding animals, corticosterone is basal prior to meals, but elevated after meals. Insulin does not change and is lower than RC due to the availability of running wheels. In FR rats, corticosterone is elevated prior to sucrose, indicating anticipation of and entrainment by the sucrose meal, and it decreases rapidly following meals. In the same FR rats, insulin is low prior to meals, and rises to near RC levels after drinking sucrose. The differing responses between Ad Lib and FR rats may indicate that FR rats preferentially shunt newly acquired energy away from mesenteric fat, whereas Ad Lib rats shunt energy toward it (Pecoraro et al., 2002).

2.3. Aperiodic stimulus pathways

In addition to the two main circadian inputs to HPA axis function are various non-periodic forms of stimulation most frequently associated with ‘‘classical’’ stressors, those unpredictable, adventitious insults to homeostasis, such as the inability to find food, encounters with predators or conspecific dominants, and injury that are too profound to be managed by specific local physiological mechanisms (Day, 2005). Networks mediating these inputs to the HPA axis can be grossly classified as threats that are either systemic or psychological in nature, such as hunger or fear.

2.3.1. Extra-hypothalamic inputs

2.3.1.1. Systemic inputs

2.3.1.1.1. Ascending noradrenergic bundle. Critical ‘‘bottom-up,’’ extra-hypothalamic inputs to PVN that mediate signaling of actual threats to homeostasis include various biogenic aminergic cell groups throughout brainstem, but particularly including cell groups in and around the nucleus of the solitary tract and lateral reticular nucleus, which appear to overlap with the ascending fibers also known to mediate some meal-related circadian signals. The PVN receive about 90% of their catecholaminergic (noradrenergic and adrenergic) innervation through the ventral noradrenergic bundle originating in A1–C1 cells in ventrolateral medulla and A2–C2 cells of the dorsomedial medulla (Palkovits et al., 1999; Sawchenko and Swanson, 1981). Some of these fibers arrive not at the PVN, but rather at CRF nerve terminals in the median eminence (Palkovits et al., 1998), suggesting selective regulation of secretion.

As with NPY stimulation, stimulation of the PVN with epinephrine (E) or NE results in pronounced bouts of feeding and stimulation of the HPA axis (Leibowitz, 1978; Leibowitz et al., 1989), whereas interference with the VNAB through 6OHDA lesions, interference with transmitter synthesis, blockade of alpha-1 or beta receptors or CRF immunoneutralization in PVN, all impair HPA axis responses to various aperiodic stressors, such as glucoprivation, ether, and hypotensive hemorrhage (Buller et al., 1999a,b; Daftary et al., 2000; Gaillet et al., 1993; Guillaume et al., 1987; Plotsky et al., 1989; Smith et al., 1995; Stricker et al., 1975; Szafarczyk et al., 1985, 1987). Both ingestive and counter-regulatory responses to acute glucoprivation resulting from 2-deoxyglucose (2-DG) and insulin injections are dependent on E and NE stimulation (Ritter et al., 2003). In addition to the critical extra-hypothalamic input from the VNAB are various other inputs from brainstem aminergic cells groups, including the dorsal raphe, parabrachial nuclei, locus coeruleus, peripeduncular, midbrain raphe, central gray, dorsal thalamic, A11–13, and zona incerta cell groups (Palkovits et al., 1998).

2.3.1.1.2. Pain pathways. Nociceptive stimuli, e.g., sharp pinch, thermal or visceral pain, stimulate the HPA axis through systemic and psychogenic networks. Spinohypothalamic pathways transmit pain stimuli to LH, which projects ipsilaterally to PVN CRF neurons. The spinothalamic pathway projects from the spinal cord to ventral posterolateral thalamus, then to sensory cortical areas. The spinoreticulothalamic pathway

projects from spinal cord to reticular formation, then to midline and intralaminar thalamic nuclei, and on to limbic cortical areas (cingulate, piriform and entorhinal cortices). Vagal and glossopharyngeal nerves convey visceral pain to NTS, then to the parabrachial nucleus, thalamus, and visceromotor prefrontal cortex. A2 and C2 cell groups also project to A1 and C1 neurons in the ventrolateral medulla, locus coeruleus, amygdala, and to the PVN, which shows strong bilateral activation of CRF parvicellular neurons in response to many noxious stimuli. VNAB hemisections reduce PVN activation primarily on the hemisected side. Non-catecholaminergic neurons in NTS terminating in PVN also express fos after nociceptive stimuli (Pacak et al., 1998). Cognitive control of the HPA axis is discussed later.

2.3.1.1.3. Immune signaling. Systemic inflammatory responses to immune challenges can be powerful stimuli for autonomic outflow and HPA axis activation, which inhibits pro-inflammatory processes. Pro-inflammatory molecules include tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), and interleukin 6 (IL-6). The brain vasculature expresses receptors for TNF-α, IL-1β, and IL-6 under basal conditions that are further induced following immune challenge when plasma cytokine concentrations increase. Activation of cytokine receptors in the blood brain barrier results in the transcription of various substances, including prostaglandins (PG) following signaling cascades involving cyclooxygenase 2 (COX-2) and nuclear factor kappa B (NF kB). The brain vasculature and irrigation systems are thought to be the primary source of central PG following systemic cytokine treatment, as COX-2 expression is highly co-expressed in areas staining for Von Willebrand Factor, a marker for cerebral endothelium. Activation is particularly striking in blood vessels, choroid plexus, and the CVOs (Rivest, 2001).

PGE2 is involved in neuronal responses to systemic immune challenge. Injection of IL-1 results in PGE2 expression in the CVOs, preoptic nuclei, PVN, dorsal hippocampus, and choroid plexus in the lateral ventricles. Central administration of PGE2 increases HPA axis and autonomic outflows. Febrile responses may originate in MEPO, whereas HPA activation may originate in PVN, as PGs induce CRF mRNA and type 1 receptors in the PVN. Immune challenge activates specific receptors for PGE2 (EP1–4) in brain regions controlling HPA axis and autonomic outflows. Neurons expressing EP4 particularly showed *c*-fos activation after systemic IL-1β in CVO and central stress networks, with highest expression in PVN CRF neurons. Central HPA axis and autonomic outflows following systemic immune challenge appear to be coordinated by known central stress response networks in part by activation of brain endothelial and leptomeningeal tissues resulting in signal transduction to neuronal tissue (Rivest, 2001).

Faster immune signaling may originate in liver, as hepatic vagotomy eliminates febrile responses, and blunts brainstem *c*-fos responses, PVN noradrenergic levels and ACTH responses to endotoxin. Endotoxin-clearing Kuppfer cells also release PGE2 in response to immune challenge, and this stimulates excitatory vagal afferents, which relay signals to sites involved in febrile (MEPO) and HPA axis (PVN) responses. One argument suggests that rapid febrile responses to immune challenges occurring prior to cytokine elevations utilize this pathway (Li et al., 2006). Whether the argument holds for rapid HPA activation has not been thoroughly tested. Hepatic vagotomy has reduced HPA output by about 50% in response to endotoxin, but vagotomy had a much smaller effect on responses to IL-6. Similar results were obtained for changes in hypothalamic NE content. Unfortunately, HPA responses were not measured until 2 h after injections, and not all studies agree on the effects of vagotomy. Inactivating Kuppfer cell phagocytotic activity using gadolinium chloride failed to reduce HPA responses to LPS, but again, ACTH and corticosterone were measured many hours later, long after cytokines were acting in brain. Some evidence suggests immune signaling through hepatic vagus to the HPA axis (Blatteis, 2006).

2.3.1.2. Psychogenic inputs. Top down inputs to the HPA axis are largely indirect and complexly layered cortico-striato-pallido-hypothalamic networks consisting of triple-descending inputs from both excitatory (glutamatergic) and inhibitory (GABA-ergic) fast transmission networks (Swanson, 2000). Such a degree of removal from the PVN and complexity of control hardly implies a lack of importance to HPA axis function. On the contrary, prefrontal control centers are probably the highest levels of coordination of the HPA axis and autonomic function (Buijs and Van Eden, 2000; Cechetto, 1987; Delgado, 1960; Delgado and Livingston, 1955; Neafsey, 1990; Saper, 2000; Van Eden and Buijs, 2000a). Cortical networks, particularly prefrontal areas, are demonstrably responsive to stressors, exert control over neuroendocrine and autonomic outflow, display executive (i.e., decision-making) sensitivity to visceromotor feedback (Bechara et al., 1994; Damasio, 1994), stress-dependent plasticity (Pecoraro and Dallman, 2005; Roozendaal et al., 1999a; and see below), and are frequently jointly dysregulated with the HPA axis in psychiatric conditions (Sullivan and Gratton, 2002b).

The medial prefrontal cortex (mPFC) appears to be a prime target for stressors in terms of immediate early gene (IEG) expression (Beck and Fibiger, 1995; Handa et al., 1993; Morrow et al., 2000), ADX-reversible glutamate release (Moghaddam, 1993; Moghaddam et al., 1994), high levels of GR expression, and heavy inputs from stress-responsive ascending dopaminergic, noradrenergic, and serotonergic neurons (Deutch et al., 1990; Finlay et al., 1995; Gresch et al., 1995; Jedema et al., 1999; Sullivan and Gratton, 2002a,b; Thierry et al., 1976; Yoshioka et al., 1995). Fronto-temporal systems (e.g., orbital cortex and basolateral amygdala (BLA)) involved in memorizing incentive value are clearly stress-responsive (Pecoraro and Dallman, 2005; Roozendaal et al., 1999a), and probably inform the mPFC output concerning predictions about the environment.

Direct efferent projections from the mPFC to brainstem (hypothalamic, and premotor sympathetic, and parasympathetic) centers are of special interest for visceromotor control. The dorsal mPFC projects (primarily contralaterally) to NTS, A5/A1, and preganglionic sympathetic motor neurons in the spinal cord (IML). The ventral mPFC also projects (mainly ipsilaterally) to

NTS and A5/A1, but unlike the dorsal mPFC, the ventral portion has substantial inputs to hypothalamic areas controlling the PVN, including the sub-PVZ, DMH, and LH (Van Eden and Buijs, 2000b). Both areas also project topographically to the periaqueductal gray (PAG), in areas known to control threat displays and arterial pressure (Carrive et al., 1989a,b; Holstege, 1991).

Manipulations of the mPFC, electrically, chemically, or through selective lesions, selectively alter HPA output (Akana et al., 2001; Diorio et al., 1993; Sullivan and Gratton, 2002b; Van Eden and Buijs, 2000a). Neurochemical influences include fast transmitters, as well as monoaminergic and peptidergic neuromodulators, and GCs. Infusions of both γ-aminobutyric acid (GABA) agonists and *n*-methyl-D-aspartate (NMDA) antagonists into mPFC elevate adrenocortical responses to cage-change stress (Van Eden and Buijs, 2000a). Corticosterone implants into the dorsal mPFC (anterior cingulate and prelimbic areas) blunt ACTH responses to restraint but not ether, whereas lesions result in increased HPA responses (Diorio et al., 1993). In contrast, lesions of ventral mPFC (infralimbic area) inhibit stressor induced HPA activity, particularly after repeated restraint (Sullivan and Gratton, 1999), whereas electrical stimulation increases plasma corticosterone (Feldman and Conforti, 1985). It further appears that the right hemisphere may be dominant, insofar as only right-sided infralimbic lesions are needed to produce inhibition, and rats with left-sided lesions do not differ in their responses from shams (Sullivan and Gratton, 1999). Thus, the dorsal mPFC may play a role in inhibiting HPA output, whereas the ventral regions may participate in facilitating output. In addition, symmetrical bilateral control cannot be assumed.

Exact multi-synaptic pathways that mediate cortical control over HPA responses have not been fully delineated but involve striatal and pallidal structures receiving cortical inputs, and particularly involve those that are strongly implicated in emotional and incentive processing, such as the amygdala, septum, and bed nucleus of the stria terminalis (BNST), that also share control over structures such as visceromotor pattern generators (see below), the PVN, or peri-PVN regions (see Herman et al., 2003). For example, stimulation of the BNST or septal nuclei, which gate amygdalar and hippocampal inputs to PVN (Mulders et al., 1997; Sawchenko and Swanson, 1983), stimulates HPA output (Dunn, 1987a,b). Lesions of the BNST also impair HPA responses to medial amygdala stimulation in anesthetized rats, but do not prevent ether-induced responses (Dunn, 1987a,b). BNST and CeA CRF pathways converge on PVT (Otake and Nakamura, 1995), which plays a role in the dynamic of HPA responses to repeated stress (Bhatnagar and Dallman, 1998; Bhatnagar et al., 2002).

There are several lines of indirect evidence for top-down control of the HPA axis. Obliteration of ascending inputs to the PVN, while preventing responses to systemic stressors such as ether, do not prevent HPA responses to cognitive stressors such as restraint or swim stress (Ritter et al., 2003; Sawchenko et al., 2000). In addition, different patterns of brain activation ensue from different types of stressors that segregate largely along cognitive and systemic dimensions (Emmert and Herman, 1999; Herman et al., 1998).

Third, learned conditional stimuli predicting various schedules of reward have been known for some time to control rather fluid variations in adrenocortical output, such that stimuli that predict an improving reward environment reduce, whereas those that predict a worsening reward environment increase HPA output (Coover, 1983, 1984; Coover et al., 1971a, 1977, 1980; Goldman et al., 1973; Levine and Coover, 1976). While this latter fact could implicate other non-neo-cortical regions as well, these results are consistent with an important role for prefrontal systems. Thus, areas involved in executive and memorial processes clearly affect HPA output, and often do so independently, or in prediction of actual systemic imbalances.

In addition to neo-cortical influences over the HPA axis, the hippocampus plays a role in controlling HPA responses to psychogenic stress. Excitotoxic lesions of the subiculum result in increased adrenocortical responses to restraint and open field exposure, and increased CRF mRNA in the PVN, without affecting basal HPA output (Herman et al., 1998). In contrast, ether inhalation produced normal HPA activation in lesioned rats, again revealing distinctive pathways for processing differing stressor types.

2.3.2. *Intra-hypothalamic coordination*

Residing between these bottom-up and top-down inputs to the HPA axis are at least two related, but distinctive intra-hypothalamic networks coordinating behavioral, neuroendocrine, and autonomic output systems involving energy intake and expenditure.

2.3.2.1. The arcuate complex/melanocortin/NPY systems. The first network is the circumventricular arcuate complex and the circuitries related to the melanocortin system. Strictly speaking, included within this system are pro-opiomelanocortin neurons in NTS and any downstream targets expressing melanocortin receptors. The arcuate nuclei contain NPY/agouti-related peptide (AgRP) and POMC/cocaine and amphetamine related transcript (CART) neurons that are highly sensitive to many energy signals, prominently including adipostatic hormones (e.g., leptin and insulin) and GCs. These neurons project prominently to the median eminence, PVN, DMH, BNST, CeA, lateral hypothalamus (LH), lateral parabrachial nucleus (LPBN), NTS, and the reticular nucleus (RET; Cone, 2005). Many cells that receive NPY/AgRP fibers also receive POMC/CART fibers (Haskell-Luevano et al., 1999). In general, stimulation of NPY/AgRP neurons promotes feeding (orexigenic) and reduces metabolic rate, whereas stimulation of POMC/CART neurons inhibits feeding (anorexigenic) and increases metabolic rate. The POMC molecule is processed into several peptides in addition to ACTH, including α-melanocyte stimulating hormone (α-MSH). Melanocortins act as agonists at melanocortin receptors, whereas AgRP acts as an antagonist, interfering with secreted α-MSH at its receptors. Leptin and insulin excite POMC neurons and inhibit GABA release from their NPY neighbors onto POMC neurons (Cone, 2005; Cowley et al., 2001; Elias et al., 1999; Flier, 2004; Saper et al., 2002). I.c.v. administration of leptin inhibits feeding and stimulates heart rate, arterial pressure, and renal sympathetic

activity (Shirasaka et al., 2003), whereas NPY stimulation of the PVN increases feeding (Stanley et al., 1985, 1986, 1992), and suppresses sympathetic activity to brown fat (Egawa et al., 1991). The inhibitory effects of α-MSH on food intake and thermogenesis by brown fat appear to be mediated through CRF (Cerri and Morrison, 2006; Lu et al., 2003). Arcuate circuitry is highly plastic insofar as it is known that leptin is a critical regulator of axonal guidance during the stress hypo-responsive period postnatally (Bouret et al., 2004a,b; Bouret and Simerly, 2004), and also inhibits excitatory synapse formation on NPY neurons, while encouraging excitatory inputs to POMC neurons in adults (Horvath, 2005; Pinto et al., 2004). These plastic neurons act as dueling rheostats on energy balance by influencing feeding, arousal, and sympathetic outflow (Cone, 2005).

NPY networks are glucose sensitive (Oomura et al., 1969; Routh, 2002; Routh, 2003), and mediate glucoprivic feeding, as NPY antibodies delivered to PVN impair the feeding response to 2-DG (He et al., 1998). Although arcuate neurons are glucose sensitive, targeted lesions of arcuate neurons containing NPY receptors via NPY-saporin conjugates (i.e., NPY/AgRP and POMC/CART neurons) impair inhibition of feeding responses to leptin and stimulation of feeding by ghrelin, but do not impair feeding stimulated by 2-DG treatment (Bugarith et al., 2005). Because this conjugate is apparently not retrogradely transported to medullary NPY neurons, and the medullary NPY network is necessary for the full response (see below; Ritter et al., 2003), the NTS dominates glucoprivic feeding in the absence of arcuate input (Bugarith et al., 2005).

As GCs and adipostatic signals signal opposite states of energy balance (Strack et al., 1995c), one might expect generally opposing effects on activity of cells in the arcuate complex. GCs stimulate NPY gene expression, peptide synthesis, receptor activity, and NPY-induced feeding (Akabayashi et al., 1994; McKibbin et al., 1992; Savontaus et al., 2002; Stanley et al., 1989; Tempel and Leibowitz, 1994), whereas insulin and leptin, signals of plenty, inhibit these responses (Abe et al., 1991; Kalra et al., 1999). Although GCs stimulate NPY, they are not necessary for increases in PVN NPY during overnight fasts (Hanson et al., 1997). In turn, acute increases in hypothalamic NPY stimulate CRF mRNA and peptide, ACTH, and corticosterone secretion through direct NPY innervation of CRF neurons (Liposits et al., 1988; Mihaly et al., 2002; Sainsbury et al., 1997). At this level, there appears to be positive feedback between GCs and anabolic arcuate peptides.

GCs also reciprocally interact with CART function. POMC/CART neurons exhibit GR immunoreactivity and CART inhibits feeding when delivered i.c.v. (Aja et al., 2001; Kristensen et al., 1998; Lambert et al., 1998; Vrang et al., 1999), and is down-regulated by fasting (Mizuno et al., 1998; Schwartz et al., 1997). ADX reduces CART expression in both arcuate and PVN in a dexamethasone-reversible fashion, whereas POMC expression is only slightly altered (Savontaus et al., 2002; Vrang et al., 2003). Metyrapone, an inhibitor of GC synthesis, also reduces CART (Vicentic et al., 2004). The peripheral daily rhythm in plasma CART, possibly originating from the pituitary (Stanley et al., 2004) is slightly phase-delayed relative to the GC rhythm (Vicentic et al., 2005b). CART mRNA in the nucleus accumbens is also stimulated dose-dependently by GC administration (Vicentic et al., 2005a).

Like NPY, CART appears to positively regulate HPA axis function. There are three main populations of CART neurons contributing to its PVN innervation, including adrenergic C1–3 neurons, arcuate POMC neurons, and a third group of unknown origin (Wittmann et al., 2005). I.c.v., but not i.v. injections of CART produce substantial activation of ACTH and corticosterone, suggesting that a direct action of CART at pituitary is not required (Stanley et al., 2001). This centrally mediated effect is reversible by CRF antagonists (Smith et al., 2004), suggesting that, like NPY and α-MSH, CART excites the HPA axis through stimulation of hypothalamic CRF secretion.

Although CART is considered a catabolic peptide, the major CART input to PVN comes from medullary neurons that co-express the epinephrine-synthesizing enzyme phenylethanolamine-*N*-methyltransferase (PNMT; Wittmann et al., 2005) and is known to be involved in glucoprivic feeding (Smith et al., 2004). Similar to α-1 adrenoceptor stimulation, CART phosphorylates CREB in CRF neurons, suggesting an additive effect on the CRF promoter (Sarkar et al., 2004). CART function remains obscure, as it has been multiply associated with stress, anxiogenesis, inhibiting food intake, and behavioral responses to drugs via mesolimbic reward pathways, among other proposals.

2.3.2.2. The hypothalamic visceromotor pattern generator. A second intra-hypothalamic network that coordinates HPA function involves various medial periventricular nuclei. Based on anatomical evidence, Thompson and Swanson (2003) have suggested the existence of a periventricular hypothalamic network that functions as a "hypothalamic visceromotor pattern generator," or HVPG, nodes of which include five preoptic nuclei and the dorsomedial nucleus of the hypothalamus (DMH; see Fig. 5). All of these cell groups are highly interconnected, and project to PVN neuroendocrine and pre-autonomic cell groups (Thompson and Swanson, 2003). Hodologically, the HVPG appears to involve coordination between neuroendocrine, autonomic, and skeletal motor systems.

The structural centrality of the DMH in this network is consistent with the importance of the DMH in stress responsiveness more generally (DiMicco et al., 2002). The DMH project to both pre-autonomic and neuroendocrine cell groups in PVN, as well as to the neighboring subPVZ (ter Horst and Luiten, 1986; Thompson et al., 1996), and receive ascending catecholaminergic and descending cortico-striato-pallidal inputs, and input from the SCN, which thus positions this cell group as a central coordinator of these critical motor systems; it also projects to the central gray and to RVLM, a major cell group that regulates premotor sympathetic outflow (Fontes et al., 2001).

Electrical stimulation of the DMH results in defensive behaviors and autonomic responses suggesting emotional distress (Hilton et al., 1979). Stimulation with $GABA_A$ antagonists or excitatory amino acids results in increased sympathetic outflow and circulating catecholamines (DiMicco

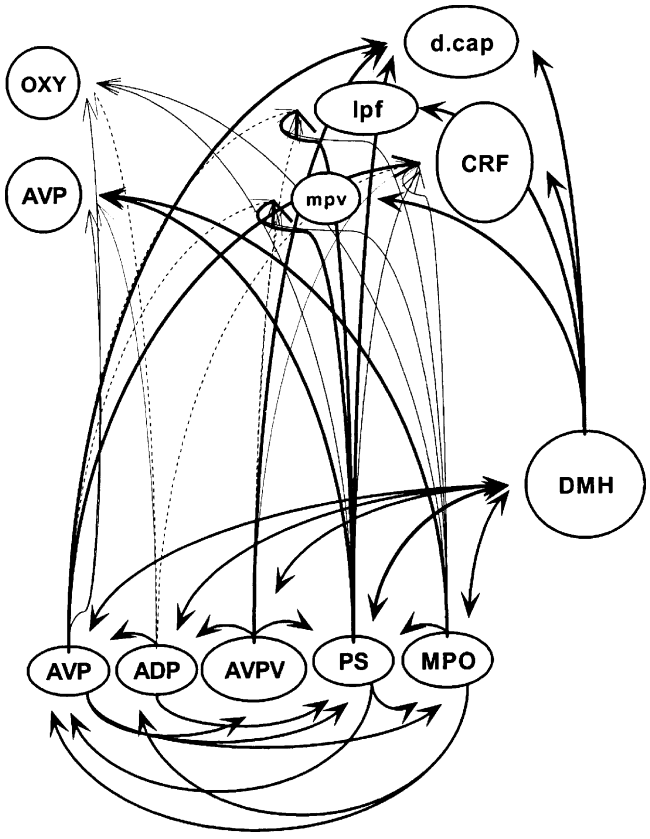

Fig. 5. The hypothalamic visceromotor pattern generator (HVPG). This schematic is based on Thompson's and Swanson's (2003) hodological analysis of relations between various hypothalamic nuclei in relation to neuroendocrine and autonomic divisions of the paraventricular hypothalamus (PVN). The HVPG itself consists of the the dorsomedial hypothalamus (DMH), its major hub, and five preoptic nuclei, including the anteroventral preoptic (AVPO), anterodorsal preoptic (ADP), anteroventral periventricular preoptic (AVPV), parastrial nucleus (PS), and medial preoptic nucleus (MPO). Magnocellular oxytocinergic (OXY) and vasopressinergic (AVP) neurons are shown in the upper left. Parvicellular corticotropin releasing factor-containing neurons (CRF) are shown in the upper right. The descending division of the PVN includes pre-autonomic neurons in the dorsal cap (d.cap), the caudo-lateral perifornical PVN (lpf), and the medial parvicellular (mpv) neurons residing between neuroendocrine cell groups. Heavier projections are indicated by heavier lines. Note the massive interconnectivity between the DMH and preoptic nuclei, and their more idiosyncratic relations to neuroendcrine and autonomic divisions of the PVN.

et al., 1986; Wible et al., 1989; Wible et al., 1988), decreased visceral blood flow, greatly increased blood flow to skeletal muscle, and increases in heart rate and arterial pressure (DiMicco et al., 1986; Soltis and DiMicco, 1991a,b). In a direct comparison with PVN stimulation, much lower doses of GABA antagonists or excitatory amino acids were required in DMH to achieve these results (Stotz-Potter et al., 1996). Fig. 6A–C show autonomic and neuroendocrine responses to air puff stimulation when either the DMH or PVN are incapacitated by muscimol injections. Clearly the coordination of heartrate (panel A), blood pressure (panel B), and ACTH (panel C) by this psychogenic stressor is more heavily determined by stimulation of the DMH than the PVN (Stotz-Potter et al., 1996). Increases in blood pressure resulting from DMH stimulation can be completely blocked by incapacitating the RVLM with muscimol (Fontes et al., 2001), whereas relays in PAG (ter Horst and Luiten, 1986; Thompson et al., 1996), or raphe pallidus (Morrison et al., 1999), may be involved in the observed DMN-induced tachycardia.

Disinhibition of the DMH also results in increases in ACTH (Bailey and Dimicco, 2001; Keim and Shekhar, 1996), which may be mediated by glutamatergic inputs to PVN (Boudaba et al., 1997). *c*-Fos activation in DMH neurons results from footshock, and these neurons have been double-labeled retrogradely from the PVN (Li and Sawchenko, 1998). Finally, it has been shown that muscimol-induced inhibition of the DMH reduces activation of the PVN by air-puff stimuli but not by hemorrhage (De Novellis et al., 1995), suggesting that the DMH is an important site mediating psychogenic stressors (DiMicco et al., 2002). Electrical stimulation of the medial hypothalamus of anesthetized cats provoked both excitatory and inhibitory ACTH responses, suggesting that throughout the medial hypothalamus there are nested sites that either stimulate or inhibit the PVN (Grizzle et al., 1974). Further functional delineation of this putative pattern generator should prove to be very important for investigations of the integrated responses of an organism to real or predicted threats to homeostasis, particularly in relation to the coordination of behavioral, neuroendocrine, autonomic outflows. Nonetheless, it is already abundantly clear that the HVPG channels input from both major circadian oscillators, the immune system, and psychogenic pathways, and is highly positioned to coordinate visceromotor outflows.

In summary, although the essence of the HPA axis is rather simple, its function is controlled by a diverse set of networks having diverse functions. Two distinct periodic drivers control the circadian rhythmicity of HPA output, and hence cycles of energy balance, under free-feeding and restricted feeding conditions. Whereas the SCN have clearly been identified as the light-entrainable oscillator, an ascending medullary NE/NPY network may be involved in the food-entrainment and other non-periodic systemic events. In addition to these periodic drivers are networks responsive to adventitious threats. Responses to psychogenic stimuli, such as predicted threats and responses to conditioned stimuli, appear to involve cortico-striato-pallido-hypothalamic networks. One important target of these descending networks likely involves a putative intra-hypothalamic pattern generator that appears to coordinate neuroendocrine, autonomic and behavioral outflows to circadian, immune, and psychogenic stimuli. A second intra-hypothalamic network involving the NPY and melanocortin systems also appears to coordinate motor output, but this system seems more responsive to direct metabolic need as signaled by circulating leptin and insulin concentrations. Together, these diverse drivers allow highly flexible control of HPA function.

2.4. The HPA axis response to metabolic deficits

Perhaps the essential function of HPA activity is to respond to, and anticipate, metabolic need. It seems likely that the circadian peak in GCs occurring just prior to the daily activity

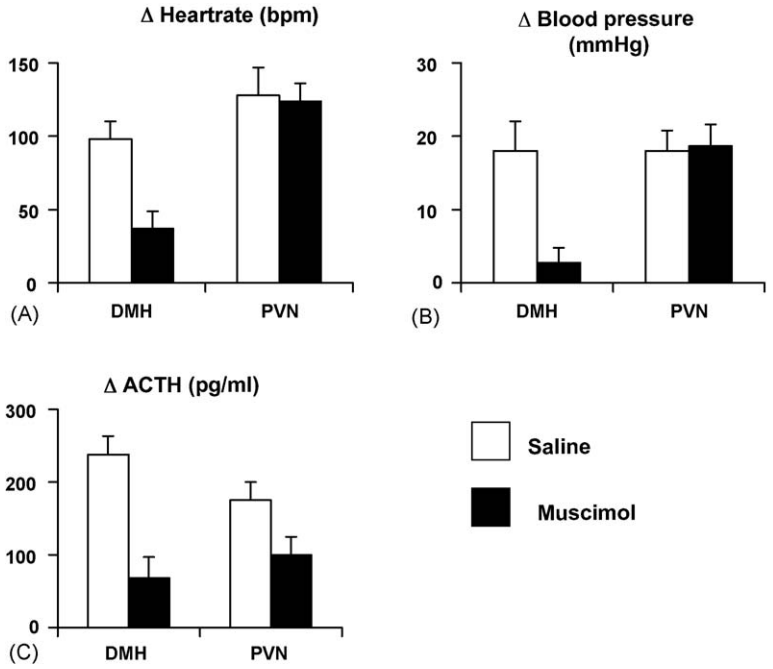

Fig. 6. A comparison of paraventricular (PVN) and dorsomedial (DMH) hypothalamic nuclei on coordination of autonomic and neuroendocrine outputs. When the DMH is inactivated by local muscimol infusion, heartrate (panel A), blood pressure (panel B), and ACTH output (panel C) are all reduced. By contrast, similar inactivation of the PVN only results in reduced ACTH output, suggesting that the DMH plays a more central role in coordinating motor outputs, consistent with structural evidence that it is a major node of a hypothalamic visceromotor pattern generator (Thompson and Swanson, 2003). Data adapted from DiMicco et al. (2002).

cycle, when glycogen stores are depleted and energy fluxes have shifted toward lipolysis, is a case in point. There also appear to be many other forms of metabolic deficits, from specific appetites, e.g., arising from sodium depletion, to various temporal scales and magnitudes of caloric deficits, from acute glucoprivation to the more gradual tempos of starvation, that animals respond to, and which set in motion a complex array of counter-regulatory events, all involving HPA activation. Although a number of these systems are known in some detail, the integrated actions of these systems are far from being resolved.

2.4.1. Acute deficits

Acute glucoprivation induced by insulin or 2-deoxyglucose injections produces pronounced counter-regulatory ingestive and adrenal responses (Karteszi et al., 1982; Ritter et al., 2001). Ritter et al. (2003) demonstrated the critical role of ascending adrenergic inputs to HPA responses to 2-DG or insulin injections by selectively destroying brainstem NE/E neurons using a retrogradely transported toxin injected into PVN that was directed at NE/E neurons. Food intake, CRF hnRNA (not mRNA), and corticosterone increased dramatically following acute glucoprivation, whereas these were strongly blunted after selective destruction of NE/E neurons. However, the same lesions had no effects on adrenocortical responses to a swim stress, again suggesting dissociation of psychogenic and systemic stressors. The lesions also did not affect the normal circadian variations in corticosterone. The latter finding is of interest given Honma's results on the role of NPY-induced circadian elevations of corticosterone during food-restriction (Ishizaki et al., 2003; Yoshihara et al., 1996a,b,c), insofar as the locus of circadian control appears to shift from SCN to other, perhaps pontine/medullary structures under conditions of food-restriction.

2.4.2. Starvation

In the direst cases of metabolic need, prolonged fasting or starvation, GCs are prime movers of both physiological and mental adaptation. In the initial phases of deprivation a great number of physiological changes ensue. For example, removal of food from young rats in the hours just prior to activity, when glycogen stores are minimal and animals must rely on other endogenous sources of fuel, results in fairly rapid and progressive reductions in body weight, plasma glucose, insulin, and leptin, whereas free fatty acids (FFA) and corticosterone increase significantly. Both the mean value (mesor) and the amplitude of the corticosterone rhythm are amplified within the first 24 h of fasting. In addition, CRF mRNA is reduced, whereas NPY mRNA is increased (Bradbury et al., 1991a,b; Dallman et al., 1999). As starvation proceeds, GCs also increase species-specifically according to the animal's ability to proceed to inanition. In rats, ''resting'' corticosterone values may quadruple after 2 days, and increase by a factor of 10 after 4 days of starvation (Makino et al., 2001) whereas young adult humans have only a minor cortisol response after 60 h of starvation (Samuels and Kramer, 1996). Larger, fatter animals, such as young seals, are capable of enduring 60 days of starvation, during which time their plasma GC levels slowly, but progressively increase (Ortiz et al., 2001).

Fasting and starvation are unusual among stressors, in that, from a functional point of view, there is no indication of a need for stress-related defensive behaviors, but rather there is an

essential primary need to get food. Consistent with this functional view, is the fact that GRs are not down-regulated during starvation (Makino et al., 2001), whereas GRs in the hypothalamus down-regulate following chronic, repeated restraint, thus increasing the anorexigenic effects of PVN CRF via reduced inhibitory feedback on CRF. Similarly, in limbic fear systems involving the central nucleus of the amygdala (CeA) during the metabolic derangement of ADX or during fasting, CRF mRNA is decreased in CeA (Duclos et al., 2005b; Laugero et al., 2001a; Timofeeva et al., 2002; Watts and Sanchez-Watts, 1995), possibly serving to reduce competition from anxiety-related behaviors on feeding behaviors. CRF binding protein is also reduced in pituitary of fasted animals (Timofeeva et al., 1999), whereas NPY expression increases and POMC expression decreases in the arcuate nuclei, while maintaining peripheral levels of GCs (Brady et al., 1990). Thus, in the absence of the recruitment of defensive systems, the system may be biased toward peripheral energetic management and recruitment of central motive states primarily aimed at replenishment, as opposed to defensive strategies that are less useful under these conditions.

2.5. Post-prandial responses: fed, fasted, or entrained?

The HPA axis also directs post-prandial resource management. The data in Fig. 4C and D distinguish corticosterone and insulin responses to meals, depending on feeding status. Rats fed ad libitum had low, basal corticosterone prior to the sucrose meal and corticosterone, but not insulin increased after the meal. This post-prandial elevation in GC appears to be mediated by stimulation of central a-1 adrenoreceptors (Al-Damluji et al., 1987). Fed humans also exhibit feeding associated elevations in cortisol just after meals (Brandenberger et al., 1982; Follenius et al., 1982; Krieger et al., 1971). Rats that have been fasted for 24 h also show marked increases in corticosterone and insulin responses to re-feeding (Dallman et al., 1989b), whereas the same does not hold for a single brief period of water-restriction and re-watering (Dallman et al., 1989b; Shiraishi et al., 1984), and the response seems to be specific to energy storage.

In contrast to fed animals or 24-h fasted animals, chronically food-restricted, food-entrained rats showed anticipatory elevations in corticosterone that are suppressed to basal levels following the meal. Similarly, hungry rats show a larger post-prandial insulin response (Pecoraro et al., 2002). Similar post-prandial inhibition of HPA axis in rats during restricted feeding schedules has been noted before (Honma et al., 1992; Wilkinson et al., 1979).

The exact conditions under which these opposite responses of the HPA axis to meals occur are not entirely clear, but they may have some functional relevance with respect to the activity of particular energy depots. Mesenteric white adipose tissue (mWAT) is essentially a labile and high capacity energy sink (Bjorntorp, 1997; Dallman et al., 1999). mWAT is the most GC-sensitive fat depot, particularly in the presence of insulin, and released fatty acids have preferrential access to the liver in times of need. Metabolic status may cause the brain to switch the HPA control over this sink on and off. Simply put, fed animals taking a meal direct it to the sink, whereas hungry animals direct it elsewhere. Because short-term deprivation does not inhibit the post-prandial hormonal responses, the switching process could also be a function of chronic deprivation only, or even circadian predictability.

2.6. Peripheral metabolic roles of GCs

The fact that starved ADX rats die, whereas fed ADX rats survive stress is a puzzling phenomenon, that may testify to the importance of metabolic reserves during stress (Darlington et al., 1989; Selye, 1936). The fact that corticosterone replacement in fasted ADX rats also allows survival suggests the critical role of corticosterone in managing energetics. Fig. 7 shows the marked metabolic effects of providing ~200 μg dexamethasone, a potent synthetic glucocorticoid, in the overnight drinking water on adult male rats. Body weight gain was markedly inhibited (Fig. 7A), reflecting decreased chow intake, nonetheless circulating insulin (Fig. 7B) was increased, but glucose concentrations did not differ from those in controls drinking plain water (Fig. 7C). These results show the rapid induction in peripheral insulin resistance in the glucocorticoid-treated rats. In the livers of these rats, gluconeogenesis was increased as shown by both increased activity of phosphoenolpyruvate carboxykinase (PEPCK; Fig. 7D), the rate-limiting enzyme for gluconeogenesis, and by increased glycogen storage (Fig. 7F). Additionally, the activity of fatty acid synthase (FAS) was increased suggesting that there was increased fatty acid synthesis (Fig. 7E). To acquire substrate for the increased hepatic synthetic activity, glucocorticoids inhibit protein synthesis, increasing the capacity of muscle and skin to deliver amino acids, and also increase the capacity of fat cells to release free fatty acids, to liver—although in the presence of high insulin, it is likely that fat depots are relatively preserved at the expense of protein.

In summary, the HPA axis responds both to starvation and restricted feeding with elevations in corticosteroids prior to obtaining food, and reductions immediately after food ingestion. Under these conditions, it is unlikely that any potential activation of fear systems dominates appetitve routines, as such activation would interfere with the primary goal of finding and ingesting calories. The actions of the GC centrally promote hunger and peripherally mobilize calories from peripheral stores in the form of small molecules for use by the liver in glucocorticoid-enhanced gluconeogenesis. As we see in later discussions, the inverse actions of GC peripherally and centrally are orchestrated to promote phenotypic remodeling appropriate to resource poor and/or hostile environments.

3. Stressor-induced HPA axis responses

3.1. Acute stressors

3.1.1. Acute responses

In addition to the slow daily circadian rhythm in GCs and HPA responses to metabolic need are the variations in secretion

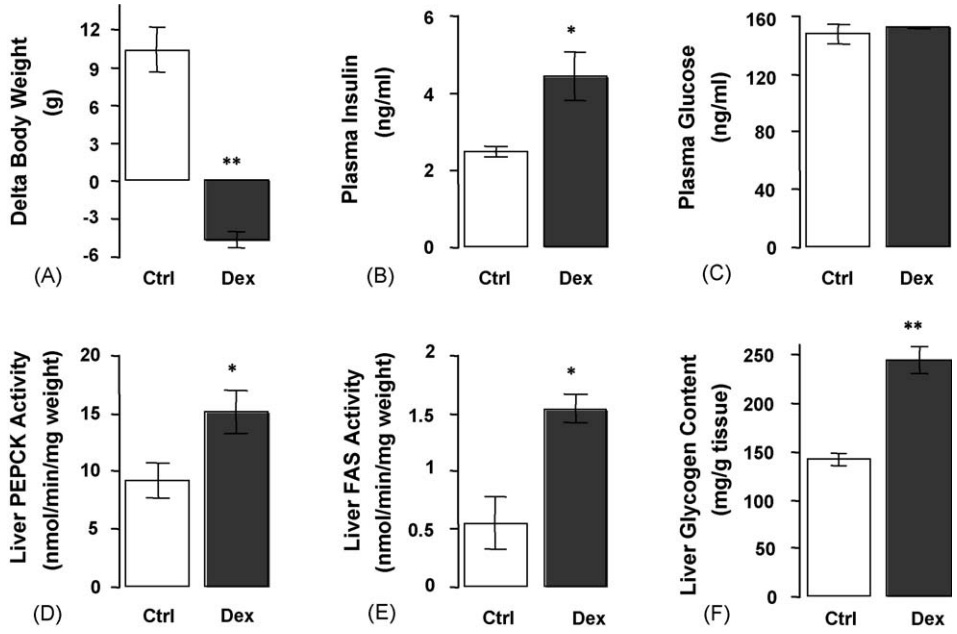

Fig. 7. Effects of synthetic glucocorticoid dexamethasone on remodeling peripheral energy fluxes toward fat. DEX in the drinking water overnight reduces body weight (top left) and increases plasma insulin concentrations (top middle) without affecting net glucose concentrations (top right). In the liver, phosphoenolpyruvate carboxykinase (PEPCK, bottom left) and fatty acid synthase (FAS, bottom middle) activities increase, and glycogen stores also increase (bottom right) in response to DEX (data from J. Warne).

resulting from acute stressors. Although individual, strain, and vendor differences exist, the ACTH and corticosterone responses of rats tend to follow a common, prototypical pattern to stressors of rapid onset. Fig. 8 shows ACTH and corticosterone responses in plasma collected by rapid sampling after a rat has been introduced to a plastic restraint tube (S.F. Akana, unpublished). When blood is sampled from the tail within 1 min, this represents a basal or resting value for both ACTH and corticosterone (B; Time 0). After that, the pulsatile ACTH responses are quickly mounted and peak between 10 and 20 min, after which they tend to fall off toward 60 min, and even further by 120 min, where they often have returned to baseline, despite continued restraint. The adrenocortical response closely follows and tends to mimic the pattern of

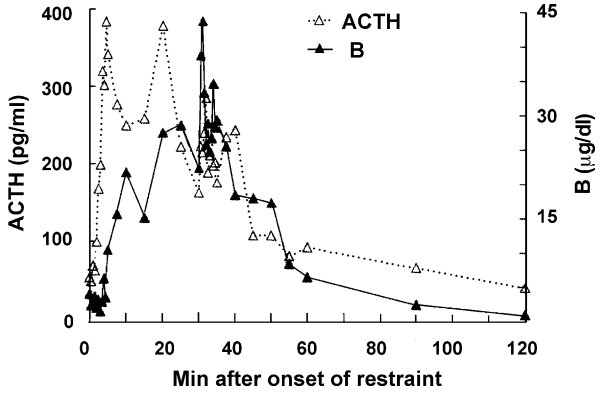

Fig. 8. A prototypical profile of ACTH and corticosterone (B) responses in one rat to restraint stress achieved via rapid sampling. The ACTH response is rapidly elevated within minutes of restraint, peaking here between 5 and 20 min before being trimmed by the slower adrenocortical response that closely follows ACTH (data from S. Akana).

ACTH, with the exception that the adrenal response is saturable, so that the GC response may be somewhat prolonged, as the integrated GC response tends to be proportional to the integrated ACTH response (Keller-Wood et al., 1983).

The temporal dynamic of the stress response depends upon the type, and temporal dynamic of the stressor. For example, injecting rats subcutaneously with polyethelene glycol (PEG) results in a slowly developing hypovolemia as the PEG gradually sequesters bodily fluids in the subcutaneous space (Tanimura et al., 1998). The ACTH response develops gradually over hours, peaking approximately 4 or 5 h after the injection, in parallel with increasing hematocrits and volume deficits (Tanimura and Watts, 2001). Although hematocrit is significantly elevated by 1 h, ACTH does not increase until 1–2 h after the injections, when the volume deficit is approximately 12%. By contrast, rapid hemorrhage through controlled removal of blood directly from the vascular system results in rapid ACTH and corticosterone responses, but again the threshold for the response is the removal of about 12–15% of the blood volume (Dallman et al., 1987a; Darlington et al., 1992). These results suggest that there is an absolute magnitude of volume depletion in the cardiovascular system at which the HPA axis begins to respond.

3.1.2. Canonical "fast" feedback

The typical ∩ shape of the ACTH response results from the rapid initial increase due to central drive from CRF/AVP neurons, followed by a subsequent decline. The decline, or off response, is determined by feedback from adrenal steroids themselves acting at several levels and receptors, including the pituitary and hypothalamus, the high affinity mineralocorticoid receptor (MR) and the lower affinity glucocorticoid receptor.

Providing animals with glucocorticoids prior to stressors dose-dependently inhibits subsequent ACTH output (Dallman et al., 1989a, 1987b; Dallman and Jones, 1973; Keller-Wood and Dallman, 1984; Keller-Wood et al., 1984; Kovacs et al., 2000), and appears to require occupation of both receptor subtypes for optimal effect (Bradbury et al., 1994; Dallman et al., 1994; de Kloet et al., 1999; Jacobson and Sapolsky, 1993; Ratka et al., 1989; Spencer et al., 1993, 1991, 1998).

Although we refer to acute feedback as ''canonical'' feedback regulation in reference to its widely cited operation as a simple servo-mechanism, it remains inadequately understood with respect to the mechanisms, substrates, and temporal dynamics of feedback. At the pituitary, there is both rapid feedback that occurs within minutes of a GC signal (e.g., Ginsberg et al., 2006; Widmaier and Dallman, 1984; Young et al., 1990), and slower, transcriptional effects. GCs bind cytosolic receptors, translocate to nuclear GREs to inhibit gene expression for CRF receptors and POMC. Elevated GCs also inhibit the vesicular release of ACTH. Because pituitary corticotropes are rich in transcortin which tightly binds the steroid, higher-than-basal levels of steroid are required to produce feedback effects (Cole et al., 2000; Koch et al., 1974a,b), consistent with the high density of GR in pituitary.

In the hypothalamus, GCs feedback on CRF neurons may inhibit transcription, as well as the release of presynthesized CRF. Dexamethasone (a potent synthetic glucocorticoid) implants into the PVN inhibited CRF and AVP expression and ACTH release (Kovacs et al., 1986; Kovacs and Mezey, 1987; Sawchenko, 1987), whereas the natural ligand, corticosterone, either did (Feldman et al., 1992) or did not (Kovacs and Makara, 1988). Corticosterone implants into hippocampus, amygdala, and septum of ADX rats also inhibited ACTH secretion (Kovacs and Makara, 1988), which as we will see is not always the case.. The hippocampus has been of particular interest with respect to steroid-mediated feedback inhibition (Cullinan et al., 1993; Van Haarst et al., 1997). However, lesions of the fornix, the main efferent pathway from hippocampus to PVN has shown minor (Herman et al., 1995) to no effects on stress-induced HPA output (Bradbury et al., 1993). Diorio et al. (1993) showed that bilateral implants of corticosterone in the cingulate gyrus/prefrontal cortex reduced ACTH responses to restraint, but not ether stress (Diorio et al., 1993), and similar findings have been also reported (Akana et al., 2001). Overall, the consensus on brain feedback sites is not as strong as one would hope, but this may be largely due to the sheer complexity of the system. However, feedback of GCs at the pitutitary corticotrope is clear and unambiguous (Ginsberg et al., 2003; Roberts et al., 1987).

Feedback inhibition of ACTH secretion to basal levels is not inevitable, and can be overcome with sufficient drive. For example, PEG-induced sustained hypovolemia produces significant increases in corticosterone within 3 h of injections, but the HPA response continues to build for at least 2 more hours, as volume loss from the cardiovascular system continues to increase. Therefore, with sustained hypovolemia, the usual fast feedback at CRF neurons or corticotropes does not appear to be effectively operational, or may simply damp the ongoing response. In addition, CRF heteronuclear RNA (hnRNA) transcription also continues to increase for up to 5 h, appearing to maintain translation of CRF mRNA throughout this time, for stressed, but not unstressed animals, suggesting that the ACTH response is actively sustained by primary transcription of CRF (Tanimura and Watts, 2001).

Fig. 9 shows apparent GC feedback under basal conditions observed at the level of CRF mRNA in the parvocellular motorneurons of the PVN. Moderate expression of CRF mRNA is observed after sham ADX (left panel), whereas ADX results

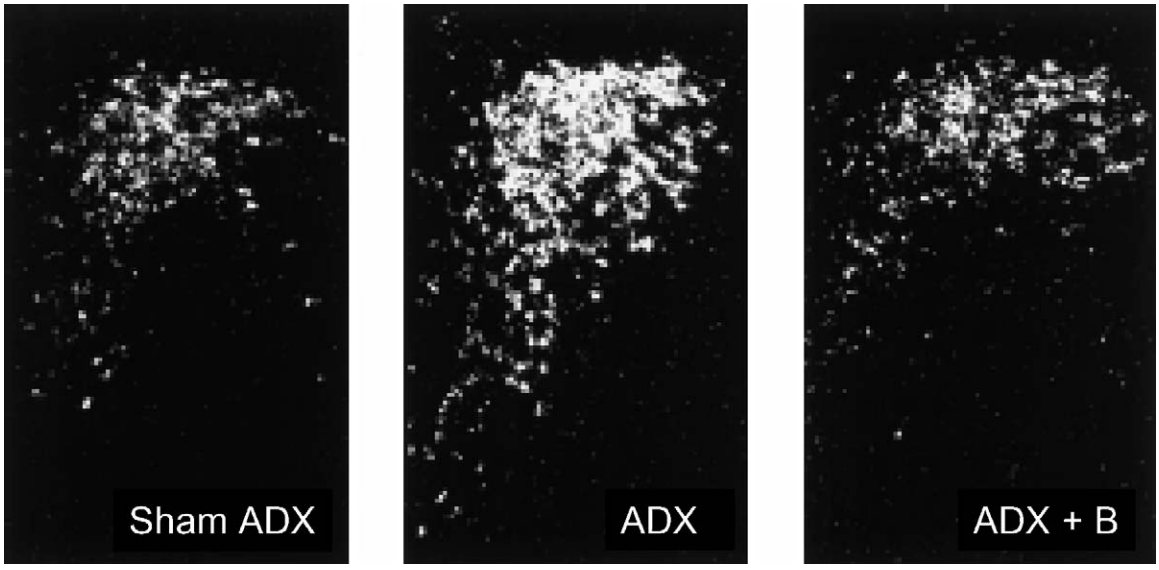

Fig. 9. An apparent inhibitory feedback effect of B on the expression of corticotropin releasing factor (CRF) mRNA in paraventricular hypothalamus is revealed by adrenalectomy (ADX) and corticosterone (B) replacement. CRF mRNA in sham-operated rats (left panel) increases following the loss of corticosterone (via ADX; middle panel), and is then restored to normal by corticosterone replacement (right panel). The effect of corticosterone on CRF mRNA in the PVN can be mimicked by feeding ADX rats high density sucrose (see Fig. 13) suggesting that it is the metabolic, rather than the direct effects of B replacement on brain, that normalizes CRF expression.

in disinhibition of CRF expression (middle panel), indicating the loss of feedback. Finally, normalization of expression is observed with corticosterone replacement (right panel). Although the site of such feedback is generally presumed to be at the level of the PVN motoneurons, we will present evidence later that challenges the notion of direct feedback as a potentially facile interpretation.

3.2. Chronic stress

Under conditions when stressors are applied repeatedly and intermittently or continuously, further dynamics of the HPA axis become evident. Briefly, two main forms of adaptations may occur. Repeated stressors can result in habituation, a progressive diminution of the response over days, or they can lead to the opposite, a progressive facilitation, or sensitization of the response. In conventional usage by endocrinologists, the terms habituation and sensitization do not necessarily connote the same theoretical meanings as they do for psychologists for whom these terms refer to non-associative forms of learning. Rather, they tend to be used descriptively. The degree to which habituation and sensitization within the HPA axis depend on associative or non-associative events in the psychological sense remains to be determined.

3.2.1. Habituation

It is frequently observed that repetition of the same stressor results in a progressive diminution of the HPA axis response over days (Cole et al., 2000; Natelson et al., 1988; Pitman et al., 1988; Sakellaris and Vernikos-Danellis, 1975; Vernikos et al., 1982). Habituation has been observed for restraint (Bhatnagar et al., 2002; Cole et al., 2000; Hauger et al., 1990; Viau and Sawchenko, 1995), handling (Dobrakovova et al., 1993), cold (Bhatnagar et al., 1995), noise (Armario et al., 1986), water immersion (de Boer et al., 1990), immobilization (Giralt and Armario, 1989), and ethanol injections (Spencer and McEwen, 1990). There is at least one report of brainstem catecholaminergic habituation to a homotypic stressor, as well (Spencer and McEwen, 1990). Some homotypic stressors, such as footshock, frequently do not result in habituation, possibly due to their perceived severity (Kant et al., 1985; Pitman et al., 1990), because they involve a component of particular metabolic exertion, such as forced running (Kant et al., 1985), or in the case of intermittent morphine injections, because the schedule of the stressor rocks the system severely between the positive and negative effects of the stressor (opponent processes) within central stress networks (Houshyar et al., 2003, 2004) (and see below).

Habituation of the HPA response to restraint can be prevented by lesions of the posterior paraventricular nucleus of the thalamus (pPVT; Bhatnagar and Dallman, 1998; Bhatnagar et al., 2002). Blockade of MR or MR and GR via specific antagonists also prevents habituation (Cole et al., 2000). Both findings are of interest insofar as both PVT and hippocampus project to BNST, which appears to be part of a pathway involved in contextual conditioning of HPA output (Gray, 1993; Sullivan et al., 2004; Ledoux, 2004), suggesting potential associative processes that are invoked to inhibit the HPA response when the animal expects that an event will be unpleasant, but perhaps not unexpectedly traumatic. However, essentially all major drivers of the HPA axis project to the PVT (Fig. 2), and many complex events could be involved in HPA plasticity.

3.2.2. Facilitation

Facilitated, or sensitized HPA responses in chronically stressed individuals are most often elicited by presentation of an acute, novel stimulus. After repeated stress, CRF mRNA increases to a greater extent after an acute novel stressor (Harbuz and Lightman, 1989; Houshyar et al., 2003; Imaki et al., 1995).

However, the sensitized HPA response in chronically stressed rats appears to require persistently or repeatedly elevated concentrations of glucocorticoids. Clamped high corticosterone in ADX rats that have been exposed to chronic cold, or to streptozotocin-induced diabetes facilitates HPA responses to acute restraint, whereas lower, replacement concentrations of corticosterone do not provoke a facilitated response compared to rats not exposed to chronic stress (Akana et al., 1996; Scribner et al., 1991). Fig. 10 shows ACTH responses to a third session of restraint stress in animals infused with saline or corticosterone given i.c.v. during 4 days. It is clear that chronically elevated steroid in brain facilitates the HPA output to stress.

That chronic stress recruits central stress response networks can be seen when comparing CRF mRNA expression in the PVN of chronically stressed versus unstressed animals during basal sampling and following an acute restraint stress. In this case, the chronic stress used was a regimen of intermittent, twice daily morphine injections (Houshyar et al., 2004). Fig. 11A–D shows CRF mRNA expression under four conditions. Control rats under basal conditions show low levels of CRF expression (Fig. 11A). Following a regimen of morphine treatment, CRF mRNA is upregulated under basal conditions (Fig. 11B). Following an acute restraint stress in

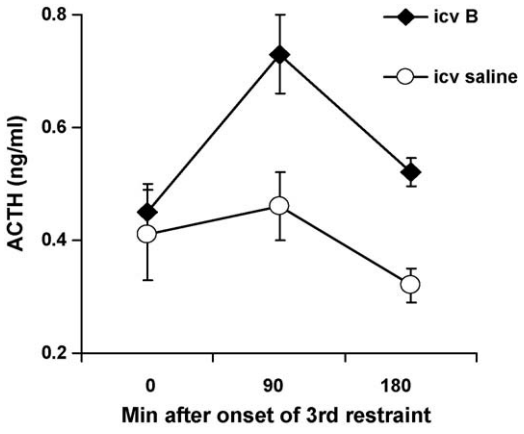

Fig. 10. Effects of intracerebroventricular B infusion (black diamonds) on adrenocorticotropin hormone (ACTH) output during a 3 h restraint stress compared to saline infusions (empty circle). Actions of B directly on brain facilitate the ACTH response. Data adapted from Laugero et al. (2002).

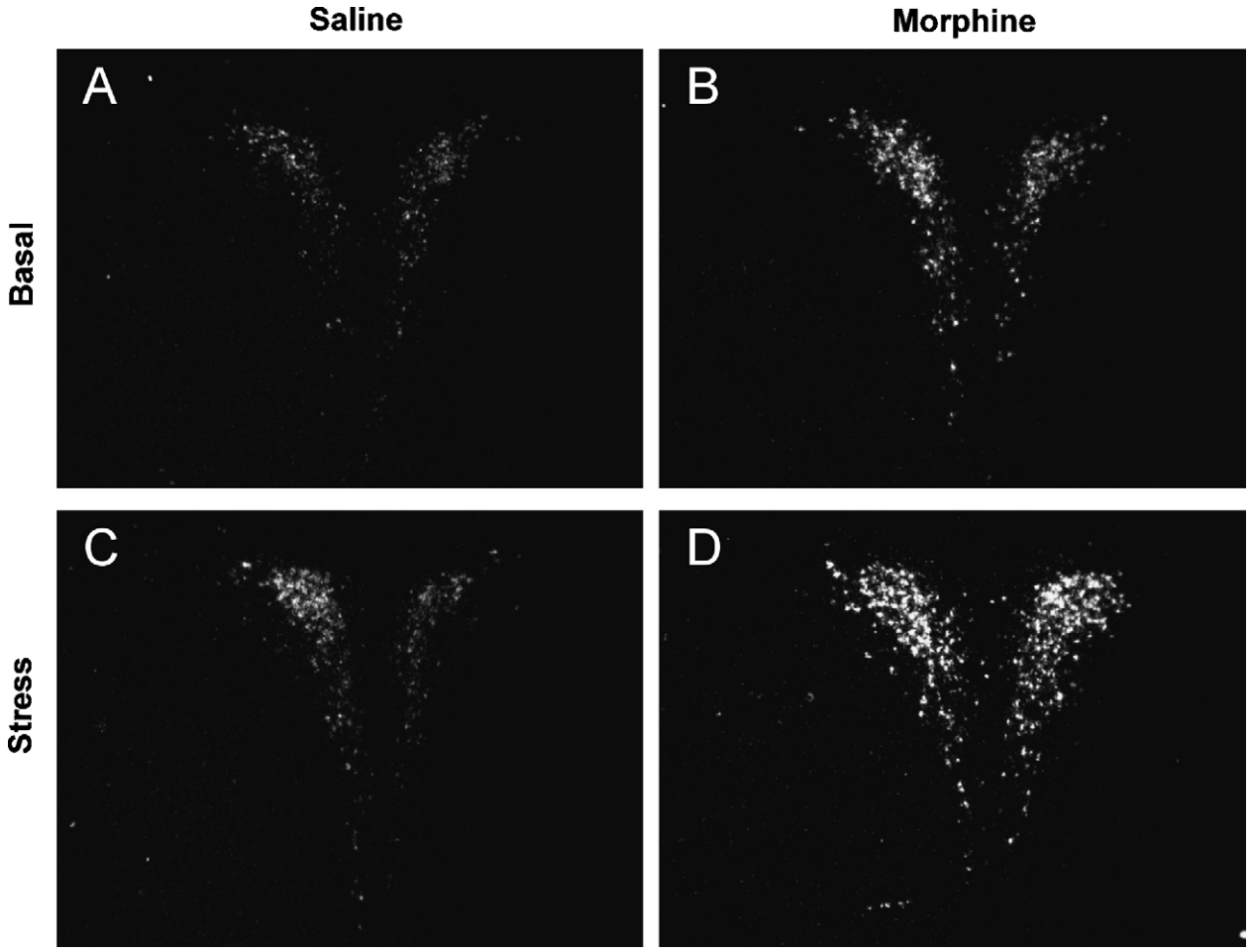

Fig. 11. Facilitating effects of a chronic stressor (intermittent morphine injection in escalating doses) on CRF mRNA expression in paraventricular under basal conditions and after novel restraint. Basal expression of CRF mRNA in vehicle treated rats (panel A) increases in response to morphine treatment (panel B), to levels resembling vehicle treated rats after restraint (panel C). Intermittent morphine treatment further increases expression of CRF mRNA in restrained animals (panel D). Intermittent morphine injections are a chronic stressor, and chronic stress facilitates drive of the neuroendocrine motoneurons in the HPA axis. Data adapted from Houshyar et al. (2003).

control animals, CRF is upregulated (Fig. 11C), semi-quantitatively resembling the basal levels seen in chronically stressed animals. Finally, compared to controls receiving a single acute restraint, chronically morphine-stressed animals show facilitated upregulation in CRF mRNA (Fig. 11D). Thus, the chronic stressor of intermittent morphine treatment clearly upregulates activity in HPA motoneurons under both basal conditions and following an acute heterotypic stressor.

Facilitated responses may result from sustained elevations of GCs acting on neurons in the CeA to stimulate CRF synthesis and secretion (Cook, 2001, 2002; Greenwood-Van Meerveld et al., 2001; Shepard et al., 2003). Activity of the elevated CRF in CeA is required for the altered behavioral, autonomic and neuroendocrine responses that accompany chronic stressors (Myers et al., 2005). Although GCs rapidly elevate CRF levels in CeA, it appears to take several days of elevated steroid to initiate recruitment of the chronic stress-response network (Laugero et al., 2002). However, once recruited, the central CRF network appears to activate the locus coeruleus and other monoaminergic cell groups (Jedema et al., 2001; Lowry et al., 2003; Ortiz et al., 1996). Lesions of the locus coeruleus inhibit HPA responses to stress (Ziegler et al., 1999).

Repeated activation of the paraventricular, or ‘‘neuroendocrine’’ thalamus (Turner and Herkenham, 1991) results in reduction of ACTH responses to repeated restraint, whereas lesions of this structure augment ACTH responses to restraint in chronically stressed rats. Such lesions do not affect the response to an acute novel restraint. Thus, the PVT may be generally inhibitory to HPA output only after chronic stress (Bhatnagar and Dallman, 1998, 1999; Bhatnagar et al., 2002). Moreover, tonic glucocorticoid inhibition of chronic stress responses may also be mediated through this structure (Jaferi et al., 2006). The paraventricular thalamus is innervated by both forebrain and hindbrain structures that are known to regulate the HPA axis (Bubser and Deutch, 1998; Canteras et al., 1994), and in turn innervates amygdala, prefrontal cortex, BNST, hypothalamus and brainstem (Moga et al., 1995; Van der Werf et al., 2002), and is therefore in position to determine whether the HPA axis exhibits habituation or sensitization to chronic stress. It may be that chronic stressors invariably activate the central stress

response network, but that the expression of HPA responses is modulated by the PVT via memorial and comparator processes that inform the animal whether the current stressor is familiar or not. Under familiar chronic stress, the PVT may be recruited to blunt the stress response, whereas the experience of a heterotypic stress under chronic stress conditions may fail to recruit the PVT, thus allowing normal, and even facilitated HPA responses.

3.3. Chronic GCs, ADX, and metabolic feedback

3.3.1. Chronically high GCs on the central stress response network

Consistent with facilitation of HPA output under chronically high concentrations of GCs, and the view that chronic stressors typically recruit central stress networks, chronic elevations of GCs in depression are associated with ''paradoxically'' elevated cerebrospinal fluid concentrations of CRF (Gold et al., 2002). Under these conditions, DEX fails to inhibit HPA output (Gold et al., 1988a,b; Nemeroff et al., 1984), and CRF and AVP mRNA are elevated in PVN (Raadsheer et al., 1994b). Part of this effect may owe to reduced feedback efficacy at these various sites in the central stress network. After acute stress, ADX rats replaced with constant B showed relatively elevated CRF mRNA in PVN and tyrosine hydroxylase (TH) mRNA in LC compared to sham-operated rats, indicating normal GC-mediated feedback in intact animals. However, repeated stress elevated both mRNAs in sham rats, potentially indicating a loss of GC feedback. Consistent with a loss of feedback was the loss of GR mRNA observed in the PVN, LC, and hippocampus of intact rats only (Makino et al., 1995a,b, 2002), an effect argued to be GC-dependent (Makino et al., 2002).

In addition to a potential loss of feedback inhibition, active upregulation of brain CRF levels may also contribute to this facilitation. Although acute restraint does increase CRF levels (Hsu et al., 1998), it may not always increase CRF mRNA (Pacak et al., 1996). On the other hand, high replacement doses of corticosterone (Makino et al., 1994a), repeated restraint (Schulkin et al., 1998; Thompson et al., 2004), chronic social stress (Albeck et al., 1997), and GC implants into CeA (Shepard et al., 2000) do upregulate CRF mRNA in CeA. The BNST, a pallidal gateway to PVN from CeA, also upregulates CRF mRNA in response to GCs (Makino et al., 1994b) and salt loading (Watts, 1992b). Although some stimuli relating to metabolic deficits down-regulate CRF mRNA in CeA, including salt loading (Watts, 1992b) and starvation (Kaneda et al., 2001), there may be functional advantages to stimulus-specific regulation in this particular structure involved in learned output: In the case of metabolic need, it may be better to reduce anxiety-related moods in order to reduce motivational or behavioral competition against feeding. GCs also increase CRF mRNA in the dorsal cap of the PVN (Swanson and Simmons, 1989), the pre-autonomic cell group projecting to brainstem LC and NTS, and spinal cord (Sawchenko and Bohn, 1989; Sawchenko and Swanson, 1989; Swanson and Sawchenko, 1983; Van Bockstaele, 1998), thus having proactive influences on autonomic output.

3.3.2. ADX, brain, metabolic derangement, and feedback

Although canonical feedback by GCs is firmly established, several key findings suggest that there are two additional axes of chronic GC actions on brain that operate in approximately opposite directions, a facilitating effect of the direct actions of GC on brain, and an indirect, inhibitory effect based on the effects of GCs on metabolism. Removal of GCs by ADX results in deficits in both energy intake and deposition (Akana et al., 1985; Freedman et al., 1986; Strack et al., 1995a,b,c). Recall also the data from Fig. 9 showing disinhibition of PVN CRF mRNA following ADX. In addition, white adipose tissue (WAT) deposition and leptin and insulin levels are decreased, whereas circulating NE is increased, suggesting increased sympathetic outflow following ADX (Akana et al., 1996; Brown and Fisher, 1986; Strack et al., 1995b). Similar effects are mimicked or mediated by manipulations of the central CRF and NE stress networks that are influenced by GC actions.

Thus, it could be argued that the central inhibitory effects of GCs are directly mediated through a loss of feedback, or through actions on other central systems, but three facts argue against direct central mediation of these effects by GCs. First, peripheral replacement of GCs using low doses that should not occupy central GR normalizes many metabolic deficits resulting from ADX (Akana et al., 1985). Second, providing sucrose also increases appetite and results in greater energy deposition following ADX, raising the possibility that normalization by GC replacement is not a direct central effect, but rather an indirect effect of GCs through alterations in metabolism (Bell et al., 2000). Third, central GR occupancy would be inconsistent with the central facilitating effects of GCs on behavior, HPA output (Fig. 10) and autonomic outflow. Because non-nutritive saccharin solutions failed to correct metabolic derangements following ADX, the restorative effects of sucrose appeared to be post-ingestive (Bhatnagar et al., 2000). Thus, the restorative effects of low peripheral doses of GCs also suggest an effect of the metabolic axis on brain.

In a direct test of this metabolic feedback hypothesis, Laugero et al. (2001a) employed designs in which rats feeding ad libitum were either ADX or not, and given a 1.0 M sucrose solution to drink or not. Fig. 12A–D show that compared to Shams, ADX rats eating chow had reduced intake, body weight gain, caloric efficiency, and relative mWAT. However, each of these derangements was corrected by providing sucrose to ADX rats. Plasma leptin, insulin, triglycerides and glucose were also normalized in ADX rats drinking sucrose. In the brain, PVN CRF mRNA was elevated in ADX rats eating chow, but not in those drinking sucrose after 2 weeks (Fig. 13, left panel). Within ADX animals drinking sucrose for an even shorter period (5 days), PVN CRF mRNA was inversely related to sucrose intake during the previous night (Fig. 13, right panel). In the CeA, ADX rats eating chow had reduced CRF mRNA content compared to other groups, including ADX animals drinking sucrose. Likewise, in A2/C2 cell groups and LC, dopamine β-hydroxylase (DBH) mRNA was elevated in ADX rats eating chow, but not in those drinking sucrose. Additional tests also revealed that when given a choice between equally sweet 1.0 M sucrose and 2 mM saccharin solutions,

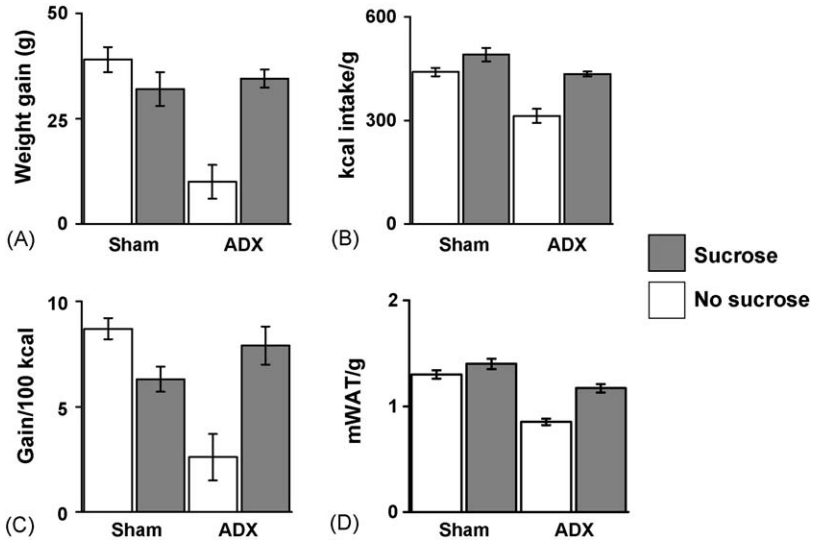

Fig. 12. Effects of ADX and 1.0 M sucrose drinking on absolute body weight gain (panel A), caloric intake relative to body weight (panel B), caloric efficiency (panel C), and relative mWAT weights (panel D) to the intact state. ADX generally deranges metabolism to inhibit these variables, whereas sucrose drinking larely restores the animal. The slight inhibition of caloric efficiency in the shams drinking sucrose is likely due to increased autonomic outflow that compensates for the extra calories ingested, maintaining normal body weight. Data adapted from Laugero et al. (2001a).

intact animals displayed no preference, whereas ADX animals exhibited a strong preference for the nutritive sucrose.

Taken together, the data strongly indicate that ADX and the loss of corticosterone disinhibits central stress response networks and causes metabolic derangement. Metabolic feedback from sucrose mimicked the effects of low doses of GC after ADX by correcting these derangements both peripherally and centrally, and ADX animals given a choice between sucrose and an equally sweet non-nutritive solution strongly favored the caloric solution, such that the animals appeared to be self-medicating through food intake.

To test that the effects of GCs themselves were not due to direct central effects, Laugero et al. (2002) asked if similar peripheral and central corrective effects would occur if GCs were infused directly into the brain of ADX rats and how such infusions interacted with sucrose intake. Rats receiving 3-day i.c.v. corticosterone infusions had reduced chow intake and weight gain relative to saline controls, reduced mWAT depots (Fig. 14A), increased CRF immunoreactivity in PVN (Fig. 14B), and exhibited somewhat higher basal and significantly higher stress-induced ACTH output (Fig. 14C), effects of central corticosterone that appear to operate in the opposite direction to sucrose drinking. In contrast, saline infused controls drinking sucrose showed the greatest weight gain and caloric intake, and had significantly reduced basal ACTH. Rats receiving both i.c.v. corticosterone and sucrose to drink had intermediate values on most measures, suggesting that the opposite effects of central corticosterone and peripheral sucrose metabolism had largely cancelled one another.

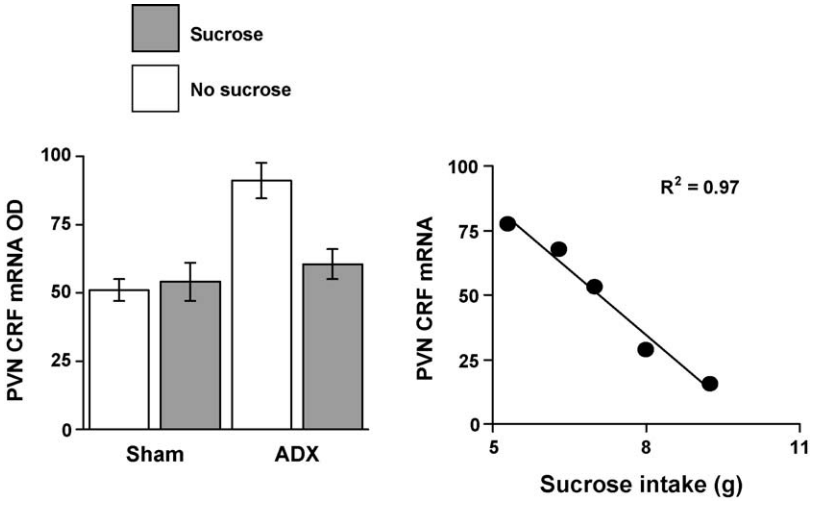

Fig. 13. Central effects of ADX and 1.0 M sucrose drinking on CRF mRNA expression in the HPA motorneurons in the paraventricular nucleus of the hypothalamus. Fourteen days after ADX CRF mRNA expression increases, and sucrose drinking in the absence of corticosterone normalizes expression (left panel). Within ADX animals drinking sucrose for only 5 days, CRF mRNA was inversely related to sucrose intake (right panel). Data adapted from Laugero et al. (2001a).

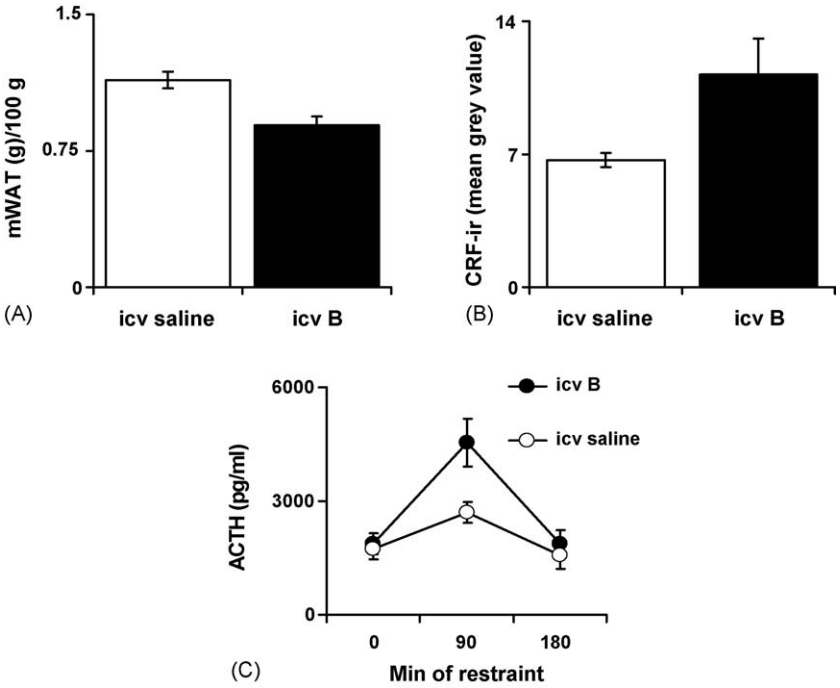

Fig. 14. Effects of centrally infused corticosterone (B) in ADX rats. In contrast to peripheral B replacement or sucrose drinking that restore metabolic and central derangements following ADX, corticosterone infused into a lateral ventricle (i.c.v.) exacerbates these derangements, reducing relative mWAT (panel A), increasing CRF immunoreactivity in paraventricular hypothalamus (panel B), and facilitating ACTH output following restraint stress (panel C), strongly suggesting that the peripheral restorative effects of corticosterone and sucrose result from metabolic correction and subsequent feedback inhibition to brain. By contrast, central B feeds forward on brain in an excitatory fashion. Data adapted from Laugero et al. (2001b).

In summary, acute and chronic responses to stressors are differently controlled. With acute stimuli, the HPA axis responds rapidly and the duration of the response is inhibited by the acute feedback effects of the secreted GC, provided that the stimulus is of low intensity; with high intensity stimuli, GC feedback can be abrogated by sufficient drive to the CRF motorneurons. With repeated stressors, the HPA axis may either reduce or increase its responsivity, depending on the type, and threat of the stimulus. Novel stimuli provided to chronically stressed animals usually provoke facilitated responses in the HPA axis, and this response requires GC concentrations above the normal daily mean value. With chronic stress, GCs appear to stimulate the brain chronic stress response network, resulting in augmented behaviors, neuroendocrine and autonomic outflows, probably as a consequence of GC-augmented CRF expression and secretion in the CeA. However, low concentrations of GC in the periphery restore metabolism and stress-responsivity of ADX rats to normal, and drinking sucrose ad libitum can do the same. By contrast, GC infused centrally inhibit metabolic recovery and stimulate subsequent HPA responsiveness. The cumulative findings suggest that there are two axes of chronic GC actions on brain. The direct actions of elevated GCs involve many excitatory effects, including facilitated HPA output, and stimulatory effects on CRF and brainstem stress networks. In contrast, the disinhibition of central stress networks by ADX can be corrected by both low peripheral GC replacement and sucrose, but not saccharin, suggesting that a metabolic feedback signal inhibits central stress response networks.

4. A new working model of stress-related GC function

The prevailing idea that stress-related HPA function is primarily self-terminating by glucocorticoid-mediated inhibitory feedback must be revised to incorporate feedforward aspects of HPA function on itself with chronic stress, and on the entire brain more generally. In addition, a new view should also incorporate an indirect inhibitory axis based on metabolic feedback. Fig. 15 shows two simplified diagrams contrasting the acute, canonical model of HPA feedback regulation (left panel) with our working model of HPA function under chronic metabolic drive (right panel). The canonical model contains a CNS drive component (solid arrow down) and feedback from GCs at the levels of pituitary and brain (left panel, dotted lines). While this type of inhibitory feedback has been repeatedly demonstrated, it is insufficient to account for the current data. For example, the canonical model cannot handle the chronic facilitating effects of steroid in brain, chronic inhibitory effects of low peripheral doses of steroid or inhibitory feedback from drinking sucrose following ADX. In addition, canonical feedback lays no claims to the other significant and wide-ranging changes in phenotype that result as a consequence of prior stress, hunger, or negative energy balance. Previous discussions of this view are available (Dallman et al., 2005, 2004, 2003; Laugero, 2001).

In addition to the apparently indirect inhibitory metabolic axis on central stress networks (right panel, curved dotted line) and the direct excitatory effects of chronically stress-induced elevations in steroid on HPA output already discussed (right panel, curved solid arrow), other data suggest even more

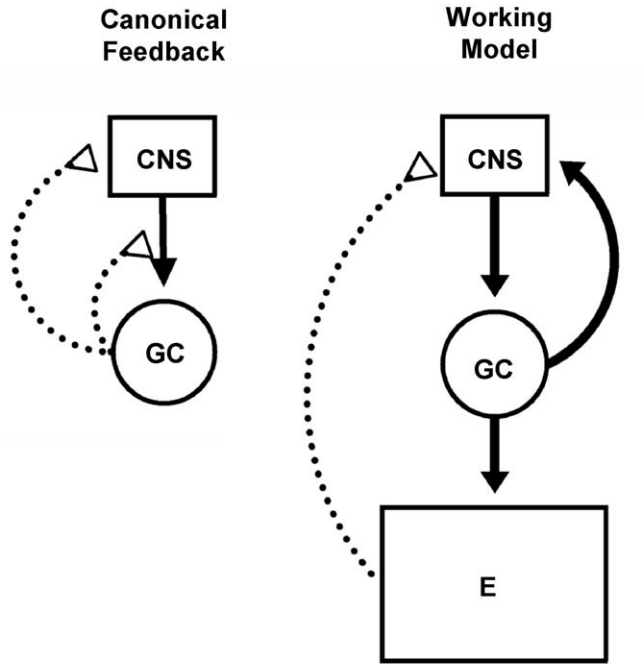

Fig. 15. Two simplified models of HPA axis regulation. In the canonical feedback model of glucocorticoid (GC) function (left panel), the central nervous system (CNS) stimulates GC secretion, which rapidly feeds back on brain and pituitary to provide inhibitory feedback that trims the neuroendocrine response. While canonical feedback is well established, it cannot account for a number of phenomena, including the ability of sucrose to reduce drive on HPA axis motoneurons. The diagram to the right is a simplified version of our working model of HPA regulation that distinguishes additional axes of GC action in an attempt to account for extant data. CNS-stimulated GC secretion crosses the blood–brain barrier to act directly on brain incentive systems in a feedforward fashion, enhancing both appetitive and aversive central motive states and facilitating various motor outflows. Peripherally, GCs remodel energy stores toward fat, which provides some inhibitory metabolic feedback to central drive states.

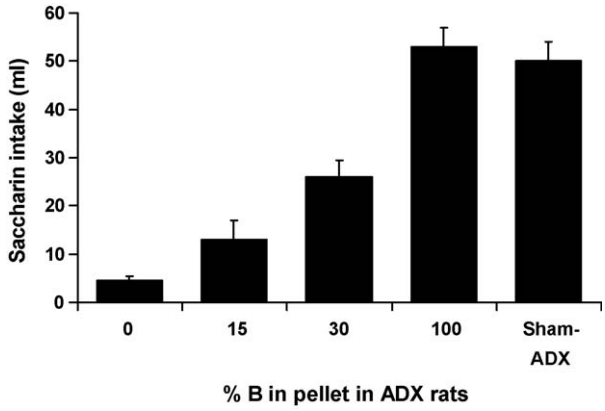

Fig. 16. Effects of steady-state peripheral corticosterone (B) concentrations in ADX rats drinking a palatable saccharin solution. Rats were ADX then given pellets containing 0%, 15%, 30%, or 100% B, or were sham-operated. Mean daily saccharin intake increased dose-dependently with corticosterone, such that the highest dose completely restored saccharin drinking to the level observed in intact rats, indicating behavioral, and perhaps incentive motivational effects of B. Data adapted from Bhatnagar et al. (2000).

wide-ranging excitatory effects of elevated steroid, not limited to chronic stress or even aversive stimulation, for that matter. Indeed, a number of motor outputs related to appetitive stimulation also appear to be amplified by elevated steroid. As we will discuss such feedforward effects of steroid in much greater detail later, the following results are offered as a down-payment on that claim for the purposes of introducing our generalized working model of HPA axis function.

Bhatnagar et al. (2000) used ADX rats and replaced them with corticosterone (B) pellets in four doses ranging in content from 0% to 100% B, then gave them saccharin to drink ad libitum in addition to chow and water. Fig. 16 shows mean daily intake by corticosterone dose. As concentration increased, daily intake increased, such that rats with no corticosterone reliably drank minimal amounts of saccharin, whereas rats with 100% B pellets drank as much as sham operated rats. Because saccharin is non-nutritive, the effect could not be attributed to differing post-ingestive reinforcement signals from saccharin. Recalling that ADX rats show a strong preference for sucrose over saccharin in two-bottle tests, which was interpreted as a form of metabolic and stress-reducing self-medication, the dose-dependent effect of GCs on non-nutritive saccharin drinking rather suggests incentive learning or motivational effects, and that elevated GCs not only recruit chronic stress response networks that facilitate HPA output, but also recruit appetitive motivational networks that amplify responding for positive incentives, as well.

The working model (Fig. 15, right panel) contains two main axes of GC action on brain, an indirect inhibitory effect resulting from GC-mediated alterations in energy metabolism, and a direct drive axis through which GCs primarily feedforward in brain. Despite the capability for habituation to repeated homotypic stress and the potential for GC-mediated inhibitory feedback shown in the left panel of Fig. 15, evidence cited above suggests that high steroid can also facilitate more than HPA output as a direct result of elevated steroid in brain, represented by the solid arrow in the right panel of Fig. 15. Elevated GCs in brain also modify other motor outputs in ways that suggest amplification of central motive states and memorial processes (detailed in Section 5 and beyond). The increase in incentive motivation with respect to both appetitive and aversive states results in both greater engagement with positive incentives and greater responsiveness to negative incentives. Note that this direct drive pathway resembles a positive feedback loop that lends itself to runaway activation. The ‘‘brake’’ on positive feedback actions between HPA output and excitatory effects in brain, a so-far unidentified metabolic signal, acts so that both GCs and food, in their own varying degrees, may correct metabolic derangements to provide metabolic-like feedback inhibition on what is potentially runaway positive feedback from the direct effects of the steroid.

Fig. 17 shows examples of how this model should work under four scenarios. The far left panel shows the case for an intact animal that is fasting. Energy stores are low (represented by a lowercase ‘‘e’’ in the box), central drive is high, and GC feedforward activation of central motive states is high. Although the high peripheral GCs will alter energy flux and efficiency to provide some feedback, this an inadequate solution, as without food, GCs will continue to increase central

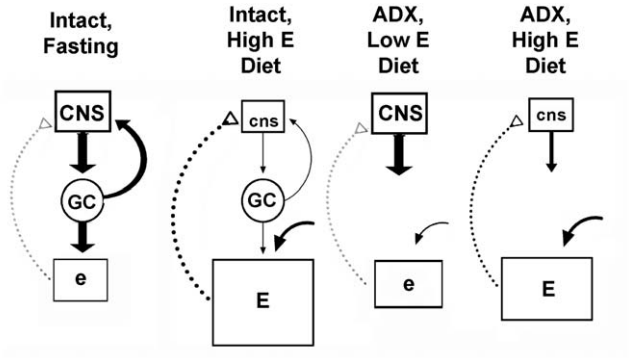

Fig. 17. Four scenarios exemplifying predictions of the working model. In the case of fasting in adrenally intact animals, reduced energy stores disinhibit central drive on the HPA axis, releasing GCs that further increase activity in central incentive networks to enhance appetitive (food seeking) moods. Although GCs also remodel energy, to provide some inhibitory feedback, without food they cannot over-ride the central drive provided by ever increasing GC secretion. In the second case, adrenally intact animals provided with high-energy, palatable foods should have enhanced inhibitory metabolic feedback on central states, including HPA axis output, thus reducing direct central GC signaling. In the third case, adrenalectomized (ADX) animals should manage peripheral resources poorly in the absence of GCs, resulting in a weakened inhibitory metabolic feedback signal that disinhibits central stress networks, resulting in high ACTH output, without increased central appetitive drive, due to the absence of GCs. In the fourth example, ADX rats on high-energy, palatable diets should have a fairly normal HPA axis despite the absence of resource management by GCs, simply because the diet itself can substitute for the effects of GCs. Central motive states, again will not be amplified in the absence of GCs.

CRF drive, and other central motive states, as energy stores are depleted. The second panel from the left shows the case for an intact animal eating a high-energy diet, which increases energy stores, providing inhibitory metabolic feedback to central drivers, reducing adrenocortical output and GC feedforward effects. The panel third from left shows an ADX rat eating a low-energy chow diet without management of peripheral energy by GCs, resulting in a weak inhibitory feedback signal from the low energy food, and high central drive. The fourth panel shows an ADX rat on a high-energy diet, wherein the diet compensates for the absence of peripheral management by GCs, thus stabilizing central drive, but in the absence of high central GCs, central motive states are not actively amplified. Thus, the working model proposes alternative mechanisms of chronic HPA axis regulation, and it more generally tries to account for the induction and reduction of central motive states by GCs and food, respectively.

4.1. Comfort food and stress: induction, reduction, and remodeling

The first direct test of the model (Pecoraro et al., 2004) was aimed at two main straightforward predictions that fall directly from this model. First, repeated stress should increase the salience of palatable, high-energy foods, resulting in an increase in intake. Second, palatable high-energy foods (along with peripheral remodeling of energy by high GCs) should provide metabolic inhibitory feedback and reduce HPA output during a repeated stressor compared to rats eating only chow. To test these predictions, rats were employed in a 2 × 2 design manipulating stress and diet. Half of the rats ate chow ad libitum, whereas the other half was presented with a choice of chow, lard, and 1 M sucrose solutions for several days prior to the stressor. After this baseline period, half of the rats on each diet were subjected to once daily 3 h restraint stress for 5 days, whereas the other half served as home cage controls. On the 5th day, an additional heterotypic stress of placing the restraint tubes on a shaker table was added to dishabituate the response to repeated restraint. At the beginning of restraint, ponderal growth diverged for each group according to the additive positive effects of diet and the negative effects of the stressor (Fig. 18A): The unstressed controls gained more weight than stressed rats, whereas rats eating preferred foods gained more weight than their counterparts with only chow. In addition, animals eating the preferred food showed greater relative adiposity than the chow eating controls in each depot tested (Fig. 18B).

With respect to the hypothesis that chronic stress increases the incentive salience of high-energy foods, Fig. 18C shows that the proportion of comfort food eaten during the stress increased to 65% of total calories, compared to their own baseline and to the stable intake of the unstressed controls throughout. However, this proportional increase in lard and sucrose was not a consequence of increased absolute intake. Rather, stressed animals reduced their absolute chow intake while maintaining baseline levels of lard and sucrose intake. Thus, the relative preference for preferred foods increased by a defense of these, but not chow intake during the restraint period.

Although total caloric intake was not increased during the stressor in rats with lard and sucrose available, the characteristic finding that stress reduces chow intake and ponderal growth in rats (e.g., for review see Dallman and Bhatnagar, 2001) suggests that absolute measures may incorrectly identify underlying support of incentive motivational structure. Relatively greater support for high-energy dieting does conform to both the model and other extant data on the effects of stressors on feeding, and makes functional sense. The model predicts that repeated stressors call forth defensive behaviors that are incompatible with feeding (Gardner and Gardner, 1988), as well as an increase in the salience of high-energy foods. In support of this line of reasoning, Fanselow (Fanselow et al., 1988) showed that electric shock reorganized feeding bouts such that rats made fewer out-of-nest foraging forays, but ate larger meals when they did go out. Therefore, in a hostile environment, a relative preference for energy-dense meals is appropriate to both minimize hostile encounters and maximize energy balance.

The second main prediction was that the eating of preferred foods would inhibit HPA output. Fig. 19 shows areas under the curve for ACTH (panel A) and corticosterone (B; panel B) responses. As can be seen, HPA output began habituating by day 3, but was dishabituated by the addition of the rotation component on day 5. Consistent with the metabolic feedback hypothesis, ACTH output was significantly reduced in rats eating comfort foods on days 1 and 3 of restraint, whereas on day 5 when the dishabituating stimulus was added, no differences were evident. Comfort food reduced corticosterone responses on days 3 and 5 relative to chow controls. In addition, we measured relative CRF mRNA in the parvocellular region of

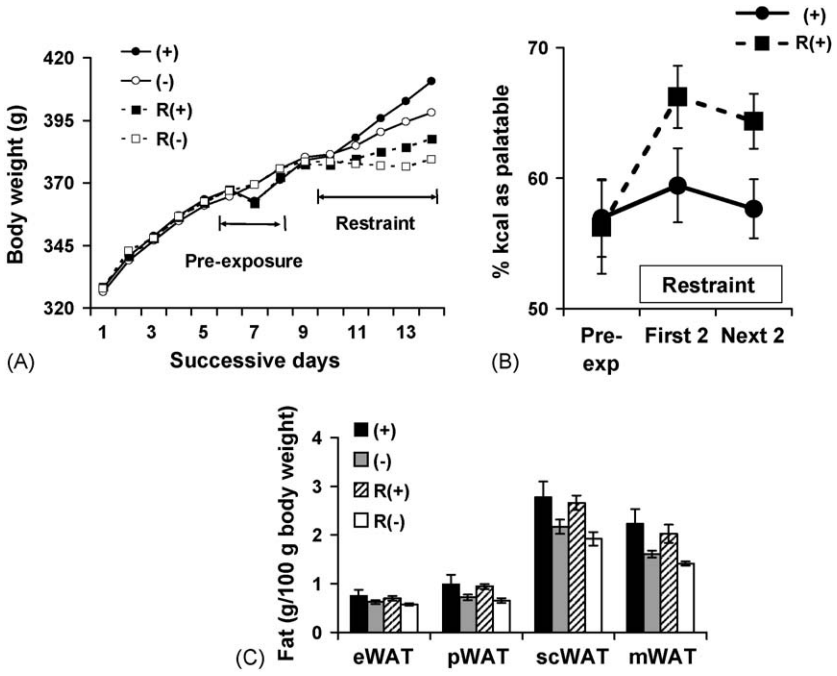

Fig. 18. (A–C) Panel A: Body weights of rats used in a 2 × 2 design test of the working model of HPA regulation. All rats were allowed to eat ad libitum. Half of the animals were given only chow (−), and the other half chow and "comfort food" (lard and sucrose (+)), and they were never restrained. The othe half were given the same two diets and were additionally restrained (R) on the final 5 days. For those receiving "comfort food", it was available during the 3-day pre-exposure period and during the 5-day period of repeated 3h restraint. Comfort food increased ponderal growth relative to chow groups, and restraint reduced growth relative to basal groups. Panel B: Percent of intake in kcal among groups provided with "comfort food". During the 3-day pre-exposure, there was no difference in intake between groups. During repeated restraint rats increased their relative intake of "comfort food", whereas the basal controls maintained a constant proportion. This effect resulted primarily from a specific decrease in chow intake in the stressed animals, as they defended comfort food intake. Panel C: Effects of "comfort food" and repeated restraint on fat depots standardized for body weight. Comfort food increased all fat depots in all groups. All data adapted from Pecoraro et al. (2004).

the PVN of the hypothalamus with the prediction that palatable food would reduce message in these HPA axis motor neurons (Fig. 19C). For unstressed home cage controls, relative CRF mRNA was significantly reduced by palatable food, whereas for the restrained animals no significant reduction occurred. While these results are largely consistent with our hypothesis, the lack of a reduction in CRF mRNA in stressed animals was complicated by the addition of the heterotypic stressor on day 5.

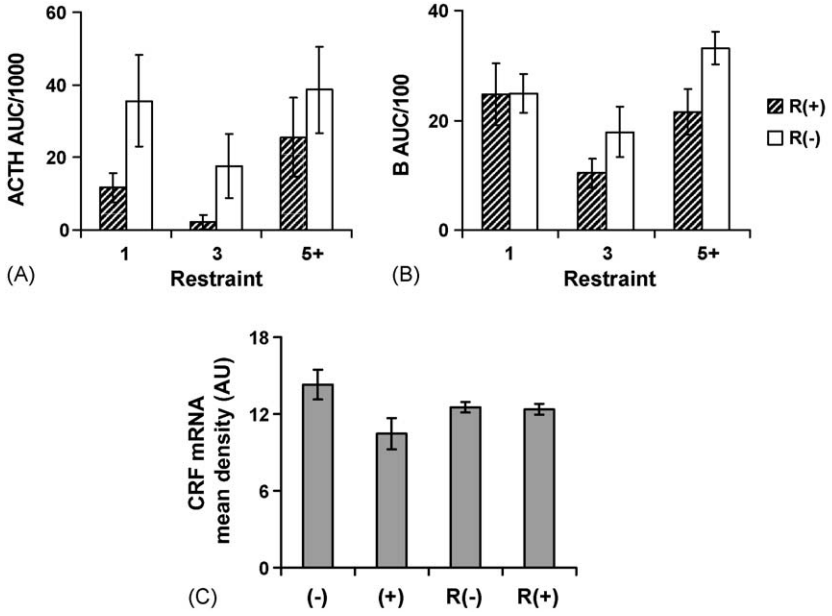

Fig. 19. (A–C) Areas under the response curve (AUC) for ACTH (panel A) and corticosterone (B; panel B) on restraint days 1, 3, and 5. Comfort food decreased AUCs on days 1 and 3, but not on day 5, probably due to the addition of the heterotypic stress of a shaker table. Panel C: Effects of restraint stress and comfort food eating on CRF mRNA in the paraventricular hypothalamus. Comfort food eating eating reduced basal CRF mRNA expression in unrestrained controls, but showed no effect in restrained animals, perhaps due to the addition of heterotypic stress on the last day. All data adapted from Pecoraro et al. (2004).

As shown in Fig. 18C, the stressed rats eating palatable food maintained high fat depot weights throughout the period of restraint, compared to the stressed rats eating only chow; although the hypothesized remodeling of fat stores was not observed, the amount of fat in the depots measured did not differ from that in the unstressed controls.

With these caveats in mind, the overall data were reasonably consistent with the model.

4.2. Evidence against inhibitory metabolic feedback

Although earlier results (Laugero et al., 2001a,b, 2002) and our initial tests (Pecoraro et al., 2004) were generally in line with the aspect of the working hypothesis that high-energy diets, or palatable foods, provide an indirect, inhibitory metabolic signal to the HPA axis, other relevant data do not support this view. The counter-evidence is sufficient for some to have proposed that high-energy diets are themselves stressful, rather than stress reducing. Therefore, we examine some of this contradictory evidence, the ambiguities involved in the experimental procedures used, and the conclusions drawn.

4.2.1. Fatty acid infusions

A number of studies have examined the hypothesis that specific metabolic signals may influence HPA axis function. Some studies were based on the assumption that circulating fatty acids may provide this metabolic signal, insofar as it was shown that fatty acids provide negative feedback to growth hormone (GH) secretion (Alvarez et al., 1991; Blackard et al., 1969; Imaki et al., 1985). Along these lines, Widmaier (Widmaier, 1992; Widmaier et al., 1992) gave conscious, catheterized, and otherwise freely feeding rats intravenous infusions of various volumes of 10% Intralipid (a suspension of soybean oil and glycerol) and heparin (to additionally activate lipoprotein lipase), and compared the HPA responses to saline-infused controls. Increasing plasma free fatty acids resulted in elevations in both ACTH and corticosterone. The authors concluded that rather than providing negative feedback, fatty acids did just the opposite, and that the site of action must be central, due to the elevation in ACTH. Those findings are consistent with elevations in corticosterone following infusions of triglyceride emulsions directly into brain (Clement et al., 2002), and the fact that fatty acids sensors exist in hypothalamus (Lam et al., 2005a,b).

Although the infusion data suggest a positive feedback role of circulating metabolic fuels on the HPA axis, interpreting the meaning of this in terms of stress responsiveness is less straightforward. As we have shown in Fig. 4C, acute post-prandial elevations in GCs are common in freely feeding animals, and may not be best interpreted as a stress response, but rather as an energy deposition response. It is interesting when one considers mWAT as an infinite energy sink with respect to our data on corticosterone and insulin before and after meals in fed and hungry rats. In fed rats, corticosterone is low before meals, and increases after feeding, with no change in insulin. However, in hungry rats, the opposite occurs: corticosterone is elevated and insulin is low before meals, whereas after meals corticosterone falls and insulin rises. If mWAT is an energy sink, and corticosterone promotes energy storage to mWAT, then fed rats appear to be satisfied in other depots, and are using the infinite sink. The post-prandial suppression of corticosterone in hungry rats may be a mechanism to store calories elsewhere, in other higher priority stores. mWAT is much less defended than, e.g., scWAT, and directly supplying liver with fatty acids from mWAT may be less critical than other WAT functions. Based on this line of reasoning, one would predict that Intralipid infusions would fail to increase corticosterone in hungry rats. Alternatively, if Intralipid infusions did increase corticosterone in hungry rats, the outcome would strongly point to looking again at other alternate hypotheses, such as the role of choice (see below).

The results of FFA infusions in rats are further complicated because the acute effects of FFA infusions are decidedly different in humans. Using an infusion method very similar to the rat studies (intravenous infusion of 10% Intralipid and heparin compared to saline infusions), Lanfranco et al. (2004) found a marked suppression of both ACTH and cortisol with increased circulating fatty acids after an overnight fast. The 24-year old, follicular phase females in the Lanfranco study had normal body mass indices (BMI = 23.1), and except for the experiment, which occurred in the morning, were otherwise freely feeding (Lanfranco et al., 2004). It is further true that like rats, freely feeding humans also show acute post-prandial elevations in cortisol, but, like chronically fasting rats, it may be that the suppression of cortisol in response to Intralipid resulted as a consequence of the infusion being performed after fasting overnight.

4.2.2. Forced high-energy diets

The working hypothesis faced more direct contradictory data in the form of animal studies much like our own, in which subjects received high-energy diets, typically high in fat, and were then subjected to tests of HPA function in comparison to chow only controls. For example, Kamara et al. (1998) tested the effects of diets containing 54% of calories from fat using a variety of fatty acid compositions (corn oil, menhaden oil, soybean oil, and olive oil) mixed with chow. The chow diet contained about 12% of calories as fat. Animals were fed the diet for 3 weeks, and then restrained for 30 min, with blood samples taken at 0, 30, and 60 min. Basal corticosterone tended to be elevated in the high-fat groups, and was significantly elevated at the 30 min time-point. At 10 weeks, another stressor test showed higher corticosterone in the high fat groups at the 60 min time-point only. The authors interpreted this to mean that high-fat diets impair some aspect of glucocorticoid feedback inhibition of the HPA axis (Kamara et al., 1998).

Similarly, Tannenbaum et al. (1997) fed rats chow (4% fat) or corn oil-supplemented chow diet (20% fat) for periods ranging between 7 days and 12 weeks, and tested both basal and restraint stress-induced HPA responses. Basal plasma samples collected at several times during the light cycle were elevated in the high fat groups after 7 and 21 days. After 20-min restraint, rats on high fat for 1, 9, or 12 weeks showed greater ACTH and corticosterone responses. These authors concluded that high fat

dieting is itself a chronic stressor (Tannenbaum et al., 1997). Thus, these and other similar studies have concluded that high-fat diets are stressful, and that the increased stress does not appear to depend on the fatty acid composition of the diet, the total proportion of kcals eaten in fat, or the duration of exposure to the diet.

4.3. The role of choice

Aside from our use of sucrose and lard, the main difference between various studies of this type appeared to be whether rats had the choice of eating the high-energy foods, or whether the studies used pre-mixed diets that forced the proportions of kcal that were ingested as fat. Therefore, it was possible that violating the rats' intrinsic preferences by constraining self-regulation somehow revoked the comforting effect of fat, and even made the diets stressful.

To test the role of choice, la Fleur et al. replicated the 7-day experiment of the Tannenbaum study with several changes (la Fleur et al., 2005). One group of rats ate chow, one ate chow mixed with 20% lard, one ate chow mixed with 50% lard, while a fourth group had ad libitum access to both chow and lard presented in separate dishes. The group given ad libitum access to chow and lard ate about 50% of its kcal from lard, thus matching one of the forced diet groups. At the end of 7 days, the animals were restrained for 30 min, with blood samples taken at 0, 30, 60, and 120 min. Fig. 20 shows ACTH responses to restraint for each group. In contrast to the Tannenbaum studies (Tannenbaum et al., 1997), there was no augmentation of HPA axis drive in the animals on forced-fat diets, and no evidence that the forced high fat diets were themselves inherently stressful, although, as in that study, basal corticosterone levels were elevated. However, there was profound blunting of the restraint-induced ACTH output in the rats freely eating lard compared to the other groups, including one group eating a forced diet that led to comparable lard intake. A replication of that study using rats from another vendor also indicated that some component of choice is critical to achieving inhibitory

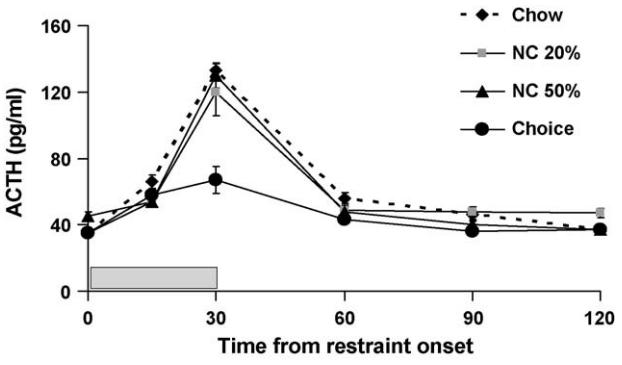

Fig. 20. The curious role of choice on the inhibitory effects of lard eating on restraint-induced ACTH secretion. Rats ate chow, chow mixed with 20% lard, chow mixed with 50% lard, or ad libitum chow and lard presented in separate dishes (choice). Although the free-choice rats ate as much as the group eating the 50% forced lard diet, only the free-choice group showed inhibitory effects of lard eating on ACTH output after 30 min of restraint. Data adapted from la Fleur et al. (2005).

metabolic feedback. In a fascinating outcome, even if rats on forced or chosen diets ate the same number of calories from fat, only the rats that freely, with choice, ate lard exhibited increased inhibitory feedback on the HPA axis.

Thus, the la Fleur study suggests that the preparedness to eat, metabolize, attain utility from, or perhaps simply enjoy different macronutrients may change throughout cycles of energy balance and/or circadian time, indifferent to total caloric intake. We unfortunately do not have a great deal of precise data on the matter of macronutrient timing, but it may be that violating the animal's intrinsic momentary preparedness to ingest various macronutrients, or combinations thereof, induces disequilibria (Timberlake, 1980), and even stress in some cases, although there was no evidence for any additional stress induced by forced diets in the la Fleur study.

These findings on choice may have additional import for the fatty acid infusion studies. Aside from the relation to last meal differences between the rat and human studies, differences in the Intralipid infusions studies, may be due to choice. Intralipid studies in human volunteers might be considered a chosen infusion, whereas in rats it might be considered a forced infusion. If that were true, it would suggest testing an alternative self-administration paradigm in the rat infusion studies.

4.4. Caveat emptor: Rat ≠ Rat ≠ Rat

In the midst of our studies on the "comfort food" hypothesis, our rat vendor (Bantin & Kingman (Harlan derived), Fremont, CA) stopped supplying rats. We were forced to do some bridge studies using rats from other vendors. We eventually deduced that each vendor's basic rat phenotype was different enough that pooling replications across vendors was pointless, and initiated experiments using rats from all three vendors simultaneously. In at least two cases, we also found that different plants within vendors provided different rat phenotypes, so we ran head-to-head studies using only animals from specific vendor's specific plants.

Fig. 21 shows body weight curves for 60 day-old rats from three vendors: Harlan (H, Seattle, WA), Charles River (CR, Raliegh, NC), and Simonsen (S, Gilroy, CA). As is abundantly evident from the body weight measurements when the rats were in the same room, eating the same chow, there are three distinct phenotypes that include the slowly growing Simonsen rats, the moderately growing Harlan rats, and the rapidly growing Charles River rats. The differences in body weight gain were not accounted for by differences in caloric intake standardized for body weight, but did correspond to differences in caloric efficiency.

As indices of energy utilization, we examined body temperature and activity levels in each vendor. Fig. 22 shows 4-day average waveforms (folded at a 24 h period) of the mean circadian temperature (Fig. 22A) and activity (Fig. 22B) profiles for each group, respectively. The shaded portion of the graph represents the dark portion of the light/dark cycle, when core temperature attains its peak (acrophase), whereas the next 12 h show temperature during the light phase, when it is at its

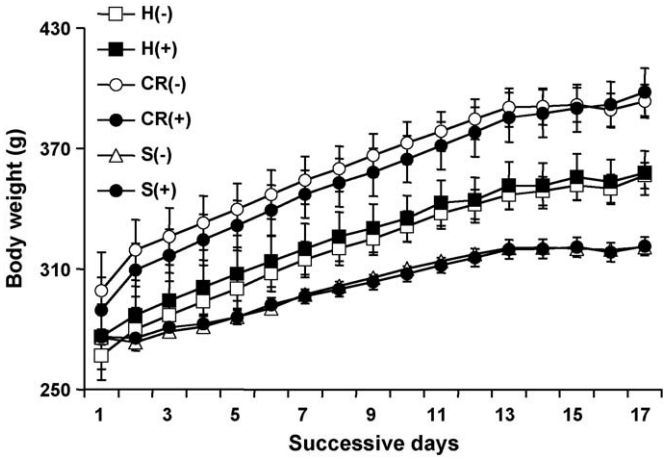

Fig. 21. Body weight curves for Sprague Dawley rats from three vendors, Charles River (CR), Harlan (H), and Simonsen (S), eating chow (−) or chow with ad libitum lard and 32% sucrose solutions (+). While there were no major effects of comfort food on ponderal growth, the vastly different growth curves for each vendor's rats indicate substantial differences in phenotype (Pecoraro et al., 2006).

nadir. It is evident that Simonsen rats had the smallest rhythm amplitude, whereas the Charles River rats had the greatest amplitude. Second, the prominence of the Charles River temperature rhythm was partly due to the fact that their resting, or light phase temperature is much lower than that in the Harlan and Simonsen rats. These group differences in temperature did not appear to reflect activity levels, which were similar across groups, but rather appeared to reflect intrinsic basal expenditure. Fig. 22C shows how different temperature outflows were reflected in differences in caloric efficiency. Differences in body weight gain also corresponded to differences in relative obesity and leptin levels. In all vendors, comfort foods increased temperature output and relative obesity.

Phenotypic differences also appeared in terms of HPA axis function. Fig. 23A–C (top panels) show mean ACTH responses to 2-h restraint pooled at each time point (0, 30, 60, and 120 min) across 3 days (days 1, 3, and 5) of restraint. The first notable differences in ACTH are the overall concentration levels, with the highest in the fastest growing and most calorically efficient Charles River rats. Second, the restraint response functions are different. We may have missed the response in Harlan rats (left panel) by the 30 min time-point, as no response appears, a result belied by their corticosterone responses. Thus, it may be possible that the ACTH molecule in Harlan rats has drifted structurally, or that the adrenocortical response was neurally mediated. Charles River rats (middle panel) eating chow showed a "typical" response, with ACTH peaking at 30 min. Simonsen rats (right panel) exhibited a smaller ACTH response, intermediate to that of the Harlan and Charles River rats. In two of the rat groups, from Charles River and Simonsens, the availability of comfort foods significantly blunted the ACTH responses. Adrenocortical (B; bottom panels) responses largely tracked ACTH, with the exception of Harlans, in which the responses were greater in animals allowed the preferred foods. This may either mean that ACTH responses were also higher, or adrenal sensitivity to ACTH was enhanced in Harlan rats eating comfort food. Either way it would appear to be a dissociation from our previous study using Harlan rats obtained from a different site (Pecoraro et al., 2004), and in this case, was not supportive of our hypothesis. Finally, we also failed to observe the significant relative increases in comfort food eating between baseline and stress phases that we had previously observed.

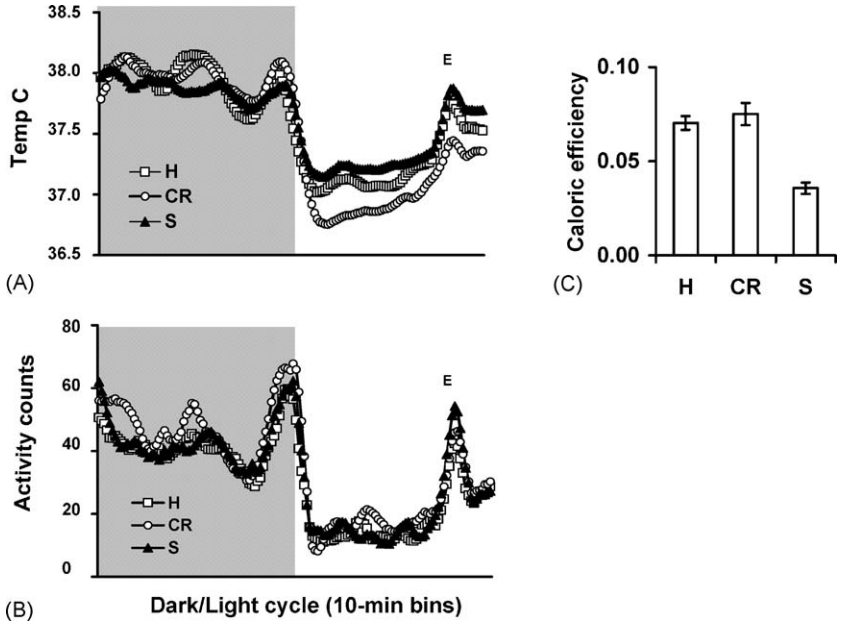

Fig. 22. Four-day mean average waveforms of core temperature (panel A) and activity (panel B) in Charles River (CR), Harlan (H), and Simonsen (S) rats. The experimenter (E) entered the room at approximately the same daily hour toward the end of the light cycle. The fastest growing rats (CR) showed the greatest rhythm amplitude and defended nadir temperature the least, whereas the slowest growing rats (S) showed the weakest rhythm amplitude and had higher resting temperatures, suggesting increased resting utilization. No differences were observed in activity rhythms (Pecoraro et al., 2006).

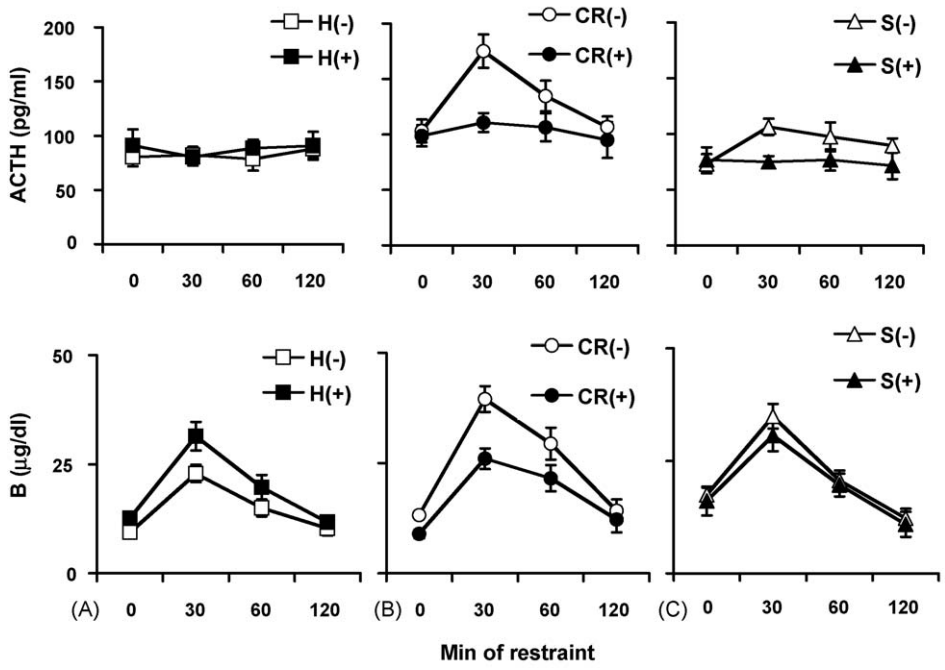

Fig. 23. ACTH (top panels) and corticosterone (B; bottom panels) responses to 120-min restraint stress by rats from Harlan (left panels) Charles River (middle panels), and Simonsen (right panels) on diets of chow (−) or chow plus lard and 32% sucrose (+). Harlan rats had no measurable ACTH response, whereas Charles River rats had a more typical response to the stressor. The ACTH response of rats from Simonsen was intermediate. Except for rats from Harlan, which produced an exaggerated corticosterone response to lard and sugar, the adrenocortical responses of rats from the other vendors more closely matched their reduced central drive when eating lard and sugar (Pecoraro et al., 2006).

We conclude that marked phenotypic differences exist between male Sprague-Dawley rats obtained from different vendors in terms of their apparent growth strategies (without knowing the exact developmental histories of these rats), and in terms of HPA responding under basal and stress conditions. In rats from three of four specific vendors/sites, eating comfort food reduces central HPA axis drive, whereas the fourth case was not conclusive, but if anything appeared to contradict the comfort food hypothesis, and our previous findings in the same line of rats. Considering the results from all of these studies, the drive reduction properties of food suggest that there is a significant metabolic axis providing inhibitory feedback to the HPA axis. With respect to drive induction effects of stress on comfort food eating, the findings are mixed. Clearly, high steroid alone induces palatable feeding, but motivational competition from anxiety or defensive states occurring during stress may compete with appetitive motives. We discuss the feedforward effects of high GCs in greater detail below.

In rats specifically directionally bred for their propensities to diet-induced obesity (DIO) or resistance to obesity (DR), there may also be differences in stress responsivity (Levin et al., 2000). In this model wherein rats are fed a moderately high-energy diet, the DIO rats tend to become obese and develop related symptoms, such insulin resistance and high leptin levels, whereas the DR rats do not (Levin et al., 1997). When subjected to chronic, variable, mild, and inescapable stressors, the DR rats developed elevated morning and evening B levels compared to DIO rats (when samples are taken ‘‘basally,’’ i.e., remotely from the stressor), and DR rats showed elevated basal CRF levels in PVN compared to DIO rats (Levin et al., 2000). That study did not examine the active stress response itself, and the diets were forced, but the data indicated that tonic drive did not appear to be affected by chronic mild stress in the obese rats.

4.5. What is the feedback signal?

The metabolic feedback signal has not yet been identified. An increased signal from mWAT remains a potential candidate, as this depot is most sensitive to GCs and has direct access to the liver portal vasulature. In some studies, a failure to show comfort food-induced increases mWAT as is typically seen in other depots remains difficult to interpret by itself, because the animals are likely to utilize this depot first, even as they remodel fat centripetally. We have previously noted that mWAT is the only depot to show an inverse correlation with hypothalamic CRF mRNA (Dallman et al., 2003). A second candidate proposed as a feedback signal is the fat hormone leptin. Leptin concentrations are increased by eating comfort food, and leptin applied to hypothalamic pieces in vitro results in reduced stimulated CRF output (Heiman et al., 1997). However, there were no differences in circulating leptin concentrations between animals having forced diets and those having choice (la Fleur et al., 2005). There is afferent neural input to the brain from both liver (Friedman, 1997), and intraperitoneal white adipose tissue (Yamada et al., 2006), which could serve admirably to signal the level of energy stores. However, before getting too far ahead of the data, one must acknowledge that the signal may not be metabolic at all, and rather could be of central origin. For example, palatable feeding may promote tonic

increases in central opioid signaling that may serve opponent functions to the excitatory effects of stress, as we suggest below. Nevertheless, the data are consistent with the metabolic feedback hypothesis.

In summary, although it is clear that GCs feedback acutely to inhibit further activity in the HPA axis, we propose a new model for chronic stress in which GCs act in a feedforward fashion in brain to stimulate not only the HPA axis but also to stimulate both positive appetitive and negative emotional motivated behaviors. In addition, there is a metabolic feedback signal induced either by low concentrations of circulating GC or by ingestion of sucrose and lard calories that intercedes to reduce activity in the HPA axis when energy stores are well filled. Several sets of studies involving high fat diets and lipid infusions appear to oppose the model and these are discussed, as are phenotypic differences among male Sprague-Dawley rats from different suppliers and facilities. However, evidence from ADX rats given pleasurable foods, and from chronically stressed rats provided with the choice of ingesting these comfort foods supports the new model.

5. Feedforward: hunger, stress, and GCs on psychological phenotypes

The orientation of this review now changes its emphasis away from physiology and metabolic feedback on HPA axis regulation, to focus on feedforward motivational effects of GCs that are centrally mediated (Fig. 13, arrow to brain). In this section we discuss primary drives and incentive salience, and describe human responses to administered GCs, trauma and hunger. In succeeding sections we examine the effects of GCs on selected transmitters, incentive and memorial systems, and conclude that the GCs may generally augment motivational states, regardless of their valence.

The distinction between primary drives and incentive stimuli is analogous to the distinction between systemic and psychogenic stressors. Primary drives, such as thirst, hunger, or sex arise from systemic states or needs that initiate persistent interoceptive stimuli and, after their transduction, ultimately provoke motor outputs, which counter and reduce these stimuli. Primary drives are also referred to as systemic, physiological, or biogenic drives. Incentive stimuli, on the other hand, are exteroceptive or remembered perceptual stimuli that inspire intrinsic psychological allure or aversion. The spectrum of incentive stimuli ranges in biological significance from the vitally relevant to the arbitrary. At the vitally relevant end of the spectrum, stimuli having obvious ethological importance release appropriate and frequently obligatory classes of behavior (Lorenz, 1950; Timberlake, 1993; Tinbergen, 1951). Such stimuli are also classified by learning theorists as unconditioned stimuli that evoke unconditioned responses. Examples of vitally relevant incentives include the sharp sound of a broken twig that evokes freezing in a foraging rat, or the predator's strike that evokes running, jumping, and biting (Blanchard et al., 1986; Fanselow, 1994).

At the other end of the spectrum are stimuli of more arbitrary significance that may evoke investigative interest or orienting reflexes, but which initially have no other obvious or strong value (Sokolov, 1963). While largely arbitrary and not vitally relevant, such incentives frequently undergo modification by being remembered in association with other incentives, including more significant incentives, and thus act as conditioned stimuli that acquire valence (Guthrie, 1938, 1953; Pavlov, 1927). In short, incentive stimuli are largely psychogenic in nature provoking anything from pupil dilation, to a turn of attention, to the paroxysm of a complete startle reaction, all of which may be conditioned into long and persistent patterns of moods and behaviors. Certain forms of incentive stimulation such as drug taking, gambling, shopping, or profiteering, may be usefully viewed as incredibly powerful, and sometimes pathological, forms of incentive motivation. We now turn to how incentive motivation is amplified by stress.

5.1. The "side-effects" of elevated GCs in humans

5.1.1. The side-effects of compound E

During the initial and largely successful clinical trials of cortisone (Kendall's compound E) for the treatment of rheumatoid arthritis, a number of side effects were reported, including not only Cushingoid redistribution of fat and water retention, but also central effects of cortisone on mood and behavior that varied with the individual (Hench et al., 1949). Notable among these were increases in appetite, restlessness, euphoria, depression, and irritability. Some of the psychological effects were potent enough so that, in accepting the Nobel Prize in Physiology or Medicine for their work, Hench warned that corticosteroids might be contra-indicated in some individuals, because they can precipitate latent psychoses (Hench, 1950). These initial observations of changes in psychological phenotype due to elevated GCs were prescient, and may be compared to observations from other illustrative conditions of stress in which GCs are elevated.

5.1.2. The side-effects of hunger

Radical cognitive and personality changes have been reported in crash dieters, bulimics, anorexics, hunger strikers, and humans in experimental studies of starvation (Fessler, 2003; Fichter and Pirke, 1984). Crash dieting or other strict regimens of therapeutic weight loss can result in hyperirritability and aggression (Crumpton et al., 1966; Kollar and Atkinson, 1966; Rowland, 1968). Elevated anger and aggression have also been reported in patients with anorexia nervosa (Fava et al., 1995; Thompson et al., 1999). Humans with eating disorders also engage in impulsive behaviors (Askenazy et al., 1998; Herzog et al., 1992a; Herzog et al., 1992b; Vandereycken and Van Houdenhove, 1996; Yaryura-Tobias et al., 1995) of sorts that are observed in experimental studies of hunger in normal humans, such as impulsive buying, kleptomania, binge eating, and self mutilation (Keys, 1950a). Self-starving humans have reported that they were not in control of their own behavior during starvation, and upon re-feeding are at a loss to explain their prior behaviors (Keys, 1950a,b; Robinson and Winnik, 1973; Taylor and Keys, 1950).

5.1.3. The side-effects of trauma

Some of the neuroses resulting from World War 2 veterans' combat fatigue included depression, restlessness, insomnia, difficulty waking, nightmares, anxiety, tension, irritability, startle reactions, impairment of memory, obsessive thoughts, phobias, paranoia, decreased appetite, difficulty concentrating, and drug abuse (Grinker and Spiegel, 1945). Similarly, after Vietnam many veterans reported guilt, depression, alienation, irritability, rage, being prone to startle, anxiety, flashbacks, preoccupation with stress, substance abuse, and marital, legal, and vocational difficulties (Haley, 1974; Langley, 1982).

Although such examples are extreme, famine and war are not uncommon, and the environment itself can be extreme, especially at carrying capacity. In a Malthusian world that is dominated by a struggle for resources, high steroid in brain resulting from negative energy balance should aggressively promote feeding and energy-seeking moods and behaviors, whereas high steroid in brain due to stress should promote increased vigilance, anxiety, and anger to actively counter threats, or should promote depressive moods or behaviors that act to decrease commerce in a dangerous environment. Under many conditions, appetitive and aversive demands must be coupled, e.g., increased foraging leads to increased danger from predation or struggle with conspecifics. Although aversive and appetitive behaviors are frequently antagonistic and may actively inhibit one another, there are also reasons to believe that these systems are often linked with overlapping demands, such that a constellation of both aversive and appetitive moods and motor outputs continually interact, particularly as the context for action clarifies which system should be dominant at any given time.

Interestingly, two distinct sub-types of unipolar depression appear to segregate along several dimensions related to metabolism. Typical, or melancholic depressive patients are hyper-aroused and reactive, anxious, under-slept, and under-fed, and have hyperactive HPA and autonomic outflows; by contrast, atypical depressive patients tend to be hypo-aroused, not anxious, un-reactive, over-slept, and over-fed, and have hypoactive HPA and autonomic outflows (Gold and Chrousos, 2002), suggesting that atypically depressed individuals may engage in self-medicating behaviors that include the potential metabolic feedback effects of over-eating, over-resting, and increasing energy stores.

Even the most sheltered individuals will experience and recognize some elements of trauma in sub-traumatic stressors in the form of anxiety about work, money, health, or social bonds. Repeated episodes of stressors frequently result in various forms and episodes of depression, known to correlate with abnormalities in HPA axis function, and CRF/NE systems in brain (Gold and Chrousos, 2002). Furthermore, depression resulting from stress may be progressive, insofar having increasing numbers of episodes of depression increase the chance of having further, deeper episodes of depression (Kessing and Andersen, 2005).

Several things are notable in these obervations. First, stress, hunger, and elevated GCs may precipitate persistent and potent alterations in mood. Second, mood disorders may involve ongoing disruptions of central stress networks and HPA axis regulation. Third, individuals appear to respond differently to stressors, wherein some succumb to an anxiety syndrome, whereas others potentially self-medicate through metabolic means (Kivimaki et al., 2006). Finally, episodes of stress and depression may have permanent, cumulative, or sensitizing effects. Before moving on to the neural effects of GCs and stress, it is worth reflecting on its potential impact and the meaning of stress-induced central phenotypic changes. Veteran activist Stan Goff (Goff, 2006) recently provided insightful commentary on the consequences of traumatic stress:

> I read a book on post-traumatic stress once. Rape is the most common cause, then combat. It said that trauma disrupts one's sense that the world is a safe place, that trauma destabilizes our sense of meaning.
>
> Let me explain something, as a veteran myself of eight conflict areas . . . the sense that the world is not a safe place is not a ''disorder.'' It is an accurate perception. And the sense of meaning many of us enjoy is an illusion, a cruel construction that normalizes the orderly activity of the suburb and nurses our children on simple-minded, Disney-fied optimism pumped through television sets in a relentless data stream.
>
> Post-traumatic stress is not a disorder. Calling it that earns it a place in the DSM IV, professionalizes and medicalizes this very accurate perception that the world is not safe, and that life is not a comforting film convention. Calling it an individual ''disorder'' cloaks the social systems responsible for experiences like Vietnam and Iraq . . ..
>
> When that word view, that architecture of meaning, collapses in the face of realities like convoy Russian roulette, and women holding babies up to prevent being shot, and daily stories of slaughter by the people one sleeps with, the profound betrayal of it is not experienced as some quiet, somber sadness. It is experienced like bees swarming out of a hive that has been broken, as a howling chaos. So we quiet it with marijuana, alcohol, heroin, and even shotguns.

This remarkable personal statement tidily sums up a good deal of what is to follow. Goff's dismissal of the term ''disorder'' is cogent. We will only slightly qualify his statement concerning the ''accuracy'' of stress-related perception and memory later, and show how acute and chronic stress results in plastic adaptive changes in perception, mood, memory, and incentive systems to remodel the phenotype to reflect even the hardest realities, and how under some circumstances, phenotypic plasticity veers into pathology.

In summary, reports of humans are replete with mention of similar alterations in behavioral expression after providing exogenous GCs, starvation, or severe stressors, and it is possible that elevated GCs in the latter instances provide the apparently common changes in mood. The next portions of this review will deal with the effects of GCs on selected neurotransmitters, learning and memory and brain remodeling as a function of

how these affect the integrated responses to primary drives and incentives.

6. GC actions on central incentive networks

In addition to their actions referred to above, GCs affect the brain across many further dimensions. In general, GCs powerfully recruit incentive pathways, including both central stress networks outside of the HPA axis, and appetitive incentive systems that are critically involved in reward. While we sub-divide these into aversive and appetitive networks for the sake of convention and convenience, they proximately and functionally overlap as recently suggested in a recent review of amygdalar function (Balleine and Killcross, 2006). Several specific brain neuromodulator systems appear to act as amplifiers of many incentive states, some operating as opponent limbs, some as proponent limbs of motivation. Our contention is that GCs act on the brain as a general amplifier of all of these central, sub-component amplifiers. The effects of GCs typically result in adaptive responses, but occasionally the responses run away under extreme forms of stimulation.

6.1. Corticotropin releasing factor

GC influence extra-hypothalamic CRF networks, through either the metabolic feedback mentioned earlier (Laugero et al., 2001a,b) or by direct actions on brain (Laugero et al., 2001b, 2002; Makino et al., 2002, 1995a,b). CRF systems are known to be critically involved in aversive situations. In addition to the neuroendocrine motor neurons in the PVN, CRF-containing cell bodies are located in the dorsal vagal complex, locus coeruleus, parabrachial nuclei, paragigantocellular nuclei, lateral hypothalamus, pre-optic hypothalamus, bed nucleus of the stria terminalis, substantia innominata, and central nucleus of the amygdala.

Behaviorally, central activation of CRF receptors (typically after i.c.v. administration) results in a broad range of responses, including decreased food intake (Arase et al., 1988; De Pedro et al., 1993; Krahn et al., 1986; Rosenthal and Morley, 1989) and sexual activity (Sirinathsinghji, 1986, 1987; Sirinathsinghji et al., 1983), increased locomotion in familiar environments (Dunn and Berridge, 1990; Koob et al., 1984; Sherman and Kalin, 1987), inhibited locomotion in unfamiliar environments (Baldwin et al., 1991; Berridge and Dunn, 1986; Takahashi et al., 1989), greater freezing during stress (Sherman and Kalin, 1987), greater acoustic startle (Liang et al., 1992b; Swerdlow et al., 1986), increased grooming (Britton et al., 1984; Imaki et al., 1987; Veldhuis and De Wied, 1984), increased defensive burying (Diamant et al., 1992a,b), and increased conditioned fear and aversion (Cador et al., 1992; Cole and Koob, 1988; Heinrichs et al., 1991). CRF can induce seizures at higher doses (Ehlers et al., 1983; Marrosu et al., 1987). Central CRF systems are clearly critical components of the central stress networks.

Similar anxiety-like effects of systemically elevated GCs have been reported (Corodimas et al., 1994; Hench et al., 1949; Lee et al., 1994; Mason et al., 1957; Rodgers et al., 1999; Schulkin et al., 2005). Accumulating evidence strongly implicates GCs not only in inhibitory feedback effects on HPA axis following acute stress, but also in the upregulation of central CRF following both acute and chronic exposure to stressors (Makino et al., 1994a; Rosen et al., 1994), or following chronic elevations in either systemic or amygdalar corticosterone above basal values (Shepard et al., 2000; Watts and Sanchez-Watts, 1995).

ADX results in upregulation of CRF mRNA in PVN and downregulation in CeA; both are reversed by systemic corticosterone replacement (Duclos et al., 2005a; Laugero et al., 2002; Makino et al., 1994a,b; Swanson and Simmons, 1989; Watts and Sanchez-Watts, 1995). As emphasized before, however, ADX results in metabolic derangements that reduce CeA CRF, effects that are also reversed by sucrose drinking, in the absence of corticosterone (Laugero et al., 2001a,b). Therefore, we suggest that the decreased amygdalar CRF may operate to reduce competing defensive repertoires when there is a need to forage.

Direct effects of corticosterone in brain are quite different from metabolic derangements and their corrections. Implants of micropellets of corticosterone results in sustained delivery of steroid to circumscribed areas in brain. When placed in the dorsal margin of CeA corticosterone pellets increase anxiety (Shepard et al., 2000), basal and stress-induced CRF mRNA, and enhance stress-induced, but not circadian elevations in ACTH and corticosterone (Shepard et al., 2003), and also increase colonic motility; all of these effects are reversed by CRF receptor antagonists (Greenwood-Van Meerveld et al., 2005; Myers et al., 2005). Fig. 24A–D show a suite of the consequences of increased corticosterone concentrations over the dorsal CeA on motor outputs. Corticosterone implants decrease entries into the open arms of an elevated plus maze (Fig. 24A), and reduce the time spent in visual scanning of the environment (Fig. 24B). In addition, 30 min after the maze session, plasma corticosterone (B) is elevated in the steroid-treated rats compared to cholesterol-pellet controls (Fig. 24C). Corticosterone implants near the CeA also amplify viscero-motor responses to colorectal distension (Fig. 24D).

All of these actions are blocked by pretreating the rats with a CRF-R1 antagonist, suggesting strongly that the effect of corticosterone is mediated by its stimulation of amygdalar CRF (Myers et al., 2005). CRF mRNA also increases in BNST following chronic elevations of corticosterone (Makino et al., 1994b), and corticosterone infused i.c.v. also increases basal and stress-induced HPA axis output (Laugero et al., 2002). Therefore, central CRF-active networks are up-regulated by corticosterone and they amplify behavioral, neuroendocrine and autonomic outflows in response to stressors.

Daily rhythms in PVN CRF hnRNA, are approximately 180 degrees out of phase with the plasma corticosterone rhythm, and they are also strongly affected by GCs. ADX sharply raises the mean value relative to intact animals, whereas animals replaced with moderate doses of corticosterone show intermediate levels and a minor phase shift in expression compared to normal (Watts et al., 2004).

Increases in brain CRF correspond to physiological increases in HPA axis function. Pulsatile increases in PVN

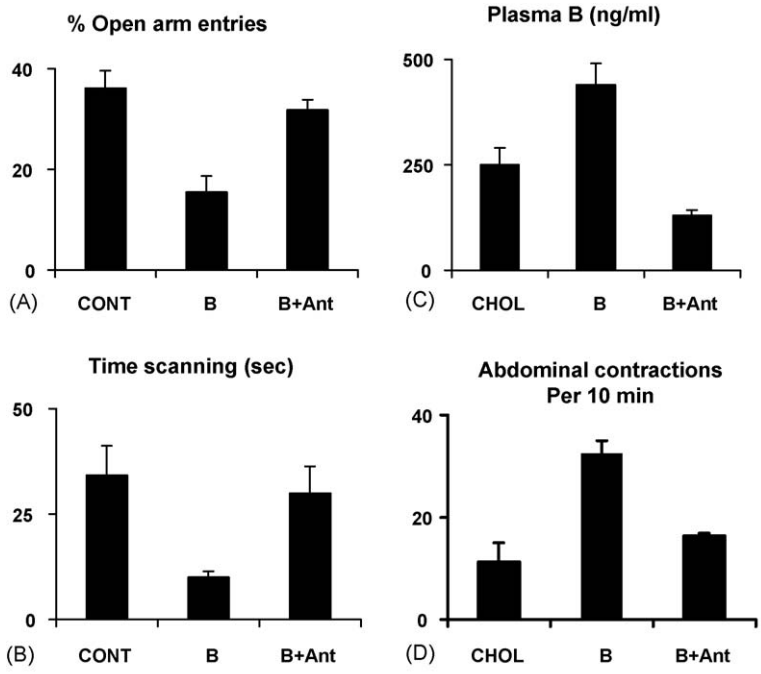

Fig. 24. Consequences of elevating corticosterone (B) in the dorsal margin of CeA on motor outputs, and reversl by treatment with a CRF receptor antagonist. B implantation decreases entries into the open arms of an elevated plus maze (panel A), and reduces time spent in visual scanning of the environment (panel B). In addition, 30 min after the maze session plasma corticosterone is elevated in the B-treated rats relative to cholesterol pellet controls (panel C). B implants near CeA also amplified visceromotor responses to colorectal distension (panel D). The blockade of the B effect with systemically administered antalarmin suggests strongly that CRF mediates the corticosterone-induced effects. Data adapted from Myers et al. (2005).

CRF naturally correspond to pulsatile adrenocortical output, but GCs rapidly enter the brain to influence extra-hypothalamic CRF, as well (Schulkin et al., 2005); intravenous injections of cortisol rapidly increase amygdalar CRF (Cook, 2002, 2004). Depolarization of sheep PVN neurons through either predator stress or neurochemical means results in increased PVN CRF, and a rise in plasma cortisol, which is followed shortly thereafter by increases in both venous cortisol and amygdalar CRF. Cook simultaneously measured plasma cortisol and amygdala CRF levels in sheep in response to the stimulus of a barking dog (Cook, 2002). Fig. 25 shows that CRF from the amygdala exhibited a bimodal response, one large peak occurring prior to the elevation in plasma cortisol, resulting directly from predatory stimulation, and a subsequent slower, more gradual increase that closely followed plasma elevations in cortisol, mimicking the effects of intravenous cortisol infusions.

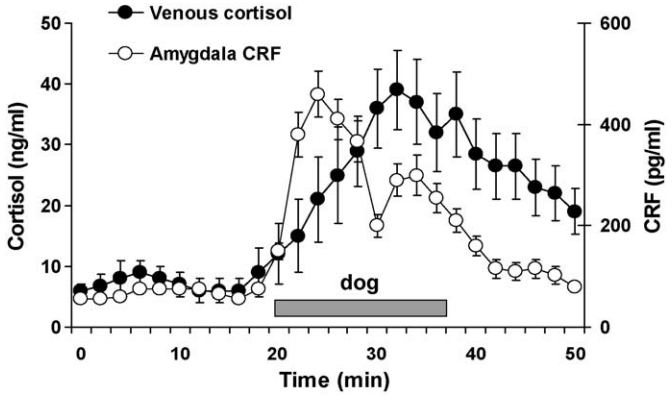

Fig. 25. Adrenocortical and amygdala CRF responses in sheep to the stimulus of a barking dog (gray bar). Amygdala CRF shows an initial rapid elevation, whereas there is a slightly slower response in venous cortisol. A second peak in amygdala CRF appears to follow the elevation in cortisol, as also occurs when cortisol is given intravenously. Data adapted from Cook (2004).

Like high peripheral steroid clamps, GC implants in brain, and continuous i.c.v. infusions, the endogenous GC response also enhances sensitivity to repeated stress, such that sustained or repeated elevations appear to recruit central stress networks. Repeatedly exposing sheep to a barking dog for 6 min/day results in a bimodal amygdalar CRF response to the novel stimulus of electrical shock to a foreleg, which is greatly amplified when the animals are not allowed an escape option (Fig. 26, left panel). Blocking cortisol synthesis using daily injections of mifepristone prior to the sessions with the dog completely blocks the amplification of the response to a novel stressor (Fig. 26, right panel). This amplification appears to result from a lasting effect of repeatedly elevated GCs on central CRF systems (Cook, 2002; Delfs et al., 2000). Thus, these and other data support the view that GCs not only acutely stimulate central networks controlling stress-related motor outputs, but also that sustained or repeated elevations of GCs provide a more permanent recruitment and amplification of these same central stress networks.

6.2. Norepinephrine

Another system that is closely related to the CRF systems is the ascending dorsal NE system originating in the locus

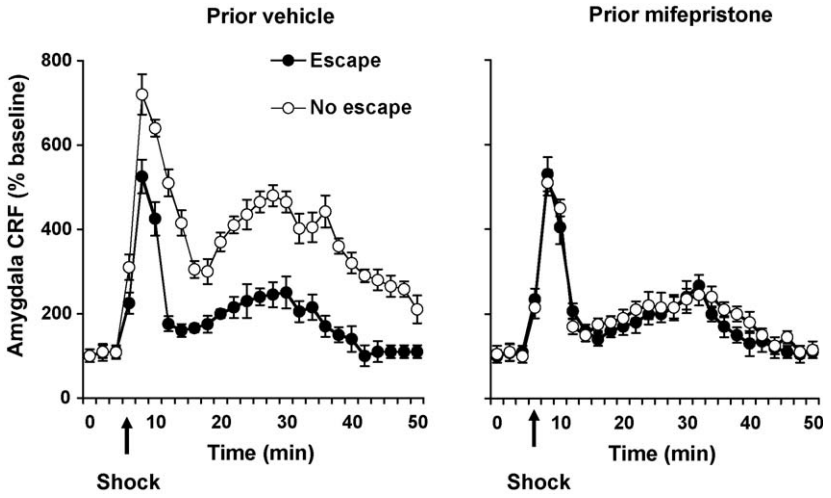

Fig. 26. Recruitment of amygdala CRF responses by chronic, inescapable stress, mediated by GCs. The left panel shows amygdala CRF responses to forelimb shock in sheep had been exposed to a barking dog once daily for 6 min per day for 7 days, and were allowed to withdraw (Escape condition) or not (No escape). Sheep in the no escape condition show a facilitated amygdala CRF response compared to sheep allowed to escape. The right panel shows that sheep that were pretreated systemically with the GR antagonist mifepristone (RU38486) 5 min prior to predator exposure failed to show facilitation after shock in the absence of mifepristone, indicating the necessity of GR occupancy for facilitation of the CRF response. Data adapted from Cook (2002).

coeruleus that supplies virtually all NE to cortical structures involved in responding to anticipated stressors. In general, psychogenic stressors nearly universally activate the LC to release NE in terminal axonal fields (Morilak et al., 2005; Pacak and Palkovits, 2001; Pacak et al., 1995b,c), whereas systemic stressors, such as hypoglycemia, often fail to do so, despite being accompanied by HPA axis activation (Graham et al., 1995; Pacak and Palkovits, 2001). Systemic stressor input is thought to be mediated by noradrenergic input from the ventral NAB. Activity in the dorsal ascending noradrenergic bundle is also associated with arousal and anxiety (Koob, 1999), as well as increased HPA activity (Ziegler et al., 1999), and autonomic function (Van Bockstaele et al., 2001). LC neurons exhibit increased activity to arousing stimuli (Abercrombie and Jacobs, 1987a,b,c), increased immediate early gene (IEG) expression (Ceccatelli et al., 1989; Cullinan et al., 1995; Pacak and Palkovits, 2001; Palkovits et al., 1997), and increased release of NE in terminal fields targeted by LC, such as mPFC (Morilak et al., 2005; Palkovits et al., 1997), amygdala (Quirarte et al., 1998), and BNST (Pacak et al., 1995a). NE depleting lesions of the dorsal NAB blunt ACTH and B responses to stress (Ziegler et al., 1999).

Reciprocal regulation between NE and CRF systems has been said to resemble a positive feedback system potentially resulting in runaway stress-related responses (Dunn and Berridge, 1990; Koob, 1999; Koob and Heinrichs, 1999). Many of the effects of stressful stimuli on LC appear to be modulated by increased CRF activity (Curtis et al., 1997), and activity in NE systems can also increase CRF activity (Dunn et al., 2004). Electrical stimulation or application of CRF to LC elicits HPA responses (Rassnick et al., 1994), behavioral activation (Butler et al., 1990), and induces changes in EEG activity in cortex and hippocampus (Berridge and Foote, 1991; Berridge et al., 1993; Foote et al., 1991).

A number of distinct CRF-containing neuronal populations project to the LC-NE system, and the PVN provides direct monosynaptic inputs to LC. About 20% of these projections form excitatory synaptic specializations with TH-immunopositive neurons, and about 30% contain CRF (Reyes et al., 2005). Although originating in parvocellular PVN, this population is not the same as those neurons that project to the ME, suggesting independent regulation of the neuroendocrine and cognitive limbs of stress responsive neurons from the PVN (Reyes et al., 2005). Similarly, both the CeA and BNST provide CRF projections to LC dendrites, with CeA projections being more prominent (Van Bockstaele et al., 1998, 1999). Barrington's nucleus, which is responsive to both psychogenic and systemic stressors, provides the main CRF input to LC core, whereas amygdala and BNST provide the major CRF input to peri-coerulear dendritic fields (Lechner and Valentino, 1999; Valentino et al., 1996).

CRF microinjections into LC result in NE-like increases in electrical activity in cortical regions, such as prefrontal cortex and hippocampus, as well as increasing autonomic output (Dunn et al., 2004) and PFC (Asbach et al., 2001; Curtis et al., 2002, 1997; Lechner et al., 1997).

Fig. 27A and B show data from Valentino and colleagues on the effects of CRF on spontaneous LC discharge rates. Fig. 27A shows the percent increase in spontaneous LC discharge rates to six doses of CRF applied locally to LC and six i.c.v. doses of CRF. By either route, there are strong dose-dependent increases in spontaneous discharge rate. When i.c.v. administration is accompanied by a CRF antagonist (D-PheCRF$_{12–41}$), the excitatory effects of CRF were largely blocked (Curtis et al., 1997). Fig. 27B shows spontaneous LC discharge with time following the local application of CRF to the LC. Again the effect was dose-dependent and was essentially blocked by administration of a CRF antagonist. In addition, the local application of CRF to the LC desynchronized cortical EEGs and enhanced NE efflux in prefrontal cortex (Curtis et al., 1997).

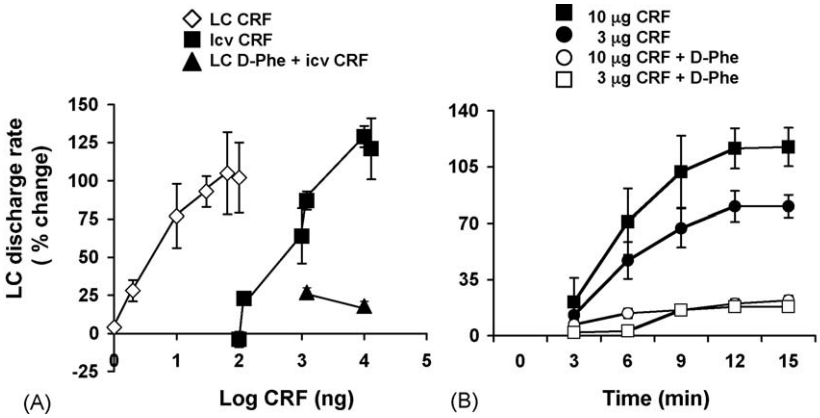

Fig. 27. Locus coeruleus (LC) spontaneous discharge as a percent of baseline after application of CRF. The left panel shows dose-dependent increases in discharge rats with increasing doses of CRF microinfused locally to LC (open diamonds) and when administered i.c.v. (filled squares), as well as the blockade of the increase via i.c.v. CRF when rats were pretreated locally with a CRF antagonist (D-PheCRF$_{12–41}$). The right panel shows the dose-dependent time course of LC activation using two doses of CRF i.c.v. (3 and 10 μg), and blockade of this activation by local application of D-PheCRF$_{12–41}$. Data adapted from Curtis et al. (1997).

NE systems also activate CRF systems. Although alpha-1 activation in PVN elicits HPA responses, the HPA activation is unlikely to be due to a direct input from LC, which provides only moderate inputs input to PVN, compared to input from A1/A2 neurons (Cunningham and Sawchenko, 1988; Sawchenko and Swanson, 1981, 1982). Thus, CRF/NE systems appear to cooperate to enhance anxiety and arousal and can be activated by central corticosterone through activation of CRF neuronal activity. A1/A2 neurons also provide substantial input to the ventral BNST. It was not determined if these projections synapse on CRF-containing neurons, but they do appear to be required for conditioned aversive responses to morphine withdrawal (Aston-Jones et al., 1999; Delfs et al., 2000).

The role of GCs specifically on NE systems is not entirely elucidated. GR co-localization with TH-positive neurons is the general rule in LC (Czyrak and Chocyk, 2001), and neurons in the peri-coerulear region are also immunoreactive for CRF (Lechner and Valentino, 1999). Although there is some evidence that GCs inhibit electrical activity in LC (Pavcovich and Valentino, 1997), it is worth considering that the study was conducted as a replacement study, with recordings in LC being made in ADX rats and ADX rats replaced with corticosterone. Corticosterone replacement reduced LC activity, and was interpreted as a direct effect (Pavcovich and Valentino, 1997), but this has yet to be demonstrated. Laugero et al. (2001a) found that increases in DBH in LC following ADX were reduced by sucrose, and it may be the case that ADX animals drinking sucrose would not show increases in LC activity compared to corticosterone-replaced animals, which would suggest that steroid replacement lowered LC discharge through indirect, metabolic effects, and that direct infusions of steroid in vivo in intact animals may exert different effects on LC activity (Dallman et al., 2003; Laugero, 2004; Laugero et al., 2001a). Such a counter-argument, however, is not supported by results showing enhanced *c*-Fos activation in LC following stress in ADX rats with low corticosterone replacement that fixes metabolism (Li and Sawchenko, 1998), although this effect might also result from a relative inactivity in opponent limbs of the response, also due to low GC activity. These issues require further elucidation. GCs do appear to effectively increase NE efflux by down-regulating the function of the transporter involved in NE re-uptake (Figlewicz, 1999a).

GCs clearly must interact with NE in the basolateral amygdala, both pre- and post-synaptically to consolidate long-term memory of fear or novel objects (de Quervain et al., 1998; Quirarte et al., 1997; Roozendaal et al., 2006a). Arousal, signaled by NE secretion in the BLA is required for the GC effect on memory of previously observed objects (Okuda et al., 2004; Roozendaal et al., 2006b).

6.3. Dopamine

Another important target of the GCs is the mesolimbic-prefrontal dopamine system. Although the mesocorticolimbic dopamine system is responsive to incentives of many kinds, including aversive incentives (Cabib et al., 1988a,b; Cabib and Puglisi-Allegra, 1994; Di Chiara et al., 1999a; Filibeck et al., 1988; Rada et al., 1998), it has most commonly been referred to as a reward or reinforcement pathway mediating appetitive behaviors for positive incentives (Beninger et al., 1981; Di Chiara et al., 1993, 2004, 1999b; Everitt et al., 1999; Hoebel, 1985; Hoebel et al., 1994; Ikemoto and Panksepp, 1999; Kalivas and Nakamura, 1999; Kelley and Berridge, 2002; Koob, 1992; McBride et al., 1999; Robbins and Everitt, 1996; Wise and Rompre, 1989). DA-ergic neurons originating the ventral tegmental area (VTA) of the mesencephalic brain stem simultaneously project to mediodorsal thalamus, prefrontal cortex, basolateral amygdala, ventral striatum and ventral pallidum, and have generally been accepted as having role as an adaptive motivational interface (Mogenson et al., 1980). Dopaminergic neurons along the A8–10 continuum also project to CeA (Hasue and Shammah-Lagnado, 2002; Swanson, 1982).

GCs have clear facilitating effects on DA function, which promotes reward-seeking behaviors (Barrot et al., 2001; Deroche et al., 1997, 1995; Marinelli et al., 1998a, 1997; Piazza and Le Moal, 1997), such as interacting with psychostimulants through DA-dependent mechanisms (Przegalinski et al.,

2000). Alterations in the levels of GCs positively correlate with DA neurotransmission, including alterations in DA efflux (Imperato et al., 1989; Kalivas and Stewart, 1991; Mittleman et al., 1992; Piazza et al., 1996b), and reuptake (Figlewicz, 1999b; Gilad et al., 1987).

GRs co-localize with 40–75% of TH-immunoreactive neurons in VTA (Harfstrand et al., 1986). Caudal A10 dopaminergic dendrites also receive ACTH-containing axon terminals, which may partly account for their stress responsiveness (Liang et al., 1992a). These caudal A10 neurons provide the bulk of DA-ergic innervation to BNST and CeA. (Hasue and Shammah-Lagnado, 2002), and approximately half of all projections from VTA to BNST and CeA are TH-immunopositive (Hasue and Shammah-Lagnado, 2002; Swanson, 1982).

Food restriction enhances behavioral responses to D-1 and D2/3 receptor agonists, and increases downstream pallidal *c*-Fos responses (Carr et al., 2003). GRs generally co-localize with D-1 receptors in virtually all medial prefrontal pyramidal, substantia nigral, and ventral tegmental neurons, with some exceptions in striatum (Czyrak et al., 2003). In addition, chronic administration of corticosterone increases D-1 receptor mRNA by 15–30% in dorsal and ventral striatum, whereas metyrapone decreases D-1 receptor synthesis (Czyrak et al., 1997a,b; Wedzony et al., 1996). Because drugs of abuse tend to elicit HPA responses, it is worth mentioning that D-1 receptors are located in both parvocellular and magnocellular PVN neurons (Czyrak et al., 2000), the activation of which could lead to increased circulating corticosterone (Eaton et al., 1996), and potential positive feedback effects on DA function. Although chronic corticosterone appears to decrease TH protein in the VTA (without changes in other DA cells), it increased TH mRNA in the VTA, and it remains possible that corticosterone acts on neurofilament proteins to enhance transport of TH to DA terminal fields (Beitner-Johnson et al., 1991, 1992; Czyrak et al., 2003).

GCs appear to be involved in plasticity within the ascending DA system, as well. Firing rates of VTA dopamine neurons in response to stimulation by excitatory ligands (NMDA, AMPA, and kainic acid) were enhanced by higher levels of corticosterone, but not aldosterone, which if anything, tended to depress firing. The effects of corticosterone were reversible by the GR antagonist RU38486. Corticosterone alone, in the absence of excitatory transmission, had no such effects (Cho and Little, 1999), suggesting a specific GR-mediated enhancement of glutamatergic transmission. Stress (and cocaine) also increase the AMPA/NMDA ratio of excitatory post-synaptic potentials in VTA in vitro (Saal et al., 2003), a process which is thought to be related to LTP at potentiated synapses (Malinow and Malenka, 2002), and which is blocked by RU38486 in the VTA (Saal et al., 2003). Therefore, GR activation within the VTA appears be involved in long-term adaptations to rewards in general. Many of the glutamatergic inputs to VTA arise in the cortex, where GR density is also high. GR-dependent plasticity in the VTA may be responsible for the fact that repeated stress sensitizes prefrontal DA release.

Central CRF systems are also involved in plasticity within the VTA. The VTA contains CRF-immunopositive fibers (Swanson et al., 1983) and CRF receptors on DA-ergic neurons (Sauvage and Steckler, 2001; Van Pett et al., 2000). CRF infused into the VTA stimulates locomotion and DA release (Kalivas et al., 1987), and probably plays a role in stress-induced drug reinstatement (Lu et al., 2002; Wang et al., 2005). CRF potentiates NMDA receptor-mediated synaptic transmission in VTA dopaminergic neurons, contributing to sensitization (Ungless et al., 2003). A footshock stressor induces CRF and glutamate efflux in the VTA and dopamine efflux in terminal fields, and promotes reinstatement of cocaine seeking, an effect that is reversible by CRF- and glutamate-antagonists. CRF infusions into the VTA enhanced glutamate release only in drug-experienced animals, whereas dopamine efflux in terminal fields was prevented by a glutamate antagonist (Ungless et al., 2003). It thus appears that stress-induced drug seeking may involve potentiation of a serial process of CRF-glutamate-DA response (Wang et al., 2005). Together, GCs and CRF may act on DA neurons both independently (in parallel) and serially through GC-mediated upregulation of CRF function.

DA-ergic terminal fields in the ventral striatum are strongly implicated in motivation. In vitro, 30-min incubations of ventral, but not dorsal striatal slices with corticosterone causes rapid, dose-dependent decreases in DA uptake, suggesting a rapid, membrane receptor-mediated, non-genomic interference with DA transporter (DAT) function (Figlewicz, 1999b). Similar effects obtain when using aldosterone (Roitman et al., 1999). In functional contrast, insulin appears to have generally opposite effects on DA uptake: insulin treatment increases DAT function and increases DAT mRNA, whereas 1 day of fasting or 7-day following streptozotocin treatment there is down-regulation of steady-state DA transporter function, which is reversible by concentrations of insulin in the post-prandial range (Patterson et al., 1998). Ketogenic diets also result in increased GCs, decreased insulin, and down-regulation of DAT function, consistent with some of the effects of hunger or GCs on incentive seeking (Figlewicz, 1999b).

Fig. 28A–C show the effects of several GC treatments on DA efflux in the NACC under various conditions (Rouge-Pont et al., 1998). In Fig. 28A rats were ADX and replaced subcutaneously with basal levels of GCs or sham operated, then given a 10-min tail pinch (black bar) to provoke DA release. Intact rats capable of mounting an adrenocortical response showed greater DA efflux than rats clamped with low corticosterone levels. In Fig. 28B, both groups were clamped at basal corticosterone levels. Just prior to the tail pinch, rats received either a pulse injection of corticosterone resulting in stress levels in plasma, or vehicle injections. Rapidly elevating plasma corticosterone to stress levels mimicked the amplification of DA efflux seen in intact rats. When rats were segregated according to whether they were behaviorally high or low responders to a novel environment, a similar tail pinch evoked a segregated DA response, with substantially higher efflux in high-responders than low responders, an effect that was completely eliminated by ADX (not shown; Rouge-Pont et al., 1998). Finally, Fig. 28C shows data from Piazza et al. (1996b) in which NACC DA efflux was measured in intact rats that were

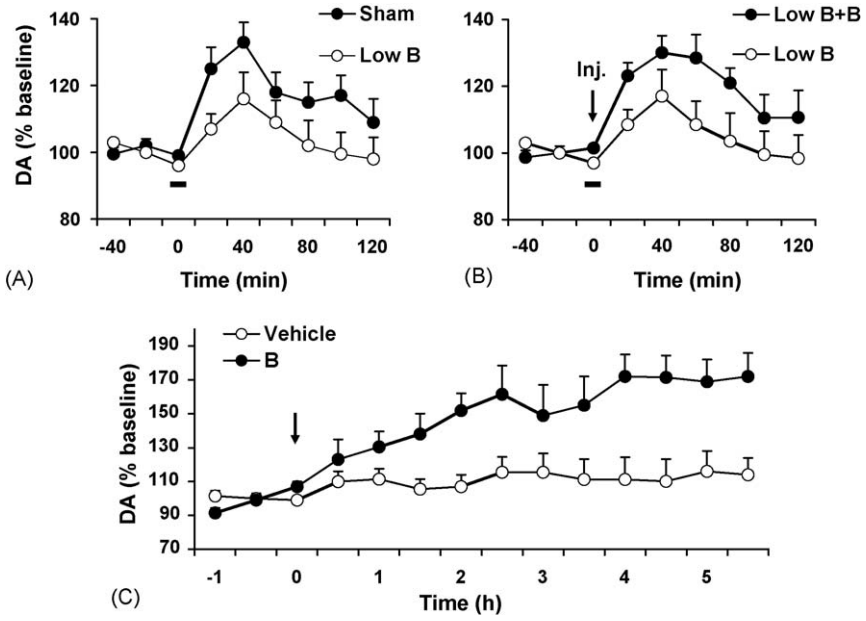

Fig. 28. Effects of GCs on nucleus accumbens (NACC) dopamine (DA) efflux. In the panel A, rats were ADX and clamped with basal corticosterone levels (Low B) or left intact (Sham). DA efflux was greater in intact animals (filled circles) capable of mounting an endogenous adrenocortical response following tail pinch (short black bar) than when clamped with low B (open circles). Panel B shows two groups of rats clamped with basal B levels and given an additional injection of B or vehicle just prior to tail pinch. Rats with elevated, stress levels, of corticosterone show an amplified DA response to stress. Panel C shows DA responses to feeding when corticosterone is dissolved in the drinking water (filled circles) or not (open circles). Oral ingestion of B (starting at the arrow) steadily increases DA efflux. Data adapted from Rouge-Pont et al. (1998).

given either corticosterone in the drinking water or plain tap water with their evening meal. The arrow shows the time of food and water presentation. Although eating slightly elevated DA efflux, the effect was much greater in animals given corticosterone, and the response increased with time in the 6 h session. Like GCs, CRF given i.c.v. also increases DA utilization in PFC, striatum, hippocampus, and amygdala, and NE utilization in frontal cortex and hippocampus, as well (Matsuzaki et al., 1989). Reciprocity between these neuromodulatory systems is further observed insofar as lesions of mesostriatal DA neurons reduces CRF mRNA in the BNST and CeA (Day et al., 2002).

Distinctive sub-divisions of the ventral striatum containing terminal fields of dopaminergic VTA neurons, namely nucleus accumbens core and shell regions, show differing responsiveness to natural rewards during hunger, differing stress responses, functionally distinctive connectivity, and some specific GR dependencies to reward. Whereas fed rats have complete habituation of phasic DA responses to palatable food in the shell, but not in the core, phasic DA efflux does not habituate in the shell under conditions of hunger (Bassareo et al., 2002). Among other facts, this has led Di Chiara to suggest that the NACC shell is distinctly more involved in associative components of motivation, whereas the core is involved more in habit maintenance and response output (Di Chiara et al., 2004). The shell is also more stress-responsive (Barrot et al., 1999; Kalivas and Duffy, 1995), drug-responsive (Pontieri et al., 1994, 1995; Barrot et al., 1999), and more responsive to atypical antipsychotics (Deutch and Cameron, 1992; Marcus et al., 1996; Merchant and Dorsa, 1993; Onn and Grace, 1995) than the core. The shell is the only part of striatum to receive substantial NE input, which comes from the A2 region of NTS (Delfs et al., 1998), and this may be related to its hunger-dependent responses. In addition, separate ventral striatal processing loops indicate a motivational and plasticity-related dominance of shell on core. Specifically, whereas the core feeds back on itself through nigral-thalamo-cortical loops, the shell feeds forward on the core through pallido-thalamo-cortical loops (Zahm, 2000).

Finally, the apparent and specific hyper-responsiveness of the shell relative to the core is strongly dependent on GCs. Barrot et al. (2000) compared DA efflux in core and shell following vehicle, morphine, or cocaine injections in ADX rats to that in ADX rats replaced with low corticosterone pellets and given corticosterone in their drinking water at night to reproduce circadian elevations. Fig. 29 shows DA responses in shell (top panels) and core (bottom panels) to vehicle (left panels), morphine (middle panels), and cocaine (right panels) administration. Clearly the shell is more responsive than the core to all three manipulations in both intact controls and replacement groups. Whereas ADX plus or minus corticosterone replacement has no effect on DA efflux from core, ADX severely blunts efflux in shell in a GC-reversible fashion (Barrot et al., 2000). Thus, the shell is clearly a target of hunger, stress, and GCs, and is in a functional and hodological position to mediate incentive learning and feedforward control over sensory-motor and habit-related components in the ventral striatum.

In short, stress heightens DA-ergic function, which from most accounts of DA function, leads to enhanced incentive salience and/or willingness to work for (or to avoid) incentives, and greatly augments responsiveness to drugs acting on DA-

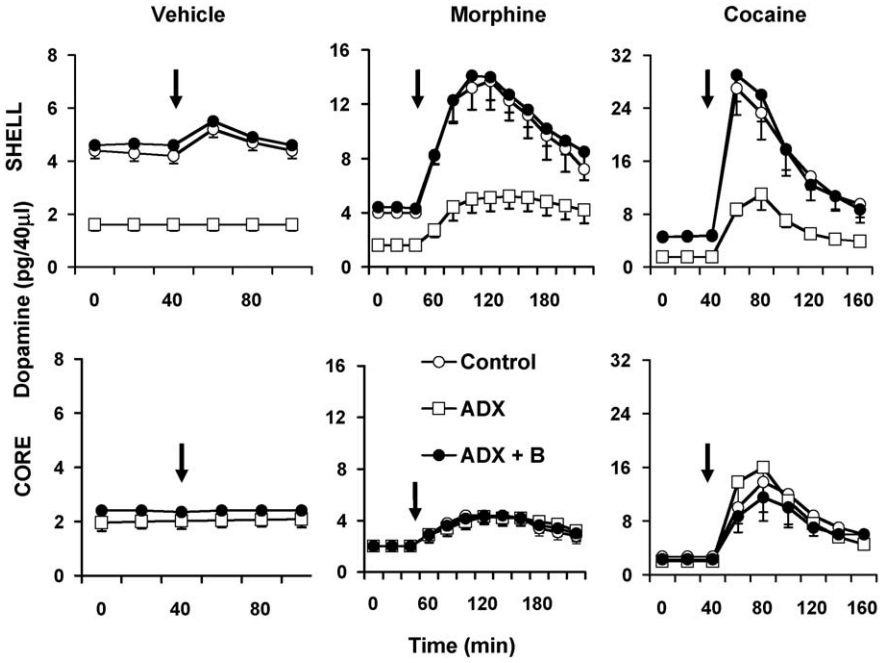

Fig. 29. GC mediated hyper-responsiveness of DA efflux in nucleus accumbens shell (SHELL; top panels) relative to core (CORE; bottom panels). Rats were adrenalectomized (ADX), ADX and replaced with stress levels of corticosterone (ADX + B), or left intact (Control). Then were then injected with vehicle (left panels), morphine (middle panels) or cocaine (right panels). GCs elevated baseline DA efflux, and particularly amplified DA responses to drugs, but only in the SHELL, not CORE of the nucleus accumbens. Data adapted from Barrot et al. (2000).

ergic systems. In addition, stress hormones are involved in learning-related plasticity in these systems, and are probably involved in phenomena such as sensitization to incentive stimuli (see below). Finally, the relative hyper-responsiveness of shell over core in ventral striatum, and the nature of their circuitries, indicates a learning or motivational dominance of shell over core that functions particularly under times of stress.

6.4. Opioids

The involvement of the endogenous opioid systems in stress responses is complex. Stressors appear to activate endogenous opioid systems, which unlike the CRF and NE systems may limit sensitivity to stressors, increase pleasure, or sensitivity to pleasure, or frankly increase or limit the stress response itself. Because opioid systems tend not to be tonically active, are activated by stress, and frequently have opposite effects on CRF and NE systems, opioids may largely operate as an opponent limb to the CRF/NE systems, specifically during stress.

Opioids decrease pain. One consequence of exposure to a stressor such as footshock is the induction of stress-induced analgesia that is reversible by naloxone (Akil et al., 1976). The recruitment of opioid systems by stress generalizes to restraint (Kelly and Franklin, 1987), cold water (Spiaggia et al., 1979), forced swimming (Cooper and Carmody, 1982), food deprivation (Konecka et al., 1985), handling stress and predator odors (Fanselow and Sigmundi, 1986), and social defeat (Miczek et al., 1982). More severe stressors can produce naloxone-insensitive, opioid-independent analgesia.

Stress can also alter sensitivity to exogenous opiates (Benedek and Szikszay, 1985; Christie et al., 1982). For example, various stressors and GCs enhance the sensitization of locomotor activity to morphine (Stohr et al., 1999). Stress also augments the analgesic effects of morphine (Stohr et al., 1999). Furthermore, stress promotes opiate abuse and relapse (Marinelli et al., 1998a,b; Piazza and Le Moal, 1998; Shaham et al., 1998, 1997; Stohr et al., 1999). Opioids are involved in palatable feeding (Giraudo et al., 1999; Levine et al., 2002, 2003; O'Hare et al., 2004), and GCs also increase palatable feeding (Bhatnagar et al., 2000; Pecoraro et al., 2005b).

CRF and AVP are both secretagogues of endogenous opioids at the pituitary and in brain (Przewlocki, 2002; Vale et al., 1981). CRF stimulates both β-endorphin and dynorphin secretion in hypothalamic slices (Almeida et al., 1986; Nikolarakis et al., 1986), and AVP also stimulates B-endorphin and ACTH secretion in vitro and in vivo (Arimura et al., 1969; Fleischer and Vale, 1968; Gillies et al., 1982; Przewlocki et al., 1979; Rivier et al., 1984).

Both the PVN and locus coeruleus are sites of convergence for the effects of stress mediated by NE, CRF, and opioids (Drolet et al., 2001; Duman et al., 1988; Nestler et al., 1994; Nestler and Tallman, 1988; Valentino and Van Bockstaele, 2001; Van Bockstaele et al., 2001). The PVN and LC are strongly innervated by enkephalinergic neurons originating in rostral ventrolateral medulla (Beaulieu et al., 1996; Drolet et al., 1992). In the LC, it has been shown that enkephalinergic fibers target LC dendrites, form synaptic specializations, and overlap with CRF-containing fibers, occasionally even co-expressing CRF, but typically being distinct (Van Bockstaele et al., 1995). The PVN also receives enkephalinergic innervation from the medial preoptic area and the DMH, two nodes of the putative HVPG (Thompson and Swanson, 2004).

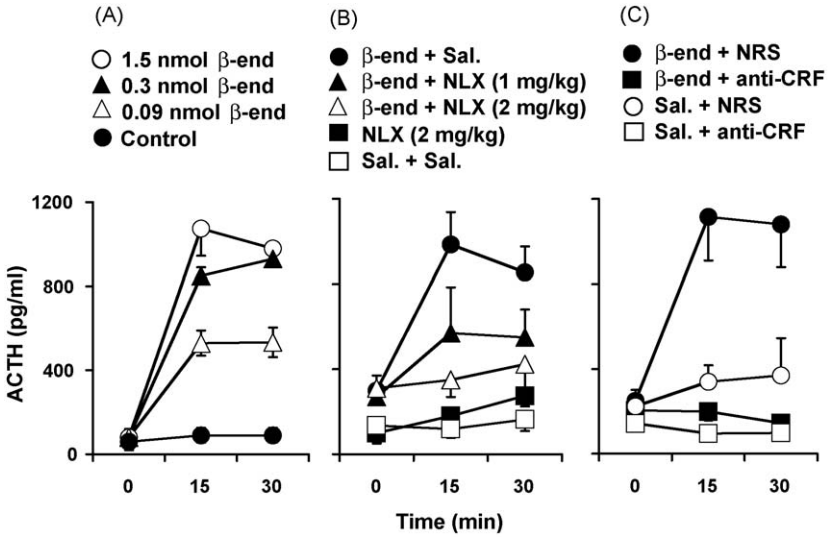

Fig. 30. Dose-dependent increases in ACTH output to intracerebroventricular (i.c.v.) β-endorphin are mediated by stimulation of opioid receptors and CRF pathways. Panel A shows dose-dependent increases in ACTH with increasing doses of β-endorphin (β-end). Panel B shows dose-dependent blockade of the response with increasing doses of the opiate receptor antagonist, naloxone (NLX). Panel C shows the stimulation of ACTH in animals given β-endorphin and normal rabbit serum (NRS) and the blockade of this response in animals receiving CRF antiserum (anti-CRF). Data adapted from Yamauchi et al. (1997).

In the PVN, ENK mRNA is increased following a variety of stressors, including hypertonic saline (Harbuz and Lightman, 1989; Lightman and Young, 1987a,b; Watts, 1992a; Young and Lightman, 1992), ether (Ceccatelli and Orazzo, 1993), restraint (Ceccatelli and Orazzo, 1993), and morphine withdrawal (Ceccatelli and Orazzo, 1993). Region-specific regulation of ENK mRNA is indicated by the facts that ENK is upregulated in PVN (Dumont et al., 2000) but is downregulated in RVLM following repeated immobilization (Mansi et al., 2000).

Opioids can also cause both activation and inhibition of the HPA axis (Buckingham and Cooper, 1986). Both opioid agonists and antagonists given i.v. stimulate the HPA axis in rats (De Souza and Van Loon, 1982; Nikolarakis et al., 1989), and in dogs (Levin et al., 1981); this is mediated through activation of central CRF pathways (Nikolarakis et al., 1989; Yamauchi et al., 1997). Yamauchi et al. (1997) gave rats i.c.v. infusions of β-endorphin and tested the effects of i.v. infusions of naloxone and CRF antiserum on opioid-induced stimulation of ACTH. Fig. 30A–C show dose-dependent stimulation of ACTH by β-endorphin (panel A), dose-dependent reversal of these effects by naloxone (panel B), and the complete abolition of the β-endorphin-induced ACTH response by a CRF antiserum (panel C). Thus, the stimulating effect of opioids was specific to opioid receptors and CRF pathways. Biphasic temporal effects (early increases followed by later decreases) have also been observed in vivo (De Souza and Van Loon, 1982; Suemaru et al., 1989), whereas in vitro some effects have been shown to be biphasically dose-dependent, with low doses activating and higher doses inhibiting ACTH (Cover and Buckingham, 1989). Thus, the situation concerning opioid stimulation of the HPA axis is complex.

The direction of opioid effects on the HPA axis may be state-dependent, as they are reported to be for learning and memory (Patti et al., 2006). In rats, ACTH activation by insulin-induced hypoglycemia is attenuated by beta-endorphin in a naloxone-reversible fashion (Suda et al., 1992). Przekop et al. (1990) nicely demonstrated such state-dependence in sheep. Sheep were fitted for i.c.v. infusions of drugs and jugular catheters for cortisol sampling and were tested under basal and stress conditions. As a stressor, once per hour, brief shocks were given periodically over 20 min followed by a 40 min rest during a 9 h period. Blood samples were collected just prior to rounds of shock. In Fig. 31, continuous infusions are indicated by the gray bars, whereas groups receiving shock are indicated by asterisks. Fig. 31A shows the elevated adrenocortical response to intermittent forelimb shock in animals given vehicle infusions compared to unshocked animals. Fig. 31B shows relative suppression of this response by naloxone infusions (compared to panel A), whereas naloxone alone had no effects in unshocked animals. Fig. 31C shows that β-endorphin stimulates adrenocortical responses in basal animals, while it inhibits the response in stressed animals. Finally, data in Fig. 31D compares the effects of β-endorphin in two unstressed groups given a brief pretreatment with naloxone or not, showing that a brief infusion of the opiate antagonist inhibited the drug-induced response. The key demonstration was that β-endorphin stimulates adrenocortical responses under basal conditions, but is inhibitory during stress (Domanski et al., 1993; Przekop et al., 1990). Thus, the direction of EOP effects on HPA-responses may depend on whether the animal is basal or stressed.

A restraining role of endogenous opioids on stress responses is further suggested by the fact that naloxone treatment results in greater sensitization of HPA axis following chronic stress (Janssens et al., 1995), whereas animals lacking delta opioid receptors (Filliol et al., 2000) or pre-proenkephalin (Konig et al., 1996) show elevated anxiety levels. In contrast, over-expression of pre-proenkephalin in amygdala enhances the anxiolytic effects of benzodiazepines (Kang et al., 2000), and injections of opioids or their analogs into the CeA reduce cued

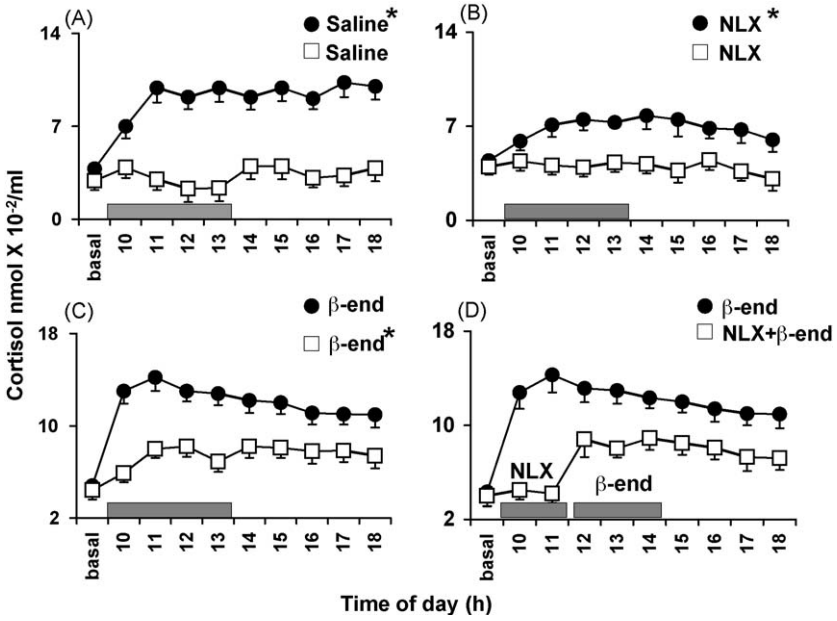

Fig. 31. State-dependent effects of the opioid β-endorphin (β-end). Panel A shows venous cortisol profiles in sheep given intermittent shocks (indicated in the legend by an asterisk) after a baseline period (basal) and infused intracerebroventricularly (i.c.v.) with saline (infusions represented by gray bar). Shocks were intermittent over a 20 min period, followed by a 40 min rest, and blood was sampled prior to shocks. Shocked sheep increased cortisol secretion. Panel B shows partial blockade of the adrenocortical response by i.c.v. infusions of the opiate receptor antagonist, naloxone (NLX). Panel C shows that the adrenocortical response to β-endorphin under basal conditions (filled circles) is attenuated when animals are under intermittent footshock stress (β-end*), indicating that there is a state-dependent regulation of the response by opioids. Finally, panel D shows that the cortisol response to β-endorphin is blunted by a pre-infusion of naloxone (NLX). Data adapted from Przekop et al. (1990).

fear (Good and Westbrook, 1995) and conditioned heart rate responses (Gallagher et al., 1982).

Endogenous opioids have also been found to specifically counter some effects of CRF on LC excitability, and probably have specific opponent roles in arousal (Shibasaki et al., 1994). In contrast to the excitatory effects of CRF on LC discharge rates and NE release (Valentino et al., 1983), opioids inhibit LC discharge rates both in vivo and in vitro (Abercrombie et al., 1988; Aghajanian and Wang, 1987; North and Williams, 1983, 1985; Valentino and Van Bockstaele, 2001; Valentino and Wehby, 1989; Wang and Aghajanian, 1987; Williams et al., 1982; Williams and North, 1984). Although opiate antagonists have no effect on LC discharge under basal conditions (Valentino and Wehby, 1989), they do increase LC discharge rates during stress (Abercrombie and Jacobs, 1988), and result in dramatic increases in LC electrical activity when rats are opiate dependent (Akaoka and Aston-Jones, 1991; Rasmussen and Aghajanian, 1989), suggesting that opioids function to restrain LC activity, particularly under stress. In line with this view, Curtis et al. (2001) showed that the inhibition of LC activity following a physiological stressor (nitroprusside-induced hypotension) is reversible by microinjection of naloxone into LC (Curtis et al., 2001). Because pretreatment with naloxone did not affect basal LC discharge rates, it indicates that the recruitment of endogenous opioids occurred in the aftermath of the stressor to restrain LC excitability.

In contrast to this endogenous restraint of LC by opioids, chronic (7-day), intermittent treatment with morphine appears to sensitize CRF-NE systems in terms of discharge to further morphine or hypotensive challenges (Xu et al., 2004). Similarly, the sensitization of prefrontal cortical dopamine release to chronic restraint stress can be blocked by pre-stressor administration of naloxone (Cuadra et al., 1999), suggesting that endogenous opioids are necessary for sensitization in this system. Both systemic morphine and local application of μ-opioid receptor agonists in prefrontal cortex suppress glutamatergically (but not cholinergically) driven activity, although the effects of systemic administration are more pronounced (Giacchino and Henriksen, 1996, 1998), perhaps reflecting additional influences of opioids on the ascending NAB after systemic administration. The sensitization of various responses by chronic, intermittent opioid treatment may constitute a special form of stress, and will be discussed later in the context of the sensitization of the HPA axis.

Still another relevant facet of opioid action is the evocation of moods and incentive states. It is well documented that opioids stimulate pleasurable moods, palatable feeding and reward processes, and clearly have some of these effects through the use of stress and incentive circuitries (Cappendijk et al., 1999; Hernandez and Hoebel, 1988a,b; Nieto et al., 2002; Wise, 1987). Opioids increase palatable feeding, and palatable feeding stimulates opioids (Glass et al., 1999). Opioids specifically appear to increase the eating of preferred foods. For example, some rats prefer carbohydrate-rich foods, whereas some prefer high-fat foods. Low doses of morphine increase intake of the preferred food only (Gosnell et al., 1990a,b). Also, low doses of naloxone reduce eating of preferred foods, whereas high doses of naloxone do not impair feeding of non-preferred foods (Welch et al., 1994). Opioids appear to increase meal maintenance; naltrexone has little effect on eating

structure early in a palatable meal, but interferes with eating structure later in the meal (Frisina and Sclafani, 2002). This effect may be fairly specific to the consummatory response itself as antagonists do not decrease the willingness to work for food, alter taste discrimination, or even the perceived pleasantness (Arbisi et al., 1999; Fantino et al., 1986; Glass et al., 1999; O'Hare et al., 1997).

Specific brain regions involved in opioid-induced feeding are gradually being mapped. Intra-nucleus accumbens infusions of μ-receptor agonists (e.g., DAMGO) result in massive increases in fat intake, and moderate increases in carbohydrate and salt intake (Zhang et al., 1998). The effect in NACC appears to require concurrent activation of other brain regions, as temporary inactivation via muscimol of DMH, LH, VTA, and NTS all block the effect (Will et al., 2003), consistent with hodological relations among these areas (Brog et al., 1993; Groenewegen et al., 1996; Wright et al., 1996; Zahm et al., 1999, 2001). Of these nodes, the NTS receives both taste (Li et al., 2003) and visceral (Silverman et al., 2005) primary afferents that target opioid-sensitive POMC neurons (Appleyard et al., 2005). Inhibitory effects of opioids on NTS excitability due to electrical stimulation of the tongue (Li et al., 2003) or visceral afferents (Silverman et al., 2005) appear to correspond to increased feeding, which was blocked by naltrexone infused into CeA (Giraudo et al., 1998). Similarly, DAMGO infusions into CeA increased feeding that was reversed by naltrexone infused into NTS, suggesting bidirectional opioid-dependent pathways between NTS and CeA. Naltrexone injected into the CeA reduces preferred food intake more than non-preferred food intake, whereas it reduces food intake generally when given into the PVN; thus it is diet specific in CeA and perhaps more generally energy or stress-related in PVN (Glass et al., 2000). In contrast to the bidirectional opioid-dependent feeding pathways between NTS and CeA, opioid-dependent pathways between CeA and PVN appear to be unidirectional, as naltrexone infused into PVN had no effect on feeding induced by opioid stimulation of CeA, whereas feeding induced by opioid stimulation of PVN was suppressed by naltrexone infused in CeA (Giraudo et al., 1998). Fat intake increases with DAMGO-induced stimulation of the BLA, as well (Will et al., 2004). Clearly, palatable feeding networks will inevitably be complex, but will involve critical nodes of GC-sensitive central stress networks that are also responsive to, or involved in, opioid-induced palatable feeding.

Interestingly, animals can develop food-dependencies that may involve opioid stimulation of both appetitive and aversive networks. It is well established that opioids stimulate DA efflux, and that there exist both DA-dependent and -independent mechanisms of opiate reward (Bechara et al., 1992, 1998; Bozarth and Wise, 1981a,b; Glick et al., 1975; Higgins and Sellers, 1994; Nader et al., 1994; Pettit et al., 1984; Shippenberg et al., 1992; Spanagel et al., 1992; Spyraki et al., 1983; Stinus et al., 1989; Van Ree et al., 1999). Interference with mechanisms of plasticity in the VTA, e.g., through inhibition of protein kinases (A) or glutamate antagonism, can prevent morphine-induced placed preferences (Aston-Jones and Harris, 2004; Harris et al., 2004), suggesting that there is an essential role for incentive learning. Opioids also decrease acetylcholine (ACh) in NACC (Fiserova et al., 1999; Pothos et al., 1991; Rada et al., 1991a,b). ACh in the NACC is associated with satiety when DA efflux is high and with aversion when DA efflux is low (Helm et al., 2003; Mark et al., 1992). Opioids also impinge on aversive NE networks. For example, morphine inhibits activity in medullary NE neurons that project prominently to anxiety-related areas in BNST and CeA (Akaoka and Aston-Jones, 1991; Aston-Jones and Harris, 2004; Ivanov and Aston-Jones, 2001; North and Williams, 1983; Shiekhattar and Aston-Jones, 1993; Wang and Aghajanian, 1987).

Food dependence can be elicited by allowing intermittent access to palatable foods. Sucrose bingeing results in progressively escalating intake (Colantuoni et al., 2001), and subsequent bouts of food deprivation can lead to signs of somatic withdrawal, such as paw fanning, teeth chattering, and wet dog shakes (Colantuoni et al., 2002). Changes in the brain include altered DA and μ opioid receptor binding in NACC (Colantuoni et al., 2001). Sugar bingeing also results in sensitized DA release and delayed ACh efflux (Rada et al., 2005). Sugar-dependent rats also show cross-sensitization with alcohol intake (Avena et al., 2004) and locomotor sensitization to amphetamine (Avena and Hoebel, 2003), suggesting substitutability of sugar and drugs (Campbell and Carroll, 2000). A deprivation rebound is observed in sugar intake following a period of abstinence (Avena et al., 2005; Bell et al., 2000), as occurs with alcohol drinking rats (Heyser et al., 2003, 1997; McKinzie et al., 1998; Rodd et al., 2003; Sinclair and Senter, 1968). A history of food-restriction also sensitizes opiate-induced food intake (Hagan and Moss, 1991).

These feeding data suggest that the stimulation of reward pathways and concurrent inhibition of aversive pathways by palatable feeding can lead to prominent signs of dependence that strongly resemble drug, and in particular, opioid dependence. The stimulation of DA-dependent mechanisms conforms to enhanced positive incentive and learning processes during bingeing, whereas the disinhibition of ACh or ascending NE systems to areas such as BNST and CeA may account for the negative signs of aversion, anxiety, and somatic withdrawal. These same systems may also sensitize the animal to cues predicting both preferred rewards and aversive incentives, thus biasing the animal toward supernormal rewards, and away from aversive stimuli. These processes take place in areas of the brain that are highly sensitive to GCs, and can be sensitized by periods of deprivation and/or intermittent exposure.

Thus, a range of evidence suggests that opioids are intimately involved in stress response networks and incentive motivational systems. The inhibition of HPA responses by opioids appears to be specific to the condition of stress. Opioid-induced, CRF-dependent stimulation of the HPA axis in basal animals is a functional curiosity, perhaps reflecting the fact that, in addition to stress, palatable foods appear to be a key regulator of opioid secretion, and the basal brain may interpret an opioid signal as activation of central feeding pathways, to which it

responds by increasing neuroendocrine and autonomic outflows. On the other hand, it could merely reflect a more generically imbalanced counter-regulatory system, in which deviations in either direction evoke compensatory adjustments in opponent limbs.

This section on central stress and incentive networks has focused on a handful of key regulators, including CRF, NE, DA, and EOPs, primarily because each has been associated with manifold processes related to adaptive behavior, and all interact strongly with the HPA axis and GCs. Although there has been a tendency to associate each regulator with partcular types of adaptive behavior, e.g., DA has been associated with amplification of appetitive responding, NE has been associated with alterations in attentional processing, and CRF has been associated with aversive processes, these systems continue to defy easy functional categorization, particularly because they overlap and reciprocally regulate one another.

While these neuromodulators are clearly involved in the amplification of incentive states that tend to be further upregulated by stress and GCs, we have argued that EOPs largely act as an opponent limb of stress-induced incentive states and HPA axis regulation. An additional example where such a scheme tentatively holds is conditioned fear, which is highly sensitive to activity of central stress networks. For example, startle responses to noise are greater in the presence of a conditioned stimulus (CS), but this effect can be greatly blunted by administration of NE antagonists (Davis et al., 1979), DA antagonists (Davis et al., 1979), and CRF antagonists (Swerdlow et al., 1989), whereas increased opioid activity also blunts the response (Davis, 1979; Patti et al., 2006). It may be too early to suggest root functions for each regulator, as counter-examples abound. For example, although CRF is associated with aversive responses, it interacts extensively with other appetitive modulators, and can itself stimulate appetitive routines, such as feeding (Ghitza et al., 2005; Samarghandian et al., 2003) and appetitive instrumental discriminative responding (Erb et al., 1998; Pecina et al., 2006; Shaham et al., 1997).

In summary (Fig. 32), the evidence cited above argues that GCs are prime movers of central stress networks that include CRF-, NE-, DA- and opioid-mediated responses. Further questions certainly arise regarding potential hierarchies among these systems. All of these sub-systems interact heavily with one another, have unexplored dynamics, and are plastic. Inherent coupling between these systems suggests coordinated activation, such that one process stimulates both opponent and proponent processes, as we have seen in some of the discussion already, and as we further indicate later in the section on the sensitization of the stress response by intermittent opioid administration. The modulation of transfer functions among signaling agents more realistically may be region- and situation-dependent. Serial stimulation of GCs and CRF could underlie activation of multiple incentive systems. Whether or not GC-induced CRF activation is the prime mover, all of these neuromodulatory systems are known to be involved in incentive processes, and each tends to be positively regulated by stress, hunger, and GCs.

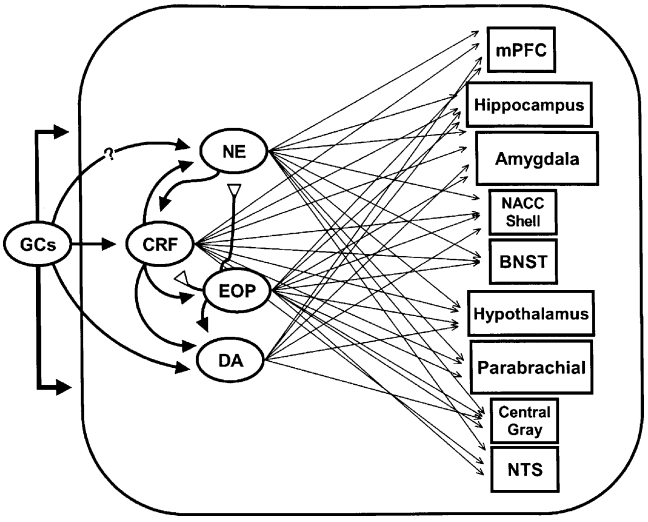

Fig. 32. Summary of the effects of GCs on selected central motive networks (see text). Through their direct actions on CRF neurons in the amygdala, as well as possible direct effects on noradrenergic (NE), endogenous opioidergic peptides (EOP) and dopaminergic (DA) neurons GCs act positively to increase motivational behavioral characteristics, both positive and negative. Innervating broad areas of brain, the neuropeptide inputs modulate the activity of neurons in medial prefrontal cortex (mPFC), hippocampus, amygdala, nucleus accumbens shell (NACC), bed nuclei of the stria terminalis (BNST), hypothalamus, parabrachial nuclei, central gray, and the nucleus of the tractus solitarius (NTS). Furthermore, in cortical structures at least, the GCs affect neuronal architecture in a site-specific fashion (see Figs. 33 and 34).

7. GCs in learning and memory

In addition to recruiting critical central motive systems, thus influencing arousal and reactivity to external incentives, stressors and corticosteroids result in brain plasticity, with varying effects that depend on chronicity. Acutely, corticosteroids influence the storage of information (de Kloet et al., 1999; Hui et al., 2004; McGaugh et al., 1996; Roozendaal, 2002; Roozendaal et al., 2001; Rose, 1995; Sandi and Rose, 1994a,b), particularly emotionally arousing information. Thus, it should come as no surprise that many of the same nodes that serve central networks of aversive and appetitive incentive motivation also serve critical memorial systems in addition to those mentioned above. Chronically, however, GCs tend to grossly remodel brain structure in ways that may be detrimental to executive processing, but which may allow continued and perhaps amplified emotional memorial processing.

7.1. Fear conditioning

The transfer of control from reactive to predictive responding is an associative form of plasticity based on the influential hypothesis that contiguous neurons firing simultaneously will strengthen synaptically (Hebb, 1949). To determine the neuronal substrates of predictive control, many researchers use Pavlovian conditioning paradigms, in which a discrete, arbitrary, but noticeable to-be-conditioned stimulus (CS), such as a tone or light, is paired with a biologically significant unconditioned stimulus (US), such as a foot shock.

The initial reaction to the CS is an orienting response, whereas the initial reaction to the US is an unconditioned response (UR), such as jumping, vocalizing, and freezing. After even a single pairing of, e.g., tone-shock, a conditioned response, such as freezing to the tone, occurs in the absence of further shocks. A good deal of evidence supports the view that specific regions of the brain critically mediate different nodes of CS-US associations (Steinmetz, 2000). Neuronal networks involved in fear conditioning are well characterized, and include the critical involvement of amygdalar nuclei (Fendt and Fanselow, 1999; LeDoux, 2003; Maren, 2001).

For Pavlovian fear conditioning, much evidence indicates that thalamic and cortical areas serving various aspects of the sensorium project to the sensory interface of cortical amygdalar regions, particularly the lateral amygdala (LA), where CS and US are associated. The LA then projects directly and indirectly through basal and accessory basal nuclei and intercalated nuclei to striatal amygdala output regions (e.g., the CeA) which then critically influence the expression of responses in the behavioral, autonomic, and neuroendocrine axes (Blair et al., 2001; Fanselow and LeDoux, 1999; LeDoux, 2000; Maren, 2001; Rosen et al., 1991). Typically, rapidly acquired, easily measured, fast behavioral responses, such as startle (Brown et al., 1951; Davis et al., 1993), freezing (Blanchard et al., 1975), or defensive burying (Bevins and Ayres, 1992; Treit et al., 1981), or the interruption of other ongoing behaviors (Millenson and Leslie, 1974) are used to assess the efficacy of conditioning (Fendt and Fanselow, 1999), but autonomic measures, such as heart rate (LeDoux et al., 1984) and blood pressure (Iwata et al., 1986; LeDoux, 2000; Maren, 2001; Romanski and LeDoux, 1992), or neuroendocrine measures, such as HPA axis activity (Coover et al., 1973b; Goldman et al., 1973; Levine and Coover, 1976; Levine et al., 1972; Sullivan et al., 2004) can also be used to measure conditioned motor activity. Various lesion studies, including reversible lesions, and pharmacological studies indicate that the basolateral amygdala are critical for acquisition, whereas the CeA appear to be critical for expression of conditioned fear responses (for reviews see Fanselow and LeDoux, 1999; Fendt and Fanselow, 1999; LeDoux, 2000; Maren, 2001).

While the CeA appear to be essential for the behavioral expression of learned fear, different pallidal or brainstem pathways downstream from the CeA control the output to different motor systems. For example, lesions of the LH prevent conditioned autonomic but not behavioral responses, whereas lesions of the PAG interfere with behavioral but not autonomic responses (Iwata et al., 1987). The BNST appear to be one downstream pathway for conditioned HPA responses (Gray, 1993). The specific pathway downstream of cortical structures that mediates a response may further depend on the nature of the predictive stimulus. For example, whereas lesions of CeA disrupt expression of conditioned adrenocortical and behavioral responses, regardless of the type of predictive stimulus used, lesions of the BNST disrupt conditioned corticosterone and behavioral responses only when contextual stimuli predict shock, but not when discrete cues predict shock (Sullivan et al., 2004), suggesting additional hippocampal influences in the case of context conditioning that are mediated by the BNST (Anagnostaras et al., 2001; Bechara et al., 1995; Fanselow, 2000; Phillips and LeDoux, 1992).

7.2. *Influences of GCs on memory*

We have already mentioned that physiological elevations in GC in brain following stressful events correspond to changes in brain activity, such as increasing CRF concentrations in amygdala (Cook, 2002, 2004). The importance of elevations in GCs in the brain in the immediate aftermath of stress can be seen in work that demonstrates the effects of corticosterone on memory.

ADX, GC synthesis inhibition with metyrapone, or selective corticosteroid receptor blockade all impair memory for aversive tasks (Borrell et al., 1983; Liu et al., 1999; Oitzl and de Kloet, 1992; Roozendaal et al., 1996a,b; Roozendaal and McGaugh, 1996b), whereas ADX-induced memorial deficits are reversed by GCs (Roozendaal et al., 1996c). It is often the case during in vivo learning or when testing the neuronal correlates of learning in vitro that the effects of GCs are dose-dependent, with moderate doses being most effective, and highest doses being less effective or detrimental (Cordero et al., 1998; Cordero and Sandi, 1998; de Kloet et al., 1998; Diamond et al., 1992; Joels, 2000; Pugh et al., 1997; Sandi and Rose, 1994a, 1997). Detrimental effects of the steroid on memory can be ameliorated or reversed by making the learning task itself less aversive (Sandi et al., 1997). However, the degrading effect of high GCs appears to hold true more often in hippocampus than in amygdala (see below), and chronic treatment with corticosterone prior to training facilitates resistance to the extinction of contextual fear and increases CRF mRNA in the CeA (Thompson et al., 2004).

Frequently, GCs positively influence memory only when given immediately post-training, but not when given hours before or after training (de Quervain et al., 1998; Flood et al., 1978; Roozendaal, 2002; Sandi and Rose, 1994b). Partly as a result of this effective time window, GCs have been said to influence consolidation of memories (McGaugh, 2000, 2002, 2004; McGaugh et al., 2002). Given before testing, GCs appear to impair retrieval for already acquired responding (de Quervain et al., 1998). Such a temporal arrangement would seem to make functional sense, given that one would want to encode whatever salient event had just elicited the stress response in the first place.

Given both the consolidation view, which posits critical time windows for acute GC effects on memory enhancement, and the more general finding that chronic stress seems to impair cognitive functioning, there would seem to be inconsistent data from reports wherein a single restraint stress given days before acquisition (Cordero et al., 2003), or repeated restraint stress (up to 21 days) resulted in facilitated performance on contextually or discretely cued aversive tasks (Conrad et al., 1999; Sandi et al., 2001). However, it may be that some prior stressors facilitate HPA axis responses to later novel training episodes, just as heterotypic stress can result in facilitation, increasing post-stress adrenocortical output, thus

influencing consolidation at a later training trial (Cordero et al., 2003).

The cortical amygdalar nuclei are again implicated in the memory consolidating effects of GCs insofar as infusions of GR agonists into BLA, but not CeA enhance retention of inhibitory avoidance, whereas lesions of the BLA, but not CeA reverse any positive effects of GC treatment (Roozendaal and McGaugh, 1996a, 1997; Roozendaal et al., 1996c). Positive effects of GR agonists in BLA may be mediated in part by NE, insofar as β-adrenoreceptor antagonist infusions into BLA prevent the effects of high steroid (Quirarte et al., 1997; Roozendaal, 2003).

Interestingly, peripheral injections of the adrenomedullary hormone, epinephrine, which does not readily cross the blood–brain barrier, also improves memory for emotional stimuli (Liang et al., 2001, 1986; McGaugh et al., 1990). The argument has been made that peripheral epinephrine stimulates β-adrenoreceptors on the vagus which then tranduces the signal to medullary NTS and thus directly to amygdala, or via the paragigantocellularis nuclei and then directly to the amygdala, or still less directly, via the LC to the amygdala. This view is supported by the facts that post-training vagal stimulation improves and inactivation degrades aversive memory (Clark et al., 1998), GR agonists infused into the NTS improve learning and can be revoked by β-adrenergic antagonism (Roozendaal et al., 1999b), footshock increases NE release in amygdala (Galvez et al., 1996), and blockade of β-adrenoreceptors in BLA prevents this (Quirarte et al., 1997), whereas NE infusions enhance memory storage (Ferry et al., 1999; Quirarte et al., 1998; Roozendaal, 2002; Roozendaal et al., 1999a). Such evidence points to a complex loop between peripheral and central stress hormone secretion that leads to modifications in the storage of memory. However, at least one study in humans using peripheral injections of two β-blockers, one that crosses the blood–brain barrier (propranolol) and one that does not (nadolol), concluded that only the antagonist with central actions interfered with memory for emotional events (Van Stegeren et al., 1998).

Similar to post-training GC administration, post-training CRF manipulations also modulate memory. CRF delivered into amygdala post-training enhances memory (Liang and Lee, 1988), whereas CRF antagonists delivered specifically to BLA, but not CeA, immediately, but not 3 h after training impair learning (Roozendaal et al., 2002). This finding is interesting considering that amygdalar cells expressing CRF mRNA or staining immunopositive for CRF are mostly restricted to CeA (Gray and Bingaman, 1996; Uryu et al., 1992). Because the BLA projection neurons do express CRF receptors (Chen et al., 2000; Van Pett et al., 2000), it was suggested that CRF diffusion from the CeA into the BLA most likely accounted for these effects (Roozendaal et al., 2002).

It appears that dopamine (DA) also plays a significant role in this network controlling value-laden memory. DA agonists attenuate thalamically driven neuronal activity in BLA, but enhance sensoricortical driven responses in BLA (Rosenkranz and Grace, 1999). In contrast, mPFC stimulation inhibits BLA activity driven by electrical stimulation of sensory cortex (Rosenkranz and Grace, 2001) or presentation of conditioned stimuli (Rosenkranz et al., 2003). The NACC also plays a role in this system, insofar as memory for inhibitory avoidance is enhanced by simultaneous DA receptor activation within the BLA and the shell (but not core) of NACC (LaLumiere et al., 2005). These findings suggest a scenario in which mesoprefrontal DA activity regulates drive from the sensorium to BLA, while concurrent DA-ergic activation in NACC shell and BLA promotes memory for associable events (Grace and Rosenkranz, 2002). In any case, it represents further layers of dynamic complexity in incentive memorial systems acted upon by GCs.

7.3. Expectancy and non-reward

Once learning has taken place, expectancies themselves contribute to HPA output. Several types of non-reward situations appear to modulate HPA axis activity, or are modulated by HPA axis activity. Reductions in expected primary reward, e.g., sucrose concentrations, are accompanied by increased adrenocortical responding (Flaherty et al., 1985; Mitchell and Flaherty, 1998). Extinction of runway behavior is also accompanied by elevated corticosterone (Kawasaki and Iwasaki, 1997). In these last two cases, the elevation of corticosterone was curiously delayed by 1 and 3 days, respectively. Given the suppressive effects of positive expectancy on HPA output, such delays might be ascribed to the persistence of a positive expectancy of reward during the initial phase of non-reward. In the latter two cases, the elevations were in addition to elevated basal levels resulting from deprivation. The function of increased adrenocortical output during the extinction of operant behavior (Coover et al., 1971a,b), may be the invigoration of instrumental behavior, insofar as the so-called ‘‘operant burst’’ or ‘‘extinction spike,’’ is eliminated by ADX (Thomas and Papini, 2001). Similar alterations in adrenocortical output occur under the control of conditioned stimuli. Generally, a relative shift from positively- to more negatively-cued reward environments increases adrenocoritcal activity, and vice versa (Coover et al., 1973a,b, 1974, 1971a,b, 1977, 1980; Coover, 1983, 1984; Goldman et al., 1973; Levine and Coover, 1976; Levine et al., 1972). Increased adrenocortical output during worsening reward cues and the invigoration of responding with enhanced corticosterone concentrations may explain the curious phenomenon of animals producing robust response rates to produce and observe discriminative cues indicating lower probabilities of reward (Lieberman, 1972). Such a view would predict that clamping corticosterone at low levels would blunt or prevent such observing responses to low probability cues.

In summary, HPA axis function plays important roles in learning and memory. The more general finding is that GCs are elevated in the aftermath of value-laden or emotional events and tend to promote memory consolidation, particularly in cortical amygdala-based plasticity. However, opposite findings often obtain for hippocampal-based plasticity. There also appear to be GC dose functions that may vary with brain region, as well as varying effects of acute versus chronic elevations of steroid. Other neuromodulators acted upon by GCs, including

CRF, NE, and DA also appear to play roles in amygdala-based learning. Like GCs, these neuromodulators tend to have positive effects on memory consolidation in the amygdala, and are likely to have additional functions related to the gating of information to and from various other brain regions. Once learning has taken place, expectancies formed subsequently influence HPA output in ways that feedback on brain and promote rapid alterations in ongoing behavior, and possibly further influence memorial systems.

7.4. GCs on brain remodeling

In addition to the recruitment of incentive systems and influencing acute changes in neuronal plasticity, stress and GCs also more broadly sculpt the brain, resulting in volumetric changes in major structures, reflecting a more global architectural plasticity. With chronic stress, the nature of this remodeling is generally as follows: structures supporting flexible executive thinking, decision-making, reasoning, planning, and declarative memorial processes are progressively degraded, whereas structures supporting basic impulses, anxieties, moods, reactivities, and value-laden memories are progressively enhanced.

Hippocampal function has been associated with declarative, or episodic and semantic memory (Eichenbaum, 2003), spatial, navigational and contextual memory (Eichenbaum et al., 1990; Morris et al., 1982), working memories, and sequential learning (Eichenbaum et al., 1990; Lisman, 1999), as well as the impaired regulation of the HPA axis with aging (Sapolsky, 1992; Sapolsky et al., 1986). In patients with Cushing's disease, impaired verbal recall and declarative memory tests correlate with reduced hippocampal volume and average cortisol levels (Starkman et al., 1992; Wolkowitz, 1994). In animal models, stress blocks hippocampal long-term potentiation (LTP), which is a neuronal correlate of learning (Foy et al., 1987; Kim and Diamond, 2002).

Acutely, GCs may influence hippocampal architecture positively. For example, in vitro, synthetic GCs rapidly (within an hour) induce spinogenesis in CA1 dendritic fields (Komatsuzaki et al., 2005). Fig. 33A shows the effects of 100 nM dexamethasone applied to hippocampal slices on spine density in CA1 apical dendrites. Compared to controls, 1 h treatment with dexamethasone (DX) rapidly induced spinogenesis, which was blocked by pretreatment with the GR antagonist RU38486. Because the effect was not blocked by the protein synthesis inhibitor cyclohexamide (CHX), and in light of the rapid induction, GC-mediated spinogenesis may involve membrane receptor mechanisms (Komatsuzaki et al., 2005).

Unlike the acute administration of GCs, chronic stress and chronic administration of GCs tend to impair hippocampal architecture. The dentate gyrus is one of the main inputs to the

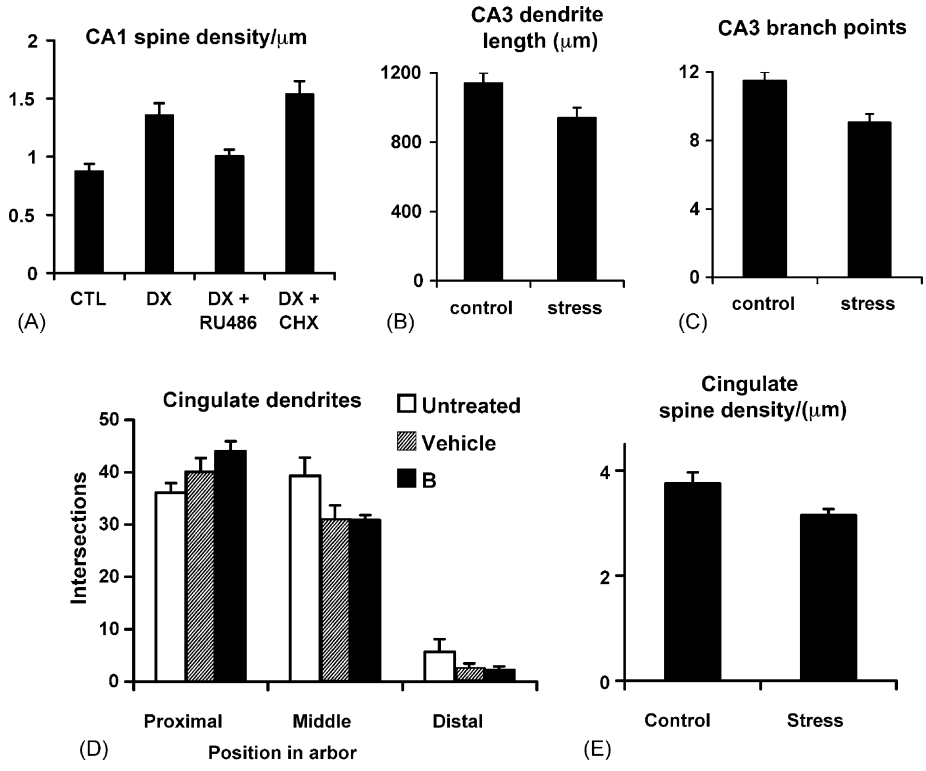

Fig. 33. (A–E) Effects of stress and GCs on neuronal architecture in the hippocampus and neocortex. Panel A: 1-h treatment with dexamethasone (DEX) acutely enhances spinogenesis in CA1 dendritic fields, which is blocked by RU38486, and unaffected by cyclohexamide (CHX; data adapted from Komatsuzaki et al., 2005). Panels B and C show destructive effects of repeated restraint on dendrite length (panel B) and arborization (panel C) in CA3 hippocampal fields (data adapted from Watanabe et al., 1992). Panel D: Constructive effects of 21-day GC treatment in cingulate cortex on apical dendrites near the soma, with destructive effects on more distal portions of the arbor (data adapted from Wellman, 2001). Panel E: Inhibitory effects of chronic stress on cingulate cortex spinogenesis (data adapted from Radley et al., 2005b).

CA3 hippocampal field and exhibits neurogenesis (about 9000 neurons/day) throughout adult life in rats; this is potently suppressed by chronic stress (Gould et al., 2000; McEwen, 1999a,b, 2003). A complete loss of GCs via ADX also impairs neuronal morphology in dentate gyrus (Gould et al., 1990). A 21-day regimen of restraint also decreased the complexity and arborization via retraction and atrophy of CA3 dendritic fields, including reducing dendritic length (Fig. 33B) and the number of branch points (Fig. 33C; McEwen, 2004; McEwen and Magarinos, 2001; McEwen et al., 2002; McKittrick et al., 2000; Watanabe et al., 1992). These same effects are mimicked by chronic administration of corticosterone (Wellman, 2001). In addition, overall hippocampal volume is reduced by chronic stress, and can be alleviated by administration of antidepressants (Czeh et al., 2001). Although basal levels of GCs may be permissive to hippocampal structure, and acute elevations can induce spinogenesis, chronically elevated stress and GCs tend to negatively impact hippocampal structure.

Like the hippocampus, neo-cortical function has been associated with executive functions, such as working and long-term memory (Goldman-Rakic, 1987a,b), managing attentional resources (Shallice, 1982), monitoring of affective or motivational state (Bechara et al., 1994; Damasio, 1994; Nauta, 1971), planning, conflict resolution, response selection, and inhibition of inappropriate responses (Miller and Cohen, 2001; Mishkin, 1964). Although less studied than stress-related hippocampal anatomy and function, the neocortex, too, is vulnerable to stress, which causes retraction and atrophy of dendrites and reduces excitatory synapses (Radley and Morrison, 2005; Radley et al., 2005a,b, 2004; Wellman, 2001). Wellman (2001) gave rats corticosterone (B) injections (10 mg) once daily for 21 days and measured dendritic reorganization in pyramidal neurons of the cingulate cortex that were reconstructed in three dimensions, using the number of intersections in three virtual, concentric spheres as a measure of complexity. Corticosterone (B) treatment actually increased the number of dendritic intersections in the sphere most proximal to the soma, but caused retraction and atrophy in middle and distal spheres (Fig. 33D). There was also some indication that the injections alone were stressful, compared to untouched controls, perhaps indicating the sensitivity of prefrontal cortex to stressors (Wellman, 2001). Repeated stress has similar consequences for prefrontal architecture (Cook, 2004). A later study showed that a 21-day regimen of restraint also significantly reduced spine density in this same region of brain, particularly in more distal arbors (Fig. 33E) (Radley et al., 2005b). Thus, as in hippocampus, stressors and GCs reduce the complexity of apical dendrites, particularly in their distal regions. Also, as in hippocampus, stressors block LTP in cortex (Diamond et al., 2004). Compromised prefrontal function has been associated with increased distractibility, difficulty grasping complex issues or mastering new tasks (Rylander, 1939), difficulty changing strategies when response contingencies change (Hauser, 1999; Jouandet and Gazzaniga, 1979), marked changes in personality, social disinhibition, hyper-aggressiveness and sexuality, euphoria, impulsivity, irresponsibility, and poor social judgement (Hecaen and Albert, 1978; Sapolsky, 2004).

Importantly, stress does not universally impair brain structure and function. In amygdala, stress appears to produce changes that are opposite to those that occur in prefrontal and hippocampal cortices (Mitra et al., 2005; Vyas et al., 2002). Vyas et al. (2004) gave rats a 10-day regimen of 2-h immobilization stress followed by a 21-day recovery period. Fig. 34A shows the increase in dendritic length in BLA at all distances relative to the soma compared to unstressed controls. In addition, because hippocampal CA3 dendrites were restored to control levels by the end of the recovery period (not shown), it would appear that not only does BLA exhibit hypertrophy to stress, this hypertrophy is long-lasting relative to the hippocampal atrophy (Vyas et al., 2004). Fig. 34 also shows that the same regimen increased spinogenesis in both primary (Fig. 34B) and secondary (Fig. 34C) dendritic branches (Mitra et al., 2005). Whereas chronic stress increases both dentritic arborization and spinogenesis in BLA, acute stress more selectively increases spinogenesis only. In contrast, although acute stress did not increase dentritic arborization, it did increase synaptogenesis (Fig. 34D) in BLA, and this effect was even greater 10 days after the stress than after 1 day, reflecting some sort of augmentation and consolidation of stress-induced remodeling over time (Mitra et al., 2005).

Consistent with such architectural changes, LTP in amygdala (Chapman et al., 2003; Maren and Fanselow, 1995) is enhanced by stress (Goosens and Maren, 2002; McKernan and Shinnick-Gallagher, 1997; Rodriguez Manzanares et al., 2005; Rogan et al., 1997). Just as the same chronic stress produces divergent effects on dendritic remodeling in hippocampus and amygdala (Vyas et al., 2002), the same chronic stress also has divergent effects on hippocampal and amygdalar LTP by enhancing only amygdalar LTP (Mesches et al., 1999; Vouimba et al., 2004). Interestingly, whereas the serotonin reuptake inhibitor tianeptine reverses the detrimental effects of stress on hippocampal LTP, it fails to prevent enhancement of stress-induced amygdalar LTP (Diamond et al., 2004; Rocher et al., 2004; Shakesby et al., 2002). Such differences may partly account for the fact that stress can result in powerful, yet inaccurate memories (Metcalfe and Jacobs, 1996).

Finally, chronic stress has some similar hypertrophic effects on neuronal architecture in the extended amygdala. Using the 10-day, 2-h/day immobilization paradigm, it was shown that like the BLA, the BNST also increases dendritic complexity (i.e., branch points; Fig. 34E) as a function of chronic stress, and tended to increase dendritic length (Fig. 34D), as well, although this latter effect was not significant. In contrast, no such effects were obtained in CeA (Vyas et al., 2003). The site-specific differential responses may indicate a sensitization of the substrates of anxiety relative to the substrates of fear (Davis, 1998).

With respect to the effects of GCs on neuronal plasticity on executive versus emotional processing, it appears that stress, and particularly chronic stress, institutes memorial and architectural enhancements that favor emotional, or value-laden responding, whereas GCs tend to be detrimental to hippocampal and prefrontal-based learning and architecture.

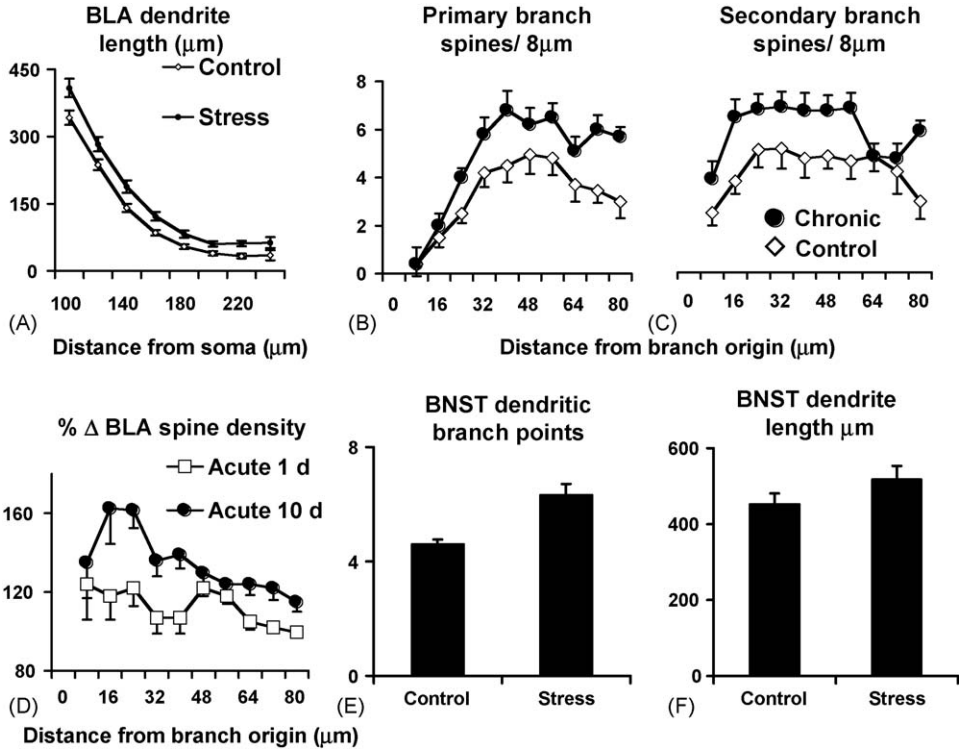

Fig. 34. (A–E) Facilitating effects of immobilization on neuronal architecture in the extended amygdala and neocortex. Panel A: 10-day immobilization increases dendritic length in basolateral amygdala (BLA) when measured 21 days after final stress (data adapted from Vyas et al., 2004). Chronic immobilization stress also increases spinogenesis in BLA dendrites on both primary (panel B) and secondary (panel C) dendritic branches. A single acute immobilization (panel D) also increases spinogenesis in BLA, but the effects are even greater 10 days after the final stress compared to 1 day later (data adapted from Mitra et al., 2005). Chronic immobilization stress also increases dendritic branch points (panel E) and slightly enhances dendritic length in bed nucleus of the stria terminalis (panel F; data adapted from Vyas et al., 2003).

The structural and functional remodeling of the brain by chronic stress paints a portrait of a thoughtful, flexible, multitasking executive giving way to a more impulsive, anxious, irritable, and inflexible phenotype operating on potent, but perhaps inaccurate emotional memories—the transmogrification of Prospero into Caliban.

8. The appetitive phenotype revealed by reduced feeding and stress

Psychologists have worked for more than a century on issues of learning and motivation, and have used two time-tested methods to motivate their subjects: food (or, similarly, water) deprivation and stressors (e.g., footshock, forced swim, avoidance schedules). Therefore, the vast majority of this literature involves procedures that have caused major alterations in HPA axis output under the conditions of study. In the process of discovering, tuning, and repeating the effective procedures of experimentation to make them reliable and expeditious, experimenters have indeed found a key: manipulations of the GCs are extremely relevant to issues of motives, motorics, and memory. In addition, for many studies, that involve food deprivation and feeding reward during the experiment, it is not uncommon that the supplemental meal is given to the animals immediately following a training session, thereby also instituting a restricted feeding paradigm that induces resetting of the FEO (Section 2.2.2), and thus brings about anticipatory peripheral drive states, including increased HPA axis and autonomic output, and central incentive preparedness.

Experimental psychology provided the initial clues to the phenotypic engineering of motive states that result from elevated glucocorticoids by using food deprivation as a routine preparatory manipulation that theoretically increases the motivation to work. Some experiments sought to demonstrate relationships between the level of drive and the degree of performance or learning by either attempting to measure drive directly, or testing hypotheses concerning the ‘‘reward’’ or ‘‘reinforcement’’ value of drive reduction. Learning was thought to be a consequence of drive reduction. For many, a reduced food allowance is largely and implicitly entrenched in appetitive research, so that variability is reduced and results are hastened, without reference to ad libitum fed controls. We focus here on food- and water-related, if not purely appetitive paradigms and the evoked phenotype, because there is little doubt that aversive paradigms result in averse phenotypes.

Early attempts to measure drive directly came from the work of Warden (1932) using the Columbia obstruction apparatus. Animals were deprived of some incentive, such as water, food, or access to a sexual mate. At night, they were allowed 20-min sessions in which they could cross an electrified grid in order to obtain 30 s of commerce with the incentive. For water, the number of grid crossings rose rapidly from 6 to 12 to 24 h of deprivation; aversive grid crossings peaked at 24 h, before

slowly declining over the next 6 days. Similarly for food, grid crossings increased over first 2 days, remained at a peak until 5 days of deprivation, then slowly declined over the next 3 days. Grid crossings for access to a sexual mate reached asymptote on the first day and never declined. Due to the nature of the competing fear reactions, and notwithstanding the HPA axis activation probably produced by the shocks, the increases in grid crossings for food and water were consistent with an increased tissue need and drive, whereas their subsequent decline in performance appeared to be due to inanition, because the sex drive never waned when food and water were freely available (Warden, 1932). In the 1970s it was shown that water restriction altered the daily rhythm in corticosterone in rats so that it peaked just prior to the water-reward trials (Gray et al., 1978; Johnson and Levine, 1973), and that the same is true for restricted feeding (Krieger, 1974). Thus, several factors, including repeated intermittent stress, deprivation, and circadian drive, appear to have conspired to increase HPA outflow in such studies.

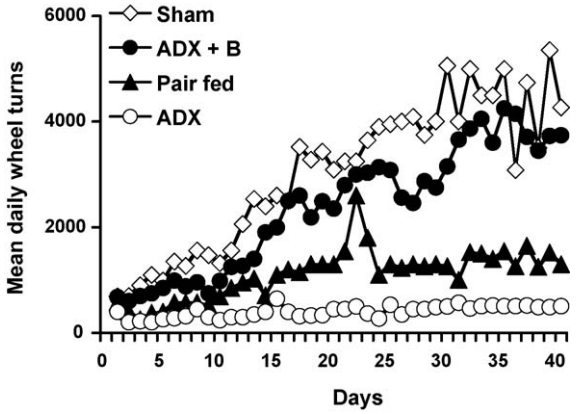

Fig. 35. Effects of ADX and GC replacement on wheel running. ADX severely retards wheel running relative to shams, and is reversed by corticosterone (B) replacement via daily injections. Intact rats pair-fed to ADX rats show moderate increases in wheel running probably due to elevated GCs (data adapted from Leshner, 1971).

8.1. General activity

Because drive was thought to involve primarily non-specific energizing effects on behavior, i.e., increases in non-directed activity, experimenters were quite interested in what they viewed as non-directed behaviors, such as increases in general activity, wheel running or exploration that are typically obtained in impoverished, cue-poor environments. Food deprivation increases general activity, such as wheel running (Bolles and Petrinovich, 1956; Reid and Finger, 1955; Wald and jackson, 1944), and such activity is highly correlated with the percentage loss in body weight (Bolles, 1963; Moskowitz, 1959; Treichler and Hall, 1962), and particularly protein utilization (Koubi et al., 1991); low protein diets, which cause weight loss, also increase activity (Hitchcock, 1928).

It has been known for decades that starvation promotes substantial sensitization of locomotor activity in rats as it proceeds (Moorcroft et al., 1971). There is evidence that such effects are dependent on adrenal activity (Durrant, 1924; Islam et al., 1995; Richter, 1927). Leshner's (1971) careful study on wheel running compared adrenal demedullated, sham-operated, and pair-fed rats to ADX rats with daily s.c. corticosterone or vehicle injections. The paired feeding regimen was employed because of a potential confound between the reduced chow intake that accompanies ADX. Fig. 35 shows data from ADX, intact rats pair-fed to ADX, ADX + corticosterone (5 mg/kg), and sham-operated rats in that study (Leshner, 1971). Corticosterone-replaced ADX rats showed substantial increases in wheel running across days that were comparable to intact controls. In contrast, activity in ADX rats was substantially blunted with little acquisition, whereas the intact pair-fed shams receiving saline showed intermediate levels, a moderately facilitating effect that probably depended on increasing GCs, as the body weight was reduced (Leshner, 1971). This is one of the earlier studies showing a positive effect of GCs on appetitive structure.

Some have reported that food deprivation decreases exploration, and these findings are not functionally counter-intuitive. Unfamiliar environments may produce "forced" exploration, whereas familiar environments allow "free" exploration, or alternatively, differences in anxiety levels. Under conditions of "free" exploration, food deprivation decreases the latency of out-of-nest episodes (Bolles and De Lorge, 1962). Increases in activity may also depend on the viability of incentive cues. One study reported that the energizing effect of deprivation depended on available incentive cues, such as a change in exogenous stimulus conditions, like lighting, whereas a plain, monotonous environment did not increase activity (Campbell and Sheffield, 1953). One might fail to find increases in exploration with deprivation simply because the incentive cues are entirely too familiar and predictably hopeless, so that the underweight animal is better off conserving energy.

Although directed behavior is often thought to depend on reward, deprivation alone without reward provokes efficient search in rats on an eight-arm radial maze (Timberlake and White, 1990). Timberlake and White compared the efficiency of maze search in two groups of food-deprived rats. For one group, all arms of the maze were baited with a 45 mg Noyes pellet, whereas for the second group the maze was always unbaited. A third group was non-deprived and non-rewarded. Both deprived groups chose a greater number of novel arms in the first eight choices than the non-deprived group, but the rewarded group was no more efficient than the non-rewarded group in choosing novel arms until after 15–18 once-daily trials. An analysis of adjacent choices revealed that the efficiency was not based on any simple "win-shift," or in this case, "look-shift"-type of strategy, because the behavior only developed slowly across sessions, possibly indicating an improvement in memorial, rather than algorithmic processes. Like many phenomena coming from the learning laboratory, the effect appears to rely on pre-existing abilities that are recruited by deprivation. "The major determinants of efficient maze search are clearly independent of local food reward," the authors concluded (Timberlake and White, 1990).

We found a similar effect (Pecoraro and Dallman, unpublished) with ADX rats that were replaced with varying doses of corticosterone and allowed to drink sucrose for 5 min on a plus maze. When freely fed, the animals replaced with corticosterone showed little interest in drinking sucrose (<0.5 ml/day over 7 days) in the context of the maze, and there were no differences in drinking among the groups. We also estimated the efficiency of maze search by counting how many of four novel arms they entered, and multiplied this by how many arms the animals entered before they exhausted all four arms. An animal entering all four arms in four attempts (4/4), had a perfect score of 4. Although there was probably a ceiling effect because of the simplicity of the maze, the high steroid animals did show increased efficiency, suggesting that the increased search efficiency that is seen in hungry rats is at least partly a consequence of high GCs on cognitive systems and/or path-following behaviors. This is consistent with reports of differing behavioral strategies that depend on differential occupation of MRs and GRs (Oitzl and de Kloet, 1992). Thus, GCs not only modify overall activity, but also influence the directedness of behavior.

8.2. Evoked behaviors

As mentioned above, hunger and stress can result in behavioral inflexibility, intractability, or impulsiveness, characteristics that are often displayed by experimental subjects. It has been customary to refer to responses conditioned by Pavlovian procedures as "elicited," implying some particular skill on the part of the experimenter. By definition, Pavlovian procedures have no response requirement, and no shaping of the response, aside from the selection of the stimuli, schedule, and apparatus. Both the unconditioned and conditioned responses to a stimulus situation are essentially prepared, or at least self-organize under reigning stimulus conditions, and perhaps "evoked" is a more appropriate descriptor.

Many interesting evoked behavioral phenomena carry exotic names reflecting the theoretical surprise with which they were greeted upon their demonstration, e.g., so-called "superstitious" behaviors, which in reality appear to be reliably self-organizing between-reinforcer, or interim behaviors (Morse and Skinner, 1957; Skinner, 1992; Staddon and Simmelhag, 1970). Even instrumental procedures can involve evoked bar pressing for food while free food is provided, a phenomenon known as "contra-freeloading," because the animal appears to work for food when it could just as easily "free-load" (Osborne, 1977). Such self-organizing behaviors frequently emerge despite explicit response requirements to the contrary, and include phenomena such as negative sign-tracking (Hearst and Jenkins, 1974), or autoshaping (Williams and Williams, 1969), and misbehavior (Breland and Breland, 1961; Timberlake et al., 1982). Essentially, hungry animals engage in many species-specific food handling or preparatory behaviors that delay or prohibit reinforcement under reigning stimulus and/or response contingencies, and thus "work to avoid food." Being thus untrained, difficult to withhold, and frequently maladaptive in terms of the homeostatic considerations of the animals, these behaviors may be considered as not only prepared, but even obligatory, resembling modal action patterns evoked by sign stimuli (Gardner and Gardner, 1988). A great number of these evoked and prepared or self-organizing responses are sensitive to energy balance.

Deprivation clearly increases the intensity of evoked responses. The prototypical Pavlovian evoked response, the ratio of conditioned to unconditioned salivation, increases with deprivation (Zener and McCurdy, 1939). The skeletal action pattern of mouse killing by rats is also amplified by deprivation: non-killer rats become killer rats, and killers become more intense killers (Albert et al., 1985; Malick, 1975; Russell et al., 1983). Thus, a fuller phenotype emerges with energy deprivation.

Further, a number of prepared responses show particular resonances with scheduled reward presentation. Moreover, certain reward schedules, aimed at stimulating one particular system induce coupling with other motivational systems and, hence, "adjunctive" behaviors appear to be dragged along as "pleiotropic" side-effects, that are amplified by deprivation (Falk, 1966b, 1971). Many of these so-called adjunctive behaviors appear to have a functional linkage to intermittent events.

One of these behaviors is schedule-induced polydipsia (SIP). Food-restricted adult rats presented with intermittent food pellets on an interval schedule with freely available water often develop excessive, non-regulatory water drinking (Falk, 1961) consuming up to 20 ml in a 30 min session (Lopez-Grancha et al., 2006), or commonly up to 100 ml in a 3 h session compared to the 10 ml they would drink if provided with the same number of pellets en masse (Falk, 1961, 1966a). Overdrinking is only slightly decreased when the rats are pre-loaded with water. Although feeding and drinking are clearly coupled in the rat, and drinking could be thought of as a functional interim behavior, the amounts drunk are excessive. SIP does resemble interim behaviors that emerge at particular times between reinforcers (Staddon and Simmelhag, 1970). It peaks within the first 12 s after pellet procurement on a fixed interval (FI) 60 s paradigm, before rapidly giving way to increased locomotor behavior (Mittleman et al., 1992). SIP exhibits a bitonic function with the optimal interval length for maximal drinking being around 60 s (Falk, 1971), and thus it appears to exhibit some sort of resonance with the schedules. SIP is enhanced by weight loss and is dramatically reduced, if not abolished, by free-feeding (Falk, 1969; Roper and Nieto, 1979; Wayner and Rondeau, 1976). CRF appears to have positive effects on SIP (Cole and Koob, 1994). Such periodic food presentation is also associated with ever-increasing DA efflux in the NACC (Church et al., 1987; McCullough and Salamone, 1992), which is probably amplified by the GCs. 6OHDA (dopamine-depleting) lesions of the NACC impair the acquisition of SIP (Robbins and Koob, 1980), without affecting later performance once acquired (Robbins et al., 1983). Removing adrenals from rats halfway through the acquisition period leaves SIP at pre-ADX levels (Mittleman et al., 1992). Thus, adrenocortical activity and central CRF and DA-ergic activation are involved in aspects of the acquisition and/or maintenance of SIP that also appear GC-dependent.

Despite the demonstrated involvement of adrenal activity in SIP, the nature of that involvement remains controversial. A FI 30 s schedule that was shown to produce SIP in one group of rats was correlated with greater adrenal activity in food-deprived controls unable to engage in drinking (Lopez-Grancha et al., 2006). Because endogenous corticosterone is inversely correlated with SIP (Mittleman et al., 1988), and post-session levels of corticosterone are lower than pre-session levels, some have argued that SIP is a coping response to frustrating intervals of non-reward (Brett and Levine, 1979; Levine et al., 1979). This view finds support with physiological measures of arousal (Mittleman et al., 1990). Others have argued that adrenal activity modulates SIP, based on finding an increase in corticosterone when water was available on a fixed time (FT) 60 s compared to when it was not (Mittleman et al., 1988).

Further discrepancies with respect to adrenal function during SIP exist, but another issue may be critical for the interpretation of future studies. Though it seems unlikely that a FI 30 s or FT 60 s using 45 mg chow pellets will entrain the FEO in shorter sessions, based on known caloric thresholds for FAA, any post-session supplemental feedings certainly would entrain the FEO; thus, these would have consequences for the corticosterone response before and after SIP sessions. Even though endogenous corticosterone is inversely related to SIP, it appears to be necessary for the response, because ADX prior to learning attenuates the development of SIP in a corticosterone-reversible fashion (Cirulli et al., 1994). Reduced adrenocortical output favoring the coping hypothesis is difficult to assess, primarily because it is seldom reported when the supplemental meals are given or at what threshold session-obtained food will reduce corticosterone output in food-deprived rats, or whether food alone or food plus water are required to reduce corticosterone in hungry rats anticipating meals. Presently, further information is required. Studies that have manipulated CRF, DA, and GCs, point to an interpretation of ''sensitized evocation,'' whereas measurement of GCs when animals are engaged in consummatory activity point to the ''coping'' hypothesis. Regardless of one's view, SIP is empirically a GC-dependent process.

Another motivation that is sensitive to schedules and deprivation is aggression. Schedule-induced aggression (in pigeons) that results from periodic food presentation also increases with the degree of deprivation (Dove, 1976). It is unclear if freely feeding animals would show it, as they were not included in that study. Schedule-induced aggression may be related to the more general finding that food deprivation or the thwarting of food expectancies increases aggression generally toward conspecifics (Lore et al., 1986). Attacks upon passive ''dummy'' animals are particularly vicious (Azrin and Hutchinson, 1967). Schedule-induced aggression has also been shown to occur in rats, monkeys, and humans (Azrin et al., 1968; Fredricksen and Peterson, 1977; Hutchinson et al., 1968a,b). Other schedule-induced phenomena in rats include wheel running (Collier and Levitsky, 1968), and air-puff ''drinking,'' (Hendry and Rasche, 1961; Treichler and Hamilton, 1967). Like SIP, schedule-induced attack shows properties of interim behaviors, and appears commonly in animals on interval schedules, predominantly after food delivery and ingestion (Flory and Smith, 1983).

Schedule-induced aggression is interesting not only because of its potential functional value in competitive feeding situations, but because stressors seem to strongly promote aggression in many species, including humans (Barnett et al., 1991; Tardiff, 1992). In rats, interference with the actions of ACTH or of corticosterone inhibits aggression (Haller et al., 1996; Kruk et al., 2004) and this inhibition is reversed by supplying exogenous corticosterone (Mikics et al., 2004). Stimulation of the hypothalamic attack area results in HPA axis activation in intact rats, even in the absence of an opponent, and replacing ADX rats with corticosterone rapidly reduces the electrical thresholds for stimulated attack (Kruk et al., 2004). Thus, aggression could exhibit positive feedback properties with stress, which may have functional value in cases where contests escalate, such as competitive foraging in areas where food becomes scarce. Such an interpretation is consistent with the observation that some schedules of food presentation, either by resonating with appetitive structure and/or by becoming leaner schedules, stimulate the HPA axis and corticosterone (Coover, 1983; Coover et al., 1971a; Levine and Coover, 1976; Lopez-Grancha et al., 2006), which can rapidly (Cook, 2002, 2004) elevate brain CRF and DA levels.

Another evoked behavior, Pavlovian autoshaping occurs when an animal trains, or ''shapes'' itself to make a response (Brown and Jenkins, 1968), such as bar pressing, when a conditioned stimulus, such as insertion of the bar, is paired with food. Bar ''pressing'' (often biting and tugging at it, if the bar affords this) self-organizes reliably, without explicit shaping of the response by the experimenter using the method of successive approximations (hence ''autoshaping'') even though no response requirement exists, and responding does not affect outcomes (hence Pavlovian). When rats are required to withhold responding in order to obtain the next pellet, they have difficulty doing so, apparently because occasional food presentations re-ignite responding (Williams and Williams, 1969). Autoshaping also depends on timing, and is clearly amplified by deprivation (Campbell and Carroll, 2001). The acquisition of autoshaping by rats is accompanied by elevated corticosterone concentrations (Tomie et al., 2002), suggesting a contribution of GCs to this behaviour, as well.

8.3. Eating

One obvious sequel to food deprivation or weight loss due to restricted feeding is an increase in food intake when the opportunity arises. The duration of deprivation (or weight loss) increases the proportion of time that is allocated to remaining in proximity to the feeding area, even when other activities are available (Allison and Rocha, 1965; Timberlake and Birch, 1967), decreases the latency to eat (Bolles and De Lorge, 1962), and increases meal size (Dufort and Wright, 1962), although it may not always correlate with next meal size (Le Magnen and Tallon, 1963).

GCs facilitate saccharin (Bhatnagar et al., 2000), lard (La Fleur et al., 2004), and sucrose (Pecoraro et al., 2005b) intake,

and each of the central incentive networks downstream of GCs (see Fig. 31), particularly DA, NE, and EOPs, are likely to play roles in various aspects of both appetitve and consummatory amplification. Although CRF is usually found to be antagonistic toward feeding (Ciccocioppo et al., 2003a; Smagin et al., 1999), this view is not monolithic, and some studies indicate that CRF (type 1 receptor) agonists increase chow intake at low doses, whereas receptor antagonists inhibit chow intake induced by tail pinch stress (Samarghandian et al., 2003). Furthermore, a positive role for CRF has also been shown in studies of the reinstatement of palatable food-seeking following yohimbine-induced stress (Ghitza et al., 2005). Moreover, CRF injected into the NACC shell promotes motivation for sucrose (Pecina et al., 2006). Such findings should not be surprising given the capacity of CRF to stimulate other pathways, as well as the general overlap among neuromodulatory systems.

Thus, the behavioral phenotype appears to be very similar under conditions when glucocorticoids are known to be elevated: during stress, negative energy balance, and exogenously administered GCs. There appears to be a general amplification of "drive," locomotor behaviors, and evoked responding under these conditions. While much of our discussion has focused on the role of stress, hunger, and GCs on the amplification of evoked responding, parallels exist in instrumental behavior, as well (see Bolles, 1975), as will be seen later in the section devoted to self-administration. The emphasis on evoked behaviors in this section was intentional, as pre-organized behavioral and motivational ensembles may be viewed as the building blocks of other forms of behavior. By extension, their amplification by stress, hunger, and GCs indicates that these variables act upon a core, primary, or species-specific phenotype, perhaps summoning this phenotype particularly under conditions of stress.

9. Incentive relativity with normal incentives

Incentives are evaluated in relation to one another.

To establish a normative basis with respect to how stress might promote a runaway sensitivity to or evaluation of incentives, we have been investigating a microcosm of adaptation that results from incentive relativity processes under conditions of natural reward. The term "negative contrast" refers to abrupt alterations in motor outputs when animals are shifted from more- to less-preferred rewards. One standardized procedure involves the use of different concentrations of sucrose. Fig. 36 shows the intake of sucrose solutions in brief, 5-min, once daily sessions in three groups of food-restricted rats with time. One group drank 32% sucrose for 12 days before being shifted to a 4% solution during the last two sessions. Two unshifted control groups drank 32% or 4% sucrose throughout the experiment. As is often the case, the 4% group drank nearly as much solution as the 32% groups, showing its acceptability. On the day of the first shift to 4%, the shifted group strongly inhibits intake relative to controls, vastly undershooting the intake levels of the 4% sucrose control. Thus, 4% sucrose that is otherwise normally acceptable is rejected if the rat has had experience with a preferred solution. The term

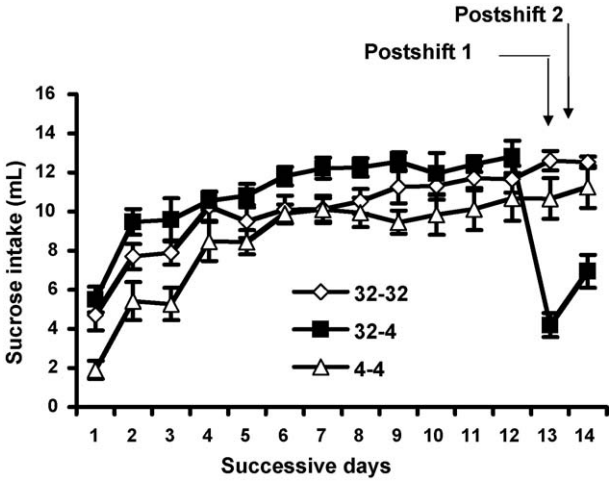

Fig. 36. Intake of sucrose in once daily 5 min sessions in rats restricted to 85% free-feeding weights. One group drank 32% sucrose for 12 days prior to being shifted to a 4% solution for 2 days (32-4), whereas two unshifted controls drank either 32% sucrose only (32-32) or 4% (4-4). The suppression of intake by the shifted group is called a negative contrast effect, and indicates that although 4% sucrose is normally reinforcing, it is actively rejected if the animals has experience with a preferred concentration, indicating that incentive value is relative to previous experience.

"negative contrast" derives from this undershooting, and may be considered analogous to perceptual contrast, e.g., as occurs in the visual system walking from a bright garden into a dark basement, except that the phenomenon is based on memorial, rather than sensory adaptation. By the second day after the shift in solution concentration, there is some recovery of the suppression in intake, and the recovery continues for several days until the shifted animals re-achieve control levels of intake.

Such contrast effects are asymmetrical in that shifting an animal in the opposite direction from 4% to 32% sucrose only elicits mild, if any positive contrast (reviewed in Flaherty, 1996). Going from better to worse evokes much more "depression" than going from worse to better evokes "elation." The suppression of intake by concentration reductions is accompanied by a suite of search behaviors, including nose-down whisking locomotion, sampling of other food sites, and orienting responses. The search behavior is directed as shown by a preference to search in the original target location only when the target location is predictable (Pecoraro et al., 1999). In addition, physiological adaptations occur following the shift to the 4% solution that depend on the day of the shift. In Fig. 36 it is clear that some recovery of drinking occurs by the second day after the shift. Fig. 37 shows adjustments in visceromotor output between the first and second days of the shift to 4% sucrose. Panel A (redrawn from Flaherty, 1986) shows adrenocortical output in the minutes following the shift on the first and second days for one shifted group and two unshifted controls. Adrenocortical output increases in the shifted group on the second, but not the first day relative to controls (Flaherty et al., 1985; Mitchell and Flaherty, 1998). Panel B shows data for body temperature only in shifted animals between the preshift baseline period and the

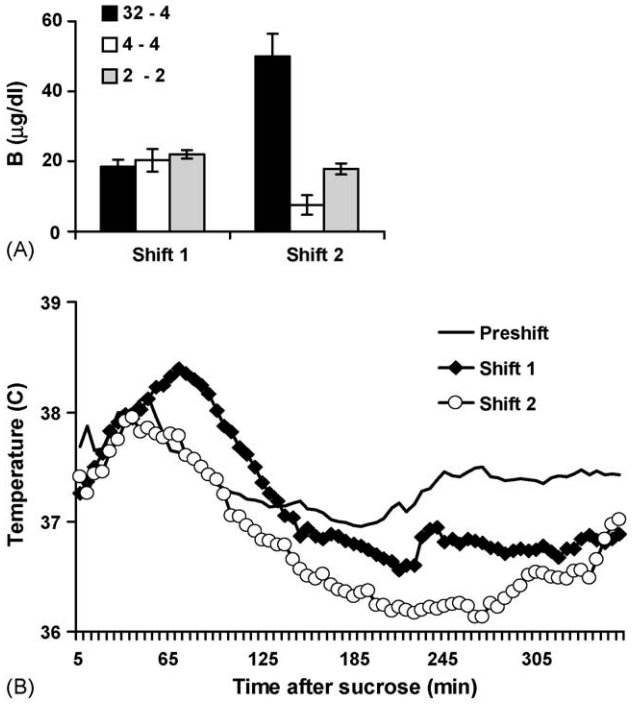

Fig. 37. Daytype-specific alterations in two motor outflows following a shift from 32% to 4% sucrose. Panel A shows an increase adrenocortical output in shifted animals (32-4) only on the second day of the postshift period compared to two unshifted controls (data were adapted from Flaherty et al., 1986). Panel B shows successive adaptation in temperature output in shifted animals across three 6 h periods after drinking sucrose, including the final preshift ingestion of 32% sucrose and the 2 subsequent days of drinking 4% sucrose. On the first shift to 4% sucrose, rats show a 2 h temperature burst compared to their preshift post-ingestive profiles. By the second day of drinking 4% sucrose, this response has normalized, and the animals cannot rescue body temperature during the light period without 32% sucrose. Along with similar daytype specific changes in somatomotor output and pharmalogical profile, the data indicate a massive one-trial learning episode concerning the governing of energy policy. Data adapted from Pecoraro and Dallman (2005).

first and second postshift days (Pecoraro et al., 2003). When rats were shifted from 32% to 4% sucrose, they exhibited a substantial increase in body temperature between the first and second hour after drinking relative to the preshift levels, and this elevation persisted for up to 6 h relative to their response on the second day after the shift that also lacks the initial burst. Pharmacologically, many agents that are effective in reducing contrast, e.g., benzodiazepines, are effective on the second, but not the first day of the shift (Flaherty, 1996). In sum, all lines of evidence indicate that an important, one-trial learning process occurs as a result of the first thwarted food expectancy that recruits or optimizes a new energy policy. Although incentive relativity effects occur weakly in freely feeding animals, they are amplified by food restriction, again suggesting interactions with elevated GCs.

9.1. GCs and incentive drive

To further test whether GCs influence incentive relativity effects, we employed the negative contrast paradigm described above in adrenalectomized rats with varying levels of corticosterone replacement on a four-arm radial maze. The subcutaneous replacement pellets were 100% cholesterol (ADX 0), 30% corticosterone (ADX 30), 80% corticosterone (B, ADX 80), or the animals were sham ADX (Sham). Animals were placed on the center platform in a holding pen, and were then allowed to freely traverse the maze for 5 min and drink a 32% sucrose solution baiting one of the four arms. After some period of acquisition they were shifted from the 32% to a 4% sucrose solution for 2 days. Our model predicted that sucrose intake during the preshift period, intake suppression during the postshift, and postshift location changes would all vary dose-dependently with corticosterone (B). In addition, it predicted that remodeling of energy toward adipose tissue would occur with increasing corticosterone.

By the end of the experiment, insulin and relative adiposity were positively and dose-dependently related to corticosterone replacement levels (not shown), indicative of peripheral remodeling. Fig. 38A shows sucrose intake in 2-day blocks for each group during the last 2 days while drinking 32% sucrose, when they had achieved 85–90% of initial body weight, and the first 2 days after provision of 4% sucrose. The dose-dependent stimulation of sucrose drinking by steroid replacement is very similar to what we saw previously when saccharin solutions were used (Fig. 16). Following the shift to 4% sucrose, all groups suppressed their intake substantially (Fig. 38A), as is typical when consummatory contrast effects are explicitly demonstrated by the use of unshifted controls. We examined the amplification of the contrast-like effect by comparing the difference between terminal preshift and postshift drinking between groups. Fig. 38B shows these difference scores that indicated a dose-dependent increase in contrast-like effects (relative intake suppression) as the steroid dose increases. Again, ADX 80 is indistinguishable from Sham. Although this appears to be an amplification of incentive contrast, it is possible that the effect was derived purely from the elevation in preshift drinking, rather than some effect on comparator mechanisms or emotional reactions to the unexpected solution. On the other hand, it remains possible that postshift intake represents a floor effect that obscures effects of the steroid. It may be possible to test this latter hypothesis by reducing the concentration disparity of the postshift solution to alleviate the magnitude of suppression that typically covaries with concentration disparity.

In addition to effects on physiological remodeling, sucrose intake, and consummatory contrast-like effects, corticosterone replacement also appeared necessary for postshift search behaviors. Fig. 39A shows locomotor responses to the shift for each group during the terminal preshift and the first postshift session. While there were no differences in locomotor activity during the preshift, the increase in postshift locomotion, was entirely corticosterone-dependent, but not dose-dependent, suggesting the sufficiency of MR occupancy for this response. As previous studies have shown that this increase in locomotor behavior is accompanied by orienting and sampling behaviors resembling search (Pecoraro et al., 1999), we also tested whether this increase in corticosterone-dependent locomotion resulted in an increase in dwell time and entries to all other

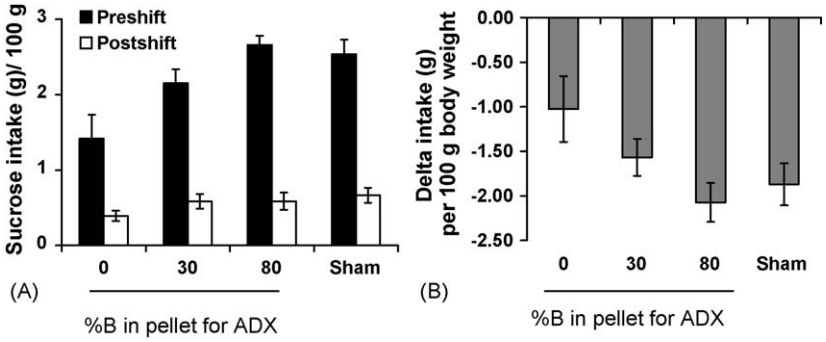

Fig. 38. Intake of sucrose solutions in corticosterone (B)-clamped rats and sham ADX. B dose-dependently increased intake of the 32% preshift sucrose solution, whereas it did not alter drinking of the 4% postshift solution (panel A). Panel B shows the change in intake following the shift to 4% sucrose, and suggests that B may dose-dependently enhance incentive relativity effects. Note the parity between high steroid rats and food-restricted shams. Data adapted from Pecoraro et al. (2005b).

platforms of the maze. Fig. 39 also shows the change in dwell time (panel B) and entries (panel C) to each platform, including the target platform compared to the average non-target platform, between preshift and postshift sessions. Whereas cholesterol replacement resulted in no change in time or entries to other platforms, corticosterone replacements (and sham surgery) all led to increased time and entries to all non-target platforms, suggesting that the corticosterone-dependent locomotion resulted in systematic search.

Taken together, these data show the pervasive, system-wide effects GCs have on metabolic remodeling and appetitive structure. Such steroid replacement strategies appear to result in a largely dose-dependent kind of phenotypic remodeling. Steroid replacement not only resulted in dose-dependent remodeling of energy stores toward fat (not shown), they also dose-dependently amplified sucrose intake and contrast effects, and corticosterone was required for the typical, reflex-like evocation of search behavior following the reduction in sucrose concentration. Thus, corticosterone biases the phenotype toward a state of greater metabolic efficiency peripherally, while centrally it facilitates consummatory and appetitive functions.

9.2. GCs and memory for food

One ambiguity that often arises from deletion and replacement studies is that they frequently do not determine whether an outcome occurs as a consequence of GC effects on ongoing performance, per se, or whether it is the result of enhanced learning that carries forward into later performance. If one observes enhanced performance only while the steroid is elevated, then such transience would indicate effects on

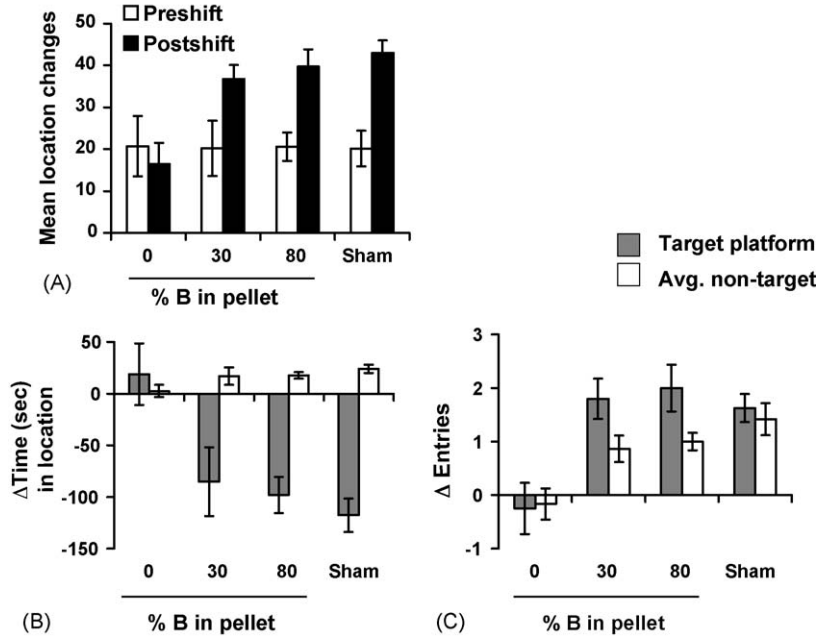

Fig. 39. (A–C) The effects of corticosterone (B) clamps on preshift and postshift locomotor behaviors. Panel A: During the final preshift, no differences in location changes were observed. During the shift to 4% sucrose, increases in locomotor behavior (location changes) was completely B-dependent. Panels B and C: Distribution of activity during the postshift on a four-arm maze as a function of B replacement. Panel B shows that B replacement and Sham ADX resulted in decreased time on the target platform (TP), and increased time on the average non-target platform. Panel C shows that entries to the average non-target platforms increased in B replaced animals only. Rats without B (ADX 0) did not show such systematic search. Data adapted from Pecoraro et al. (2005b).

ongoing performance alone, e.g., an increase in the salience of ongoing stimulation. However, if a GC elevation enhanced performance relatively permanently, even in its later absence, then a case can be made for the involvement of memorial processes, e.g., sensitization or associative learning processes. The importance of this issue is obvious, for at least two reasons: (1) cues associated with prior stressors may trigger stress-related central networks in the absence of elevated stress hormones, or (2) a single stress-related experience could permanently sensitize a stress-related behavior such that it never returns to its original state. Thus, a propensity to engage in palatable feeding may depend on either a concurrent elevation of steroid, a triggered memorial event, permanently sensitized states, or some combination of these.

Few studies have examined the role of GCs in learning of natural appetitive rewards. An interesting older study claimed to show a dexamethasone-reversible saccharin aversion following ADX (Silva, 1977). However, this ‘‘aversion’’ failed to materialize in animals that experienced the saccharin solution before ADX, suggesting that some sort of consolidation process had occurred during the initial presentation of saccharin that carried over into later experience in the absence of steroid.

As an initial test to distinguish between effects of memory and performance in the contrast paradigm, rats were ADX and given pairings of corticosterone injections (666 μl/kg or equivolume vehicle) known to produce stress levels of plasma corticosterone with presentation of a 32% sucrose solution. They were then later tested for sucrose drinking in the absence of steroid to avoid any potential performance effects of elevated steroid during testing. In addition, to test whether there was an effect of trial frequency, i.e., the number of learning experiences, rats were given 0 (unpaired), 1 (1P), or 3 (3P) pairings of corticosterone and sucrose. On days when corticosterone and sucrose were unpaired, only one or the other agent was presented, and one day intervened between further presentations. Sham ADX rats received three presentations of sucrose and saline injections. Intake was limited to avoid differences in intake. Two days after training a testing period commenced consisting of once daily access to 32% sucrose for 5-min for 12 days, followed by 2 days of access to 4% sucrose as a further test for contrast effects.

Fig. 40A shows intake of 32% sucrose on the first test and the final session in which 32% sucrose was available. The first test day is critical to measuring memory based on training alone, insofar as there have been no further intervening training trials. On this ‘‘virgin’’ test, the group that had received a single pairing drank more sucrose relative to other groups. The low intake by Shams may be attributable to their basal corticosterone levels at this time of day, and their free-feeding status, whereas the intake advantage conferred by the single pairing can only be attributed to the pairing regimen itself in the absence of any performance effects of corticosterone. All groups increased sucrose drinking on the succeeding days, and by the final session, the 1-pairing group still retained an advantage over the sham ADX rats and the ADX rats receiving unpaired presentations of sucrose and corticosterone during training, but did not differ from the group that had received three pairings during training.

Fig. 40B shows the suppression of intake upon receipt of 4% sucrose in the postshift phase as difference scores, i.e., postshift intake minus terminal preshift intake. Again, there was greater suppression of intake by the 1-pairing group than by the other ADX rats, but in this case the Sham ADX rats were similar to the 1-pairing group. Thus, contrast effects, presumably due to enhanced encoding and expectancy of 32% sucrose were also amplified by the single pairing, despite their temporal remoteness from original training.

This experiment revealed that the effects of corticosterone on memory can be complex. Clearly, the memorial effect was dependent on the pairing of sucrose and corticosterone, and this could imply either associative or non-associative processes. The effect was also frequency dependent, in that the strengthening of memory by the single pairing appeared to be largely revoked, at least in early testing, by multiple pairings. Loosely related examples of memory impairment by repeated elevations of GCs can be found in studies wherein acute stress facilitates (Goosens and Maren, 2002; McKernan and Shinnick-Gallagher, 1997; Rodriguez Manzanares et al., 2005; Rogan et al., 1997), whereas chronic stress impairs cognitive function (Starkman et al., 1992; Wolkowitz, 1994), brain plasticity (Cook, 2004; Wellman, 2001), the expression of cell adhesion molecules (Sandi and Loscertales, 1999), and

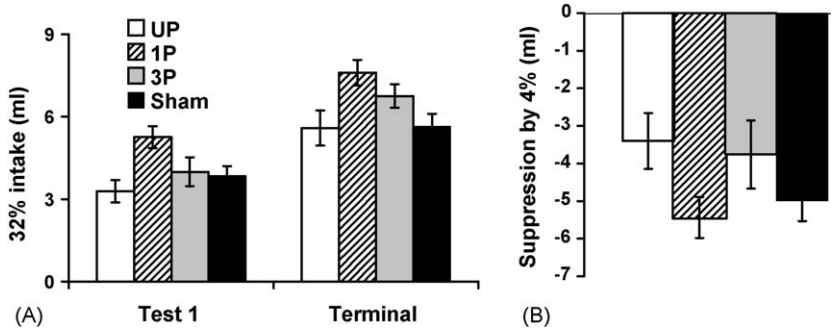

Fig. 40. Effect of pairings of subcutaneous corticosterone (B) injections and 32% sucrose solutions during training on later drinking performance in the absence of B compared to shams. Panel A shows that a single pairing B of and sucrose drinking increased intake on the first and last days of the preshift training period when animals drank 32% sucrose. Panel B shows that the suppression of intake following the shift to 4% sucrose was also amplified by a single pairing. Data adapted from Pecoraro et al. (2005a).

various in vitro neuronal correlates of learning (Foy et al., 1987; Kim and Diamond, 2002). One might also consider that retrieval deficits brought on by the GCs themselves (Roozendaal, 2003) during repeated pairings might have interfered with reconsolidation on subsequent trials (Amorapanth et al., 2000). One also cannot rule out the possibility that there was a relevant procedural difference, namely that the contexts of sucrose drinking differed for the pairing groups between training and testing, potentially resulting in differences in retrieval or proactive interference, but this has yet to be explored.

These initial results on the efficacy of GCs to influence memories for natural rewards highlight many procedural and theoretical issues of learning and performance that may interact to influence GC-dependent learning, expectancies, and reward relativity. The findings suggest that GCs influence not only appetitive performance, but appetitive memory as well, and that these memories carry over into performance over remote intervals to influence the comparison of incentive value, even after a single trial.

9.3. Expectancy, incredulity, and recovery

To examine brain structures activated by sucrose shifts that may underlie the observed alterations in somatomotor, neuroendocrine, and autonomic outputs, we compared the effects of an incentive shift on *c*-Fos expression in shifted (32-4%) and unshifted (32-32% and 4-4%) controls on the first (Shift 1) and second (Shift 2) days after exchanging the 32% sucrose solution for a 4% solution (Pecoraro and Dallman, 2005). Rats were food deprived to 85% of their free-feeding weights and drank the preshift solutions for 12 days before being shifted (or not shifted) to their postshift solutions. Half of the rats from each group were killed 1 h after Shift 1, whereas the other half were killed 1 h after Shift 2.

Two major patterns emerged. Fig. 41 shows the pattern of *c*-Fos activation in three structures, the NTS (panel A), parasubthalamic nucleus (PSTN; panel B), and the supraoptic nuclei (panel C) in the groups drinking 32% sucrose on both days compared to unshifted 4% drinkers and shifted animals.

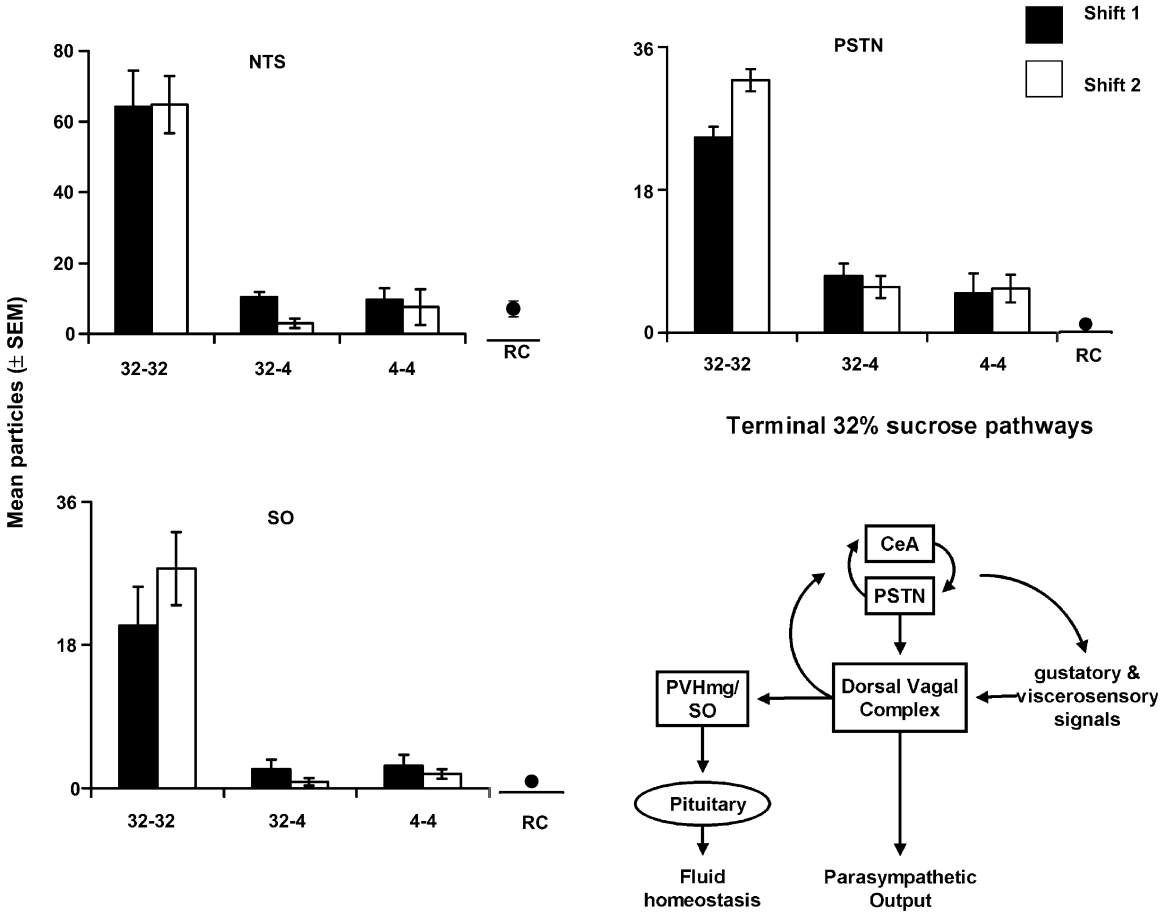

Fig. 41. *c*-Fos immunoreactivity following the first and second days after the shift from 32% to 4% sucrose in shifted animals (32-4) and two unshifted controls drinking 32% (32-32) or 4% (4-4) sucrose throughout. Freely feeding, room controls (RC) that were not given sucrose are shown for visual comparison. On both "postshift" days *c*-Fos responses occurred in rats drinking 32% sucrose in the nucleus of the solitary tract (NTS; panel A), the parasubthalamic nucleus (PSTN; panel B), and the supraoptic nuclei (SO; panel C) whereas rats shifted to 4% and unshifted 4% controls do not. The same pattern occurred in a few other brainstem areas. Bottom right: A hypothetical circuit diagram (panel D) of brain regions activated by drinking a calorically rich and hypertonic 32% sucrose solution includes minimal, primarily brainstem regions involved in palatable feeding and parasympathetic activation, such as parasubthalamic nucleus (PSTN) and the dorsal vagal complex and central nucleus of the amygdala (CeA), and paraventricular (PVHmg) and supraoptic (S0) magnocellular neurons controlling fluid homeostasis. Data adapted from Pecoraro and Dallman (2005).

Untouched, freely feeding room controls (RC) are included for reference. Essentially identical activation of *c*-Fos emerged in the dorsal motor nucleus of the vagus, PVN magnocellluar neurons, and there was partial activation in CeA. Thus, receiving an expected and calorically substantial 32% sucrose solution primarily activated a few brainstem regions involved in palatable taste (Glass et al., 1999, 2000), visceral feedback (Fox and Powley, 1992; Powley, 2000; Powley et al., 2001), fluid homeostasis (Grinevich et al., 2001; Renaud et al., 1987; Rinaman et al., 1997), and parasympathetic activation (Berthoud and Powley, 1991, 1992; Goto and Swanson, 2004; Jarvinen and Powley, 1999). Fig. 41D shows a diagram of pathways activated by the expected 32% sucrose solution.

In contrast, thwarting the expectancy of receiving 32% sucrose by reducing sucrose concentrations to 4% resulted in *c*-Fos activation in vastly different brain areas in different temporal patterns. Subjects shifted from 32% to 4% sucrose showed much more extensive, but selective activation that ranged from cortex to cerebral nuclei (striatum and pallidum) to brainstem, and this activation was almost exclusively observed on only the first, but not second shift day. Cortical areas of activation included the insular and cingulate cortices that are likely to be involved in initial taste comparison (Cechetto and Saper, 1987; Shi and Cassell, 1998) and conflict processing (Van Veen and Carter, 2002), and the fronto-temporal system, involving the orbital cortex and basolateral amygdala, which has been implicated in learning about changing reward values (Balleine and Dickinson, 1998, 2000; Schoenbaum et al., 1998, 2003). In all cases, the robust fos-like-immunoreactivity (FLI) seen on Shift 1 was absent on Shift 2, consistent with evidence for rapid (1-trial) changes in all major motor outputs mediated by an abrupt change in expectancy.

Fig. 42A–D shows that the same patterns of *c*-Fos activation occur in structures likely to be involved in motor output processing using representative regions from each major successive descending brain division, including mPFC, LS, BNST, and DMH. See Pecoraro and Dallman (2005) for a comprehensive list of structures activated for each group by day of activation. Note that in contrast to the group drinking 32% sucrose, which showed FLI in the same regions on both days, the shifted group shows FLI almost exclusively on the first day of the shift, which encompassed all major divisions of brain. Fig. 43 shows a diagram of a potential processing block that includes known connections between brain levels that are likely candidates to mediate top-down control over changes in visceromotor output. Please note that at the pre-motor output level, all three nuclei that showed significant *c*-fos activation, including the parastrial (PS), anterodorsal preoptic (ADP), and DMH, are all nodes of Thompson's and Swanson's (2003) putative HVPG (Thompson and Swanson, 2003). We have not yet determined which specific structures require GCs for their involvement in GC-dependent learning or performance issues, and as of this writing, we have only begun investigating whether, as we expect, GCs are influencing adaptive changes in motor outputs on successive shift days as animals recover to control levels of drinking.

In summary, although GCs have long been known to manage peripheral energetics, our initial studies indicate that they have equally profound effects on the brain's governance of energetics, influencing both consummatory and appetitive structure, and having effects on memorial systems, as well. Most of these effects of GCs appear to incline the animal toward greater engagement with appetitive incentives, by being permissive of, or amplifying engagement, and perhaps by amplifying the perception or responsiveness to the relative reward value of incentives. As we have repeatedly shown throughout this review, GC-dependent processes also include suites of somatomotor, neuroendocrine and autonomic out-

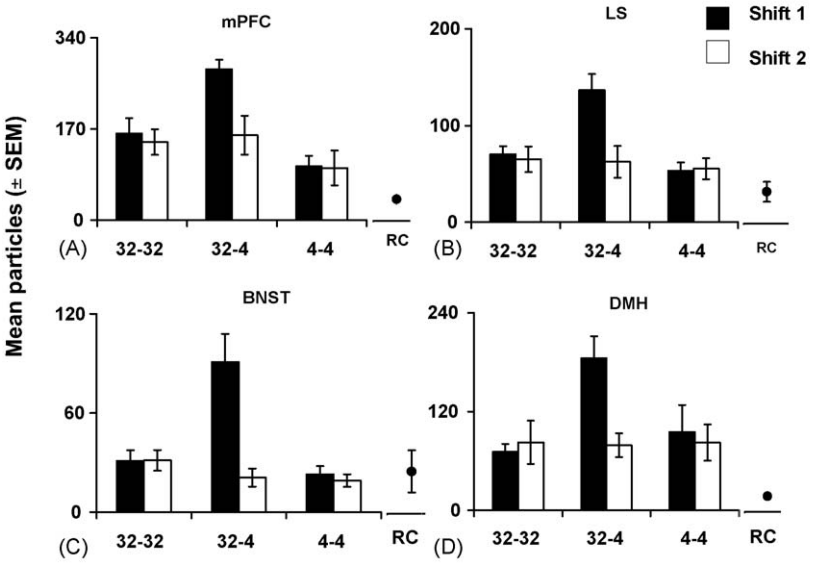

Fig. 42. A sample of successive descending brain regions involved in visceromotor output activated by shifts from 32% to 4% sucrose on only the first but not second day of the shift include the medial prefrontal cortex (panel A), lateral septum (panel B), bed nucleus of the stria terminalis (panel C), and the dorsomedial hypothalamus (panel D), indicating a one-trial learning phenomenon likely related to alterations in motor output by the second day of the shift. Data adapted from Pecoraro and Dallman (2005).

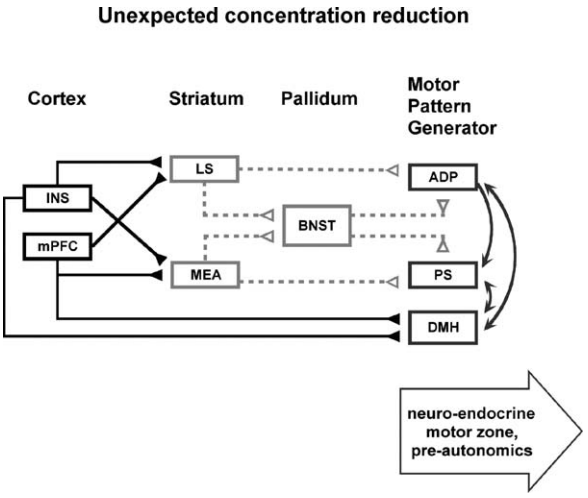

Fig. 43. A hypothetical diagram of top-down control over visceromotor adaptation following a shift from 32% to 4% sucrose based on *c*-Fos data and arranged according to Swanson's (2000) global view of triple-descending anatomy and fast transmitter function that include excitatory glutamatergic transmission from cortex and two descending inhibitory GABAergic inputs from striatum and pallidum to brainstem pattern generators. See text for details.

flows. It is very likely that the adaptive dynamics of these outflows, particularly as they are integral to incentive, and altered by memorial processes, are also to some degree dependent on elevated GCs. It is unclear to what extent such effects obtain equally under conditions of hunger, stress, or artificially elevated steroid. In some cases, such as stress-induced palatable feeding, it appears that stress-induced amplification of appetitive value can occur despite, or even because of the concurrent evocation of aversive states. Although GCs appear to promote fairly broad drive states, the generality of GC-dependent drive, or the dominance of particular drive states under any particular circumstance, will require a great deal of further study, but GC-dependent drive clearly interacts with incentive relativity effects.

10. Stress, hunger, and supernormal incentives

In the realm of natural selection, sensory biases for certain forms of stimulation have been routinely exploited by conspecifics, predators, and prey for selfish purposes, as in the cases of sexual selection for certain traits, such as the peakcock's exotic plumage, and the aggressive mimicry of firefly sexual signaling by different species for the purposes of predation (Lloyd, 1965). In a related type of exploitation, supernormal incentives are stimuli artificially exaggerated in some dimension that call forth preferred or exaggerated responding. Behavioral examples include male beetles preferring to mate with shiny orange beer bottles rather than female beetles, butterfly preferences for impossible color saturations or wing flicker rates, and the oystercatcher's preference to brood over impossibly large eggs (Gwynne and Rentz, 1983; Tinbergen, 1951).

Some types of stimulation that bypass normal sensory transduction pathways to directly stimulate the brain may also be considered supernormal incentives, including drug and electrical brain stimulation, insofar as they produce addictive behaviors. By definition, addictive behaviors involve high motivation for procurement and use, difficulty limiting voluntary use, and continued use despite negative side-effects (Association, 1994; Volkow and Li, 2005). The fact of addiction strongly implies that drug-related incentives become over-valued relative to other normal incentives. One of the most compelling lines of research relating HPA axis activation to the induction or amplification of central incentive motive states generally concerns manipulations of hunger, stress, or GCs on addictive responding. Evidence to date strongly implicates the HPA axis in the progression from the drug-naïve phenotype to the drug-dependent, drug-sensitized, compulsively self-administering, and drug-relapsing phenotype. Like many reinforcers, drugs of abuse stimulate the HPA axis, but also directly stimulate central incentive networks, without providing the usual shut-off mechanisms, such as satiety signals. The synergy between direct stimulation of central pathways by drugs and the amplification of these processes by stressors and glucocorticoids appears to result in the drug-sensitized phenotype. In the process, the drug-sensitized phenotype appears to become cross-sensitized to stressors, resulting in further mutually stimulating feedback loops, which can lead to the runaway process of ever more compulsive drug use.

10.1. Drug sensitization

10.1.1. Behavioral sensitization

Repeated administration of psychostimulants, particularly at intervals longer than a day, frequently enhances subsequent drug-induced bouts of locomotion, a process referred to as behavioral sensitization (Kuczenski and Segal, 2001; Kuczenski et al., 1997; Robinson and Becker, 1986). Findings regarding the role of adrenal steroids in this phenomenon are more variable for chronic than for acute administration, perhaps due to changing GR levels in brain over time (Shilling et al., 1996), or perhaps for procedural reasons. Rivet et al. (1989) gave rats three injections of amphetamine over 6 days, with ADX occurring between the first and second injections. Supplemental corticosterone injections were given in the evenings to otherwise normalize the rats metabolically. ADX rats showed decreases in sensitization relative to shams, and this was reversed by dexamethasone (Rivet et al., 1989).

Curiously, sensitization may be blunted when injections are given in the home cage (Badiani et al., 1995a,b,c), suggesting some potential roles of novelty, contextual cues, and perhaps stressors (Piazza et al., 1990a,b). In contrast to the Rivet study, using amphetamine in a comparison of home cage controls to rats in a novel compartment, Badiani et al. (1995a,b,c) found that both home cage and novel cage animals became sensitized, with rats in novel compartments showing greater absolute responses than rats in home cages. However, there was no effect of ADX on sensitization, per se, as both groups increased activation over days. In short, there were clear ADX-induced reductions in overall activation on three different behavioral measures, but sensitization remained evident.

In contrast to the Rivet study, only one of the Badiani et al. studies included nocturnal availability of corticosterone in the drinking water, and there were probably differences in the metabolic derangement due to ADX. Similar to Rivet et al., however, Badiani et al. provided a DA agonist to adrenally intact animals prior to ADX. Badiani et al. used an apomorphine screen in adrenally intact animals prior to ADX to test for rotational behavior following unilateral DA denervation. Potential carryover effects of the initial pairing of the DA agonists and a presumed adrenal responses seem problematic for and unequivocal demonstration of the lack of effect of GCs on sensitization, given that one-trial learning is mediated by GCs. A single training trial in rats with adrenals could have lasting consequences for the later development of sensitization, such as is seen in SIP; pretreatments with stimulants are in any case known to facilitate later sensitization (Horger et al., 1990; Piazza et al., 1989; Pierre and Vezina, 1997; Valadez and Schenk, 1994), and self-administration (Woolverton et al., 1984). Overall, with any countervailing exceptions mentioned above, there appears to be remarkably strong evidence for a role of glucocorticoids in sensitization of locomotor activity to psychostimulants (Deroche et al., 1995, 1993, 1992; Deroche-Gamonet et al., 2003; Marinelli et al., 1998b; Piazza et al., 1990a).

Administration of morphine to rodents also results in bouts of locomotor activity, but sensitization has been less studied with opiates than with psychostimulants. To test whether chronic stress potentiates morphine-induced locomotion, Stohr et al. (1999) gave intact rats daily restraint, brief handling, or repeated social stress for several days, and then gave a challenge dose of morphine several days later. Following repeated restraint (or not), saline-injected controls responded minimally, whether they were restrained or basal, whereas morphine-treated animals showed robust locomotor activation, which was significantly amplified at lower doses of morphine by prior restraint, although the differences were obliterated at the highest dose, probably by its sedating effects. Thus, only the excitatory limb of the morphine dose-response was affected by stress. Brief handling and social stress also increased locomotor responses to morphine. Similarly, both repeated DEX administration and implanted corticosterone pellets also increased locomotor responses to morphine injection (Stohr et al., 1999). When morphine is injected systemically or centrally into VTA, ADX blunts the locomotor response and this is reversed by stress levels of corticosterone (Marinelli et al., 1994). Thus, as with psychostimulants, GCs appear to promote behavioral sensitization to opioids.

10.1.2. Neuroendocrine sensitization and suppression: post-traumatic stress disorder?

The nexus of stress, opioids, energy balance, addiction, and HPA axis function is profound and complex. We have previously argued that cyclic, escalating morphine administration is itself a stressor. Remarkable changes in energy balance and HPA axis function occur during the course of intermittent administration and withdrawal from morphine. Unlike chronic constant morphine exposure via implanted pellets, which does not activate the rat HPA axis (Eisenberg, 1985; Laorden et al., 2000; Milanes et al., 1997, 1993; Sarnyai et al., 2001), twice-daily injections of morphine at 12-h intervals in escalating doses (10–100 mg/kg s.c.) appear to serve as a potent chronic stressor (Houshyar et al., 2001, 2003, 2004). During the course of a 4-day morphine regimen, body weight gain is blocked, and chow intake and caloric efficiency are reduced. Twelve h after the final morphine injection, morphine-treated rats have markedly elevated ACTH and corticosterone responses to restraint stress relative to saline-injected controls (Houshyar et al., 2003). Morphine treated rats also show increased adrenal weight 12 h after the final injection. About 36 h after the last injection, morphine-treated animals undergo a sudden, catastrophic crash in body weight and caloric efficiency that lasts for about 36 h. This is followed by a rebound in body weight gain, feeding, and caloric efficiency.

The panels in Fig. 44 show metabolic and HPA-related phenomena in rats that received an 8-day escalating morphine regimen followed by an 8-day withdrawal period. The vertical dotted line running through the left panels marks the end of morphine treatment. During treatment, body weight gain stops (top, left panel), chow intake (mid, left panel) is reduced, and caloric efficiency (bottom, left panel) decreases. Following the energetic crash in morphine-treated animals at 2 days, chow intake recovers, and growth and caloric efficiency rebound to values above those of the saline-injected controls.

Interestingly, the HPA responses of morphine-treated animals tested a day before the crash (12 h after the last injection) and following the recovery (8 days after the last injection) differ remarkably, and appear to correspond to the metabolic stages of withdrawal and rebound recovery. The right hand panels of Fig. 44 show ACTH (top panels) and corticosterone (B; bottom panels) responses to 30 min restraint at 12 h and 8 days after the final morphine injection. At 12 h, the morphine treated rats hyper-respond with ACTH to restraint, compared to controls, whereas at 8 days, they are relatively hypo-responsive. Corticosterone also hyper-responds at 12 h in morphine-treated rats, and is not different from saline-injected controls at 8 days. The main thing to note is the reversal of central HPA drive from hyper- to hypo-responsiveness.

Based on the ACTH and caloric efficiency data, it might be surmised that a negative energy budget, probably resulting from sympathetic activation during withdrawal, resulted in the hyper-responsive central drive of the HPA axis, whereas the rebound in energy efficiency to levels above control may have given rise to central hypo-responsiveness. At 12 h, CRF mRNA in PVN is elevated in morphine-treated compared to control rats, consistent with this view. However, stress-induced CRF mRNA remained facilitated at 8 days in morphine treated rats, marking a dissociation between central drive and plasma ACTH, and suggesting some intervening inhibition, perhaps through feedback at the level of median eminence or pituitary. These profiles bear some resemblance to those in humans with post-traumatic stress disorder (PTSD).

Humans diagnosed with PTSD are prone to substance abuse, including opioid dependence (Clark et al., 2001). In addition,

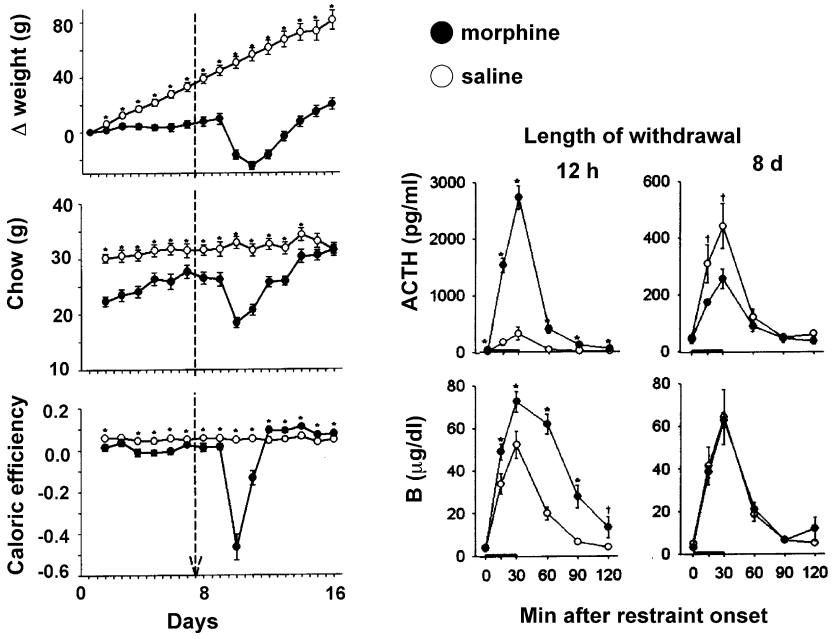

Fig. 44. Effects of twice daily, intermittent and escalating morphine injections on metabolic parameters and HPA function. Panels on the left show changes in body weight (top panel), chow intake (middle panel) and caloric efficiency in animals treated with morphine or vehicle. The dotted line drawn through the panels indicates the end of morphine treatment. The saline treated animals showed steady growth, chow intake, and caloric efficiency. Morphine treated animals do not gain weight during morphine treatment, and at about 36 h after withdrawal, exhibit a profound metabolic crash, involving body weight, chow intake, and caloric efficiency. Shortly after the crash, these variables rebound. HPA responses to restraint stress (right hand panels) appear to correspond to these differing post-withdrawal metabolic modes. At 12 h of withdrawal, ACTH and B responses hyper-respond in morphine treated animals, whereas at 8 days of withdrawal, central drive becomes relatively blunted, and adrenal sensitivity appears to increase. Data adapted from Houshyar et al. (2004).

humans with PTSD appear to have a hyperactive central CRF system judged from cerebrospinal fluid measurements, but are stress hypo-responsive, and have super-suppression of the HPA axis after dexamethasone treatment (Jacobsen et al., 2001). Thus, it appears that intermittent morphine treatment is a chronic stressor, and can result in PTSD-like symptoms. At face value, intermittent administration of morphine in rats appears to more closely model human drug usage than chronic implants via pellets, and may result in daily cycles of withdrawal that recruit central stress networks. Energy budgets may be involved in both the HPA axis hyper- and hypo-responsive stages of withdrawal. However, it appears that with some severe stressors, such as intermittent morphine, central stress networks may remain hyperactive even after downstream elements of the HPA axis fall into hypo-responsiveness.

10.2. Self-administration of super-normal stimuli

10.2.1. GC self-administration

In direct support of the view that GCs engage incentive pathways is the finding that corticosterone itself is self-administered intravenously by rats to the point of raising plasma concentrations to stress levels (Piazza et al., 1993). In that study, animals were freely feeding, and thus free of metabolic need, and the response was not merely increased general activation, because the instrumental response (nose pokes) was discriminated on active and inactive nose-poke holes. Despite the potential negative side effects of inducing stress levels of GC in plasma, such as potential anxiety or edginess noted with GC treatment (Erickson et al., 2003), euphoric effects of GCs have been reported frequently by humans (Doerr et al., 1979; Goodwin et al., 1992; Hall et al., 1979; Klein, 1992; Ling et al., 1981; Mendelson et al., 2002; Plihal et al., 1996; Swinburn et al., 1988). Moreover, GCs are self-administered, and chronic treatment may result in dependence, evident as withdrawal symptoms upon cessation of treatment (Hochberg et al., 2003; Swinburn et al., 1988).

Correlates of GC self-administration indicate shared substrates to those involved in self-administration of drugs of abuse. When rats were empirically divided into sensation seekers or non-seekers (high responders and low responders), their preferred patterns of corticosterone self-administration partitioned as well. High responders tended to have high endogenous corticosterone, high DA responses in NACC to corticosterone, and were high novelty seekers. Low responders had low endogenous corticosterone, lower accumbal DA responses to corticosterone, and were low novelty seekers. The high-responders showed greatest self-administration of low doses of corticosterone, whereas the low-responders showed greatest sensitivity to higher doses of corticosterone (Piazza et al., 1993).

10.2.2. Self-administration of drugs

Stress and food restriction both increase drug self-administration, and self-administration tends to co-vary with circulating GCs (Cabeza de Vaca and Carr, 1998; Carr, 2002; Carroll et al., 1979, 1984; Marinelli et al., 1998a; Piazza et al., 1996a; Piazza and Le Moal, 1998). Stressors that increase self-

administration have varied from tail pinch (Piazza et al., 1990b), footshock (Goeders and Guerin, 1994, 1996a,b), and isolation (Schenk et al., 1987), social stress (Maccari et al., 1991), to aggression (Haney et al., 1995; Tidey and Miczek, 1997). For an example relevant to humans, Maccari et al. (1991) housed rats in colonies with stable or unstable membership, and found that membership in unstable colonies gave rise to prolonged corticosteroid responses and increased propensities to self-administer amphetamine (Maccari et al., 1991). Studies have also shown that the predictability of stress is relevant. Compared to controllable stress (escapable footshocks), uncontrollable stress (footshocks in yoked rats) lowered thresholds for cocaine self-administration, and there also appeared to be a correlation between plasma levels of GCs and the propensity to self-administer (Goeders and Guerin, 1994). Such findings are consistent with long-held views concerning the role of social-psychological factors in HPA axis function (Levine, 2000; Mason, 1968, 1971).

ADX completely blocked the acquisition of cocaine self-administration in naïve rats, while leaving food acquisition intact (Deroche et al., 1997; Goeders and Guerin, 1996a), whereas inhibition of steroid synthesis with metyrapone or ketoconazole both retarded self-administration in experienced rats (Goeders, 1997), suggesting that there are effects of GCs on both acquisition and performance. When exogenous corticosterone is administered to rats, it lowers thresholds for self-administration of cocaine (Goeders and Guerin, 1996b).

Similar to overt, exogenous stressors, food restriction (Carroll and Lac, 1993; Carroll et al., 1984; De Vry et al., 1989), a history of food restriction (Specker et al., 1994) or GC administration also increase the rates of cocaine self-administration, some of which can be reversed by ADX (Deroche et al., 1993) and metyrapone (Marinelli et al., 1996). In one study (Campbell and Carroll, 2001), freely feeding and food-restricted rats were employed in an autoshaping task for acquiring either intravenous cocaine or food pellets. For cocaine self-administrators, free-feeding severely blunted acquisition, reducing the number of animals achieving criterion (40%) and increasing the number of days to criterion. In addition, ketoconazole treatment was without effect in freely feeding rats. In contrast, 100% of the food-restricted animals receiving vehicle acquired criterion, whereas only about 80% of the ketoconazole treated, food-restricted animals did. In addition, keotconazole severely retarded the rate of acquisition. These data are unsurprisingly consistent with the powerful positive effects of corticosterone on motivation and/or learning that are reversible by the inhibition of corticosterone secretion.

Surprisingly, the food-restricted, food-rewarded rats appeared to acquire the task at least as rapidly as the food-restricted, drug-reinforced animals, with a slight, non-signifcant effect of ketoconazole. The main difference between drug- and food-reinforced animals appeared to be the fact that the food-reinforced animals may have received extra food in the form of 45 mg pellets. Food restriction was achieved by giving a fixed percentage of the chow freely feeding rats consumed. Thus, the food-reinforced animals received up to 33% more chow than the drug-reinforced rats. In addition, the drug-reinforced animals may have actually lost more weight than intended due to thermogenic effects of the drug. Actual body weights were not reported. Finally, within session, moment-to-moment variations of corticosterone are likely to be different under the drug- and food-reinforced conditions in the presence of food-restriction, and rapid, non-genomic effects of glucocorticoids on DA function have been observed (Figlewicz, 1999b; Mittleman et al., 1992).

As with psychostimulants, GCs also facilitate opioid self-administration. Hypophysectomy results in decreased oral intake of morphine, which can be restored to normal by replacement with ACTH or corticosterone (Van Ree and Niesink, 1978). The increase in heroin self-administration that is seen with food restriction is also reversible by inhibition of steroid synthesis (Carroll et al., 2001). Restraint stress increases the locomotor response to morphine, but only in animals with intact adrenals (Deroche et al., 1992). Isolation stress also increases locomotor activity after morphine, and the response is blocked by ADX (Deroche et al., 1994).

A good deal of evidence also implicates a role for GCs in alcohol drinking. High basal levels of corticosterone are associated with alcohol intake in rats (Prasad and Prasad, 1995). Interfering with GCs also generally impairs alcohol drinking. Rats exposed to ethanol inhalation chambers for 3 weeks subsequently develop a preference for alcohol drinking, but only if adrenally intact (Lamblin and De Witte, 1996). In contrast, making rats dependent by forcing alcohol through a single drinking tube (10% EtOH), failed to result in differences between intact and ADX rats (Lamblin and De Witte, 1996). Since the two types of alcohol pre-exposures were not equally forced, the first consisting of a non-contingent exposure and the second one consisting of a forced operant, aversive qualities may have been associated with the instrumental response in training that carried over to later testing, perhaps similar to the potential aversiveness of forced palatable feeding. The suppression of corticosterone by metyrapone reduces consumption of alcohol (Fahlke et al., 1994). Alcohol intake increases under food restriction in intact, but not ADX rats (Hansen et al., 1995). The effect appears to involve occupancy of GRs, because intact animals given cyanoketone, which blocks stress-induced but not basal corticosterone secretion (Akana and Dallman, 1992), also largely prevented the hunger-induced increases in intake (Hansen et al., 1995). Infusions of GCs i.c.v. (Fahlke et al., 1996), or GCs implanted into ventral striatum, but not hippocampus, septum or thalamus (Fahlke and Hansen, 1999), also increases alcohol intake compared to controls. There is at least one report that administration of a GR blockade reduces alcohol intake (Koenig and Olive, 2004).

10.2.3. Intracranial self-stimulation

The robust self-administration of electrical pulses via electrodes placed directly in brain (intracranial self-stimulation, or ICSS) has been used as prima facie evidence for the induction of central motive states (Bindra and Campbell, 1967; Olds, 1976; Olds and Milner, 1954; Olds and Fobes, 1981; Trowill et al., 1969). The exact nature of the ICSS-stimulated central motive state, e.g., its persistence, specificity, and

whether it results from effects on performance or learning continue to be debated, and may depend on the precise area stimulated, drive state, and the availability of incentive stimuli. Nevertheless, self-stimulation of a number of brain regions that are believed to be involved in "reward circuits," e.g., mesolimbic-prefrontal dopamine pathways, particularly the medial forebrain bundle, can clearly induce very high levels of responding that may exclude other normally rewarding activities, such as eating. In addition, like many rewarding events (Goeders, 1997; Merali et al., 1998; Redgate et al., 1974; Szechtman et al., 1974), ICSS acutely increases sympathetic and HPA axis outflows (Burgess et al., 1993; Terry and Martin, 1978). Interestingly, whereas non-contingent VTA stimulation resulted in increased sympathetic outflow, only response-contingent stimulation resulted in increased HPA output (Burgess et al., 1993). Like other reward paradigms, ICSS is sensitive to endogenous factors that indicate altered energy balance or stress.

ICSS has been shown in many instances to be amplified by weight loss. For example, using electrodes placed directly in the LH, it has been shown that the amount of self-stimulation increases with weight loss, particularly when the electrode was placed in perifornical LH (Blundell and Herberg, 1968; Cabeza De Vaca et al., 1998; Shizgal et al., 2001). Thresholds for supporting self-stimulation, e.g., the necessary current intensity, are reduced with chronic administration of high doses of corticosterone in rats with intact adrenals (Barr et al., 2000). However, it is unclear what caused the threshold reduction. First, the reduction of thresholds was not apparent until around the 6th day of treatment, at about the time the animals had begun to show significant weight loss as a consequence of steroid treatment. Second, testing was carried out 3–6 h following injections of supraphysiological doses of corticosterone. Third, because the animals were pre-trained intact, learning during the initial baseline/acquisition period may have vitiated any potential differences that might have been seen in early testing. Fourth, it is not clear what effect supraphysiological doses of corticosterone given 3–6 h before testing might have on retrieval of this previously acquired task (de Quervain et al., 1998; Roozendaal, 2002, 2003; Roozendaal et al., 2003, 2001). What seemed most evident was the correlation of decreasing thresholds with weight loss, and thus the effect may have been indirect.

Another study found no effect of ADX on cocaine-amplified responding for lateral hypothalamic self-stimulation (Abrahamsen and Carr, 1997). However, training was again initially conducted in rats with intact adrenals that had already acquired stable responding, suggesting only that the loss of corticosterone did not impair performance of a pre-learned response. This result may be similar to the effects of ADX in SIP polydipsia, when acquisition of SIP occurs prior to ADX animals maintain pre-ADX levels of drinking without further sensitization of the response. A later study did indicate an increase in thresholds for self-stimulation in mPFC following ADX (Carr and Abrahamsen, 1998), a trend that suggested a loss of performance effects through the loss of corticosterone.

10.3. Stressors, relapse, and the runaway brain

10.3.1. Reinstatement

Following a period of abstinence from drug use, former users frequently relapse. Relapse has been attributed to the need to escape from aversive withdrawal symptoms (Akaoka and Aston-Jones, 1991; Koob and Le Moal, 1997, 2001) and the stimulation of incentive or memory systems (Berridge and Robinson, 1998; Bouton, 2000; Ikemoto and Panksepp, 1999; Robinson and Berridge, 2000; Shaham et al., 2002; Stewart et al., 1984). Escape from aversive withdrawal symptoms has been associated with an opponent process view of motivation (Poulos et al., 1981; Solomon and Corbit, 1973, 1974), according to which acute drug use incites primary physiological processes followed by secondary counter-regulatory processes aimed at restoring balance to the system, and contributing to drug-tolerance (but, see this qualifying review Aston-Jones and Harris, 2004). One opponent process to the analgesic effects of heroin is increased sensitivity to pain in environments associated with the drug, suggesting that some opponent processes can be conditioned. It has been argued that arbitrary stimuli, such as the sight of the drug-taking paraphernalia, even in the absence of ongoing drug use, can evoke anticipatory opponent responses to drugs, such as increased pain sensitivity, or dysphoria, thus leading to an increased desire to escape through drug use. As drug taking escalates to counter the opponent processes, the opponent processes also increase (Ehrman et al., 1992; Eikelboom and Stewart, 1981, 1982; Hinson and Siegel, 1983; O'Brien et al., 1992a,b,c; Stewart et al., 1984; Wikler, 1973a,b). By contrast, the incentive view of relapse has been referred to as a craving or proponent model, in which stimuli associated with drugs (or drugs themselves) evoke drug-like states, such as pleasure or wanting, that, when primed, serve to engender further seeking (Robinson and Berridge, 1993; Stewart et al., 1984; Wise and Bozarth, 1987).

Regardless of the exact merits of aversive or appetitive emphases in each of the above views (Self and Nestler, 1998), both significantly interact with our working model. Activation of the HPA axis through hunger, stress, or drug-taking itself should enhance activity in both aversive and appetitive networks during drug taking, improve consolidation of drug-related cues, and incite both aversive and appetitive motivation during abstinence, whereas increased metabolic feedback should reduce withdrawal symptoms and decrease incentive motivation by reducing activity in central motivational networks. The HPA axis is responsive to drugs acutely, and frequently becomes dysregulated during chronic use. Upon acute withdrawal, HPA axis activation is seen with nearly all drugs of abuse (Kreek and Koob, 1998), and dysregulation can persist well into abstinence phases (Stimmel and Kreek, 2000). In humans, the chronic use of heroin is associated with suppressed HPA responses, whereas hyperactivity ensues during acute withdrawal in an opiate-reversible fashion.

Reinstatement refers to a procedure applied to study relapse involving the acquisition, extinction, and resumption of responding following extinction. It occurs as a consequence of non-contingent exposure to a stimulus, such as a discrete cue,

learning context, unconditioned stimulus, the passage of time, or some combination thereof, that calls forth the previously acquired behavior, and presumably the underlying central motive states (Bouton, 2002; Bouton and Bolles, 1979; de Wit and Stewart, 1981; Krank, 2003; Stewart, 2004; Stretch et al., 1971).[3] For example, a rat may be trained to press a lever for drug infusions. After acquisition, lever pressing is not reinforced. Once lever pressing extinguishes, the animal is exposed to a stressor, a former cue, or a priming dose of the drug, and then begins to press the lever again without any further lever pressing-contingent reward.

Stressful stimuli appear to be powerful drug reinstatement stimuli. Footshock (McFarland et al., 2004), food deprivation (Carroll, 1985; Shalev et al., 2000, 2003), and the central administration of CRF (Erb et al., 2001) all produce reinstatement of instrumental responding for drugs. It is not always clear if the reinstatement occurs because priming stimuli produce HPA axis activation, which incites a state-dependent memory, or whether HPA axis activation incites a central motive state directly which then serves as a retrieval cue, or whether prior HPA axis activation has augmented memorial systems, and its current activation is no longer required, but GCs are likely to be involved in many cases at some level.

10.3.2. Cocaine reinstatement

Footshock or cocaine reinstates cocaine seeking after extinction, and then again, 4–6 weeks later (Erb et al., 2001). Saline controls showed little spontaneous reinstatement, whereas footshock worked best, followed by cocaine. The stressor was a more potent reinstatement manipulation than the drug. Mantsch and Goeders (1999) found that ketoconazole did not affect cocaine-primed reinstatement, but did prevent cocaine-cued reinstatement (Mantsch and Goeders, 1999), suggesting a positive effect of the HPA axis on the retrieval of discriminative stimuli. However, Deroche et al. (1997) found that ADX impaired cocaine reinstatement, and that the impairment was dose-dependently remediated by corticosterone replacement (Deroche et al., 1997).

Cocaine reinstatement resulting from acute (21 h) food deprivation was also attenuated by ADX. The attenuation due to the loss of corticosterone was not reversed by low corticosterone replacement pellets, but was completely reversed when the pelleted delivery was supplemented by a 4 h period of additional access to corticosterone dissolved in the drinking water, which was reported to result in significantly higher plasma corticosterone concentrations, presumably resulting in GR occupation (Shalev et al., 2003). Curiously, corticosterone supplementation occurred in the early light cycle, whereas training, extinction, and testing were conducted in the dark phase, suggesting that GR-occupancy was not required at the time of testing, but rather maintained other processes that are permissive to reinstatement.

10.3.3. Opioid reinstatement

Footshock (Erb et al., 1996), CRF injection, and morphine priming are potent reinstatement manipulations for opioid self-administration (Shaham et al., 1997). Post-training ADX exacerbated footshock-induced reinstatement without affecting morphine priming, suggesting a puzzling effect of ADX. First, the animals were trained intact, when corticosterone could have positively modulated memory consolidation. Once acquired, the direct action of drug on proponent systems again could render moot any further modulating actions of GCs. As for the enhanced perfomance effects to footshock, energetic derangement from ADX could disinhibit brainstem vigilance/arousal systems leading to a greater need to escape aversive stimulation. In the same study, the inhibition of corticosterone via metyrapone not only failed to prevent reinstatement, it also exacerbated it (Erb et al., 1996). One must also ask whether some special relationship exists between metyrapone and opioidergic tone. In humans, former heroin users maintained on methadone exhibited withdrawal symptoms when given metyrapone (Kennedy et al., 1991). While it is not clear that such alternative hypotheses would hold up to scrutiny, the numerous routes of action of GCs on brain and metabolism suggest that they must be entertained.

10.3.4. Alcohol relapse

An advantage of alcohol research is that alcohol is legal, and can be studied relatively freely in humans, who can provide personal reports. Relapse is extraordinarily prevalent in alcoholism (Breese et al., 2005a; Hunt et al., 1971; Miller and Sanchez-Craig, 1996), and periods of abstinence are most frequently characterized by high anxiety (Kushner et al., 2000, 1994, 2001; Willinger et al., 2002), but sometimes depression or negative affect occur, as well. Stress is frequently reported to increase craving, and is the most commonly reported cause of relapse. The initiation, maintenance, progression, abstinence and relapse to alcohol strongly resemble the opponent process model (Koob and Le Moal, 1997, 2001). Similar to human alcoholic progression, alcohol drinking in rats can be significantly sensitized by repeated periods of usage and deprivation (McKinzie et al., 1998; Rodd et al., 2003), as deprivation further enhances anxiety-like behaviors, which do not occur when alcohol is continuously available (Overstreet et al., 2002), suggesting that periods of abstinence-induced stress sensitizes or ''kindles'' the response (Breese et al., 2005b; Duka et al., 2002). CRF content is elevated in BNST during withdrawal (Olive et al., 2002), and 5HT agonists, CRF receptor antagonists, and fluazenil reduce the anxiety symptoms resulting from repeated withdrawal (Breese et al., 2004; Knapp et al., 2004; Overstreet et al., 2004, 2003). CRF antagonists dose-dependently attenuate alcohol reinstatement induced by footshock in rats (Le et al., 2000). Cued reinstatement of alcohol drinking in rats can also be attenuated by naltrexone, but the attenuation is blunted if the animal has

[3] Technically, this definition combines at least four procedural variants, including reinstatement, renewal, spontaneous recovery, and reacquisition, that have been dealt with separately by learning theorists. Our current usage is based on the proposition that each phenomenon commonly includes priming stimuli that serve as reminders of the former reinforcement context. See Bouton (2002) for a proper exposition.

experienced multiple withdrawals (Ciccocioppo et al., 2003b). The effects of stressors and drug cues appear to be additive in CRF and opioid pathways. For example, alcohol associated cue-induced reinstatement is reversible by naltrexone, whereas footshock-induced reinstatement is reversed by CRF antagonists. If both associative cues and the stressor are present simultaneously, both antagonists are required to fully reverse reinstatement (Liu and Weiss, 2002). This finding, in particular, provides evidence that both proponent and opponent processes can contribute simultaneously to resinstatement.

10.3.5. Face-off: normal versus super-normal incentives

We mentioned earlier that drug abuse implies that normal rewards become devalued relative to super-normal rewards, such as drugs. Direct evidence for this claim comes from anticipatory contrast studies. The anticipatory contrast procedure involves the pairing of two rewards, such as two concentrations of palatable saccharin or sucrose, or some combination thereof, wherein the preferred solution is the second in the pairing and the interstimulus interval varies from, say, 0 to 30 min. For example, a rat may be presented with a saccaharin solution for 5 min, a 5-min interstimulus interval ensues, and then a 32% sucrose solution is presented for 5 min. Over days, as the saccharin solution is increasingly associated with, and predictive of, the second, preferred sucrose solution, the rat begins inhibiting intake of the first, less-preferred, but still palatable saccharin solution relative to controls drinking successive saccharin solutions. It is thought that the first solution acts a conditioned stimulus for the second solution, which in comparison to the first is better, and hence suppresses intake of the less-liked solution by anticipatory comparison.

A similar suppression of the first solution occurs when the first solution is paired with drugs, such as cocaine (Gomez et al., 2000) or opiates (Gomez et al., 2000; Grigson et al., 2000). Although it was once thought that this suppression was caused by a taste aversion, this view began to lose tenability when it was shown that, unlike lithium chloride-induced taste aversions, suppression produced by pairing sweet solutions with drugs did not produce orofacial movements characteristic of rejection (Grill and Norgren, 1978; Parker, 1996, 2003). In addition, whereas the suppressive effects of drug pairings are lost after lesions of the gustatory thalamus, lithium chloride-induced taste aversions are not affected (Grigson and Twining, 2002; Reilly and Trifunovic, 1999). The suppression of commerce with a normally rewarding incentive by a drug context appears to be a case of anticipatory contrast as occurs with successive sweet solutions, thus showing contrast between normal and super-normal incentives. The degree of anticipatory suppression in the drug context also positively correlates with plasma GCs (Gomez et al., 2000), again suggesting amplification of this contrast by GCs.

10.3.6. The runaway brain

The evaluation of experience clearly involves strong components of relativity. As a complex input/output device having profound developmental transitions and memorial capacities, the brain never returns to its original state after experience, but the degree and permanence of the brain's departure from its previous state can be indexed. GCs amplify incentive relativity effects in terms of ongoing performance and memorial structure. Supernormal appetive or aversive experiences, such as substance abuse or severe trauma, can drive the brain to operate beyond its typical boundaries of control, in part due to HPA activation, which promotes and helps memorialize hypertrophic regulation of central stress and incentive networks. A near collision on the freeway is unlikely to make one fearful of driving, whereas combat experience, rape, or torture, could permanently alter one's general assessment of safety. A delicious meal will not significantly disincline one to other lesser foods in the near future when hunger arises again, whereas smoking crack cocaine once might cause permanent hyperplastic changes in prefrontal cortical neurons that prevent one from further fully appreciating and engaging natural rewards (Robinson et al., 2001; Robinson and Kolb, 1997, 1999a,b). In addition, some experiences with trauma or drugs can result in profound and long-term alterations in central stress networks and HPA function, having features in common with the post-traumatic stress syndrome.

11. Clinical side-effects of glucocorticoid excess

Although there are many unanswered questions, the integrative view of GC function that is beginning to emerge suggests significant clinical ramifications of the stress-induced phenotype. Not only do GCs engineer the phenotype for purely adaptive peripheral metabolic and central incentive, memorial and motoric structure, as seen in the case of incentive systems runaway, elevated GCs can also have adverse clinical side-effects.

11.1. Clinical disorders exhibiting excess glucocorticoids

11.1.1. Cushing's syndrome

Cushing's syndrome occurs during chronic exposure to excess GCs. The root causes of this excess can be exogenous GC treament, ACTH-dependent (80–85% of cases), and usually caused by a pituitary corticotroph adrenoma although rare extra-pituitary tumors that secrete either ACTH or CRF have been reported. Alternatively, Cushing's syndrome can be caused by ACTH-independent abnormalities (15–20% of cases) stemming from excess cortisol secretion due to unilateral adrenocortical tumors or by bilateral adrenal hyperplasia (Arnaldi et al., 2003).

11.1.2. Obesity

Obesity is not a homogeneous condition; rather it is likely to represent the end point of a number of metabolic disturbances. Location of the excess body fat appears to be critical in determining the adverse metabolic outcome. In human obesity, basal plasma cortisol levels are not consistently elevated (Asensio et al., 2004). However, total cortisol production rate has been reported to be somewhat enhanced in both obese men and women in some studies (Andrew et al., 1998; Stewart et al., 1999) and the HPA axis response to acute stressors is often

enhanced (Hautanen and Adlercreutz, 1993). However, in rodent obesity, GCs appear to be criticial. For example, adrenalectomy normalizes many behavioral and metabolic parameters of the genetically obese *ob*/*ob* and *db*/*db* mice (Shimomura et al., 1987). Pre-receptor steroid metabolism is enhanced in cohorts of obese subjects. Specifically, the expression of 11β-HSD1 is increased (Bujalska et al., 1997). This enzyme generates active cortisol from inactive cortisone, essentially increasing local tissue GC levels. Studies in mice have emphasized the importance of pre-receptor steroid metabolism in the development of obesity. Transgenic overexpression of 11β-HSD1 results in obesity and insulin resistance (Masuzaki et al., 2001). Conversely, transgenic overexpression of 11β-HSD2 specifically in adipocytes, which would act to reduce GC action in the tissue, produced mice resistant to diet-induced obesity and the consequent insulin resistance (Kershaw et al., 2005). Therefore, enhanced GC action, whether it is due to an increase in circulating GC levels or due to altered pre-GR steroid metabolism, occurs in conditions of visceral obesity.

11.1.3. Anorexia nervosa

Anorexia nervosa is a severe eating disorder that has a high incidence of mortality. A plethora of studies has consistently reported that patients with anorexia nervosa display elevated cortisol levels despite exhibiting a markedly reduced ACTH response to CRH challenge (Licinio et al., 1996). The hypercortisolemia can be restored by gradual restoration of body weight, with the plasma cortisol response to CRH challenge recovering faster than the ACTH response (Gold et al., 1986). The consequence of the hypercortisolemia, in concert with other hormonal changes—notably a reduction in growth hormone, act to promote remodeling of both body fat and body mass (Misra et al., 2005).

11.2. Adverse clinical manifestations of glucocorticoid excess

The clinical manifestations of GC excess are considerable and varied. For example, patients with Cushing's syndrome exhibit central obesity and hypertension together with many other metabolic and neuropsychological disturbances. These include glucose intolerance, depression, muscle atrophy and thinned skin (Orth, 1995). Cushing's syndrome represents extreme GC excess and can be confused with the metabolic syndrome, also known as syndrome X. The World Health Organisation's working definition of the metabolic syndrome is glucose intolerance or diabetes mellitus and/or insulin resistance together with two or more of the following: raised arterial pressure, raised plasma triglycerides and/or low high density lipoprotein-cholesterol, visceral obesity and/or high BMI and microalbuminuria. GCs have been implicated in the pathogenesis of the metabolic syndrome as each of the metabolic risk factors can be attributed to GC excess (Rosmond, 2005).

While many pathological conditions exhibit excessive endogenous GC production, it is also worth noting that exogenous GCs are used extensively in clinical practice. This is largely due to their desirable anti-inflammatory and immunosuppressive actions, however several adverse reactions can occur. These include infection, osteoporosis, obesity, skin thinning, glaucoma, cataract formation and the development of neuropsychiatric disorders (Buttgereit et al., 2005). Thus, balancing the positive and negative reactions is of the utmost importance to prevent GC-induced pathologies from arising.

11.2.1. Insulin resistance and type 2 diabetes

Insulin resistance refers to an impaired effect of insulin in target tissues, notably the liver, adipose tissue and muscle, consequently resulting in altered carbohydrate metabolism. Type 2 diabetes comes about when there is a combination of insulin resistance and insulin deficiency (Matthaei et al., 2000). The etiology of insulin resistance is not clear, however glucocorticoids appear to be important in this regard. GCs can create a state of insulin resistance by antagonizing the actions of insulin. In adipose tissue, insulin resistance is produced by GCs by reducing insulin stimulated glucose transporter 4 translocation to the plasma membrane (Carter-Su and Okamoto, 1987; Oda et al., 1995). This would consequently reduce glucose uptake and storage as triglycerides. This occurs in the absence of any alteration in insulin binding to the adipocte (Olefsky, 1975). Similarly, glucose uptake into muscle is perturbed by GC action by dysregulation of glucose transporter 4 translocation (Oda et al., 1995). In the liver, GCs increase phosphoenol pyruvate carboxykinase and glucose-6-phosphotase levels, the rate limiting enzymes of gluconeogenesis, resulting in an increase in hepatic glucose output (Argaud et al., 1996; Friedman et al., 1993). Consequently, a greater amount of insulin is thus required to stunt glucose production (Groop et al., 1993). GCs can also affect the release of insulin from pancreatic β-cells in experimental animals and reduce the frequency of insulin release in fasted humans (Hollingdal et al., 2002; Lambillotte et al., 1997). The glucose-associated aberrations of type II diabetes were increased with increasing cortisol in a cross-sectional study of type II diabetics (Oltmanns et al., 2006). When cortisol values were divided into tertiles, those in the upper tertile had higher glycosylated hemoglobin, systolic and diastolic pressure, plasma insulin and glucose, and, after accounting for marked glucosurea, abdominal obesity. Plasma lipid concentrations were not associated with the tertiles in cortisol (Oltmanns et al., 2006). Recently, a prospective study of the number of episodes of work related stress on the incidence of the metabolic syndrome, which is frequently prodromal for type 2 diabetes, showed a positive dose-response relationship, and provides a biologically plausible link between psychosocial stressors and the metabolic syndrome (Chandola et al., 2006). Hence, chronic stressors and GC excess can ultimately be shown to result in the development of type 2 diabetes.

11.2.2. Adipose tissue dysfunction and distribution

Intimately associated with the development of insulin resistance is dysregulation of adipose tissue function. GCs play regulatory roles in the differentiation, function and distribution of adipose tissue. GCs are critical in the differentiation of immature preadipocytes into mature, lipid storing adipocytes in

vitro (Rosen and Spiegelman, 2000). GCs also positively influence the gene expression of a number of key genes, including leptin, lipoprotein lipase, and hormone sensitive lipase (Wang, 2005). Cortisol acutely activates lipolysis in adipose tissue (Bjorntorp, 1996), however studies have also shown inhibition of catecholamine-stimulated lipolysis (Lafontan and Berlan, 1993; Ottosson et al., 2000). GCs also modulate the release of endocrine products from the tissue, notably increasing leptin (De Vos et al., 1995) and decreasing proinflammatory cytokines IL-6 and TNFα (Fried et al., 1998; Zhang et al., 2001) release. The increased release of leptin could provide a false signal to the brain as to the amount of energy stored. TNFα and IL-6 have been reported to be linked to the development of insulin resistance (Kern et al., 2004), IL-6 has been strongly correlated to insulin resistance, type 2 diabetes and is overexpressed in obese patients (Bastard et al., 2000). TNFα has not been consistently found to be elevated in human obesity (Bastard et al., 2000). Lipoprotein lipase activity is critical in determining adipocyte size due to its important role in converting circulating triglycerides into free fatty acids for uptake into the adipocyte (Ramsay, 1996). Differences in lipoprotein lipase activity account for differences in the cell size of subcutaneous versus visceral adipose tissue (Wajchenberg, 2000). Importantly, combination of insulin and GCs in vitro increases lipoprotein lipase expression in adipocytes, with adipocytes from the omental fat of male subjects (Fried et al., 1993) being most sensitive. This would consequently favor adipose tissue development in the abdomen over subcutaneous development a common feature of patients with Cushing's syndrome.

11.2.3. Osteoporosis

Osteoporosis occurs when the balance of bone formation and resorption is tilted towards excess resorption over formation. Osteoporosis is a common side effect of GC therapy and is associated with reduced bone formation. Clinical studies have shown that oral GCs increase fracture risk in a dose-dependent manner (Van Staa et al., 2000) by ultimately impacting and reducing bone mineral density (Van Staa et al., 2000). It is unclear if inhaled GCs have the same effect (Tamura et al., 2004). GCs achieve the effects on bone by reducing the proliferation and function of osteoblasts, evident by a reduction in serum markers of bone formation (Tamura et al., 2004). GCs increase apoptosis of osteoblasts and osteocysts (Weinstein et al., 1998). The formation of key bone matrix components, such as type I collagen (Delany et al., 1995), as well as expression of key growth factors (Chang et al., 1998) are also inhibited by GCs. The jury is still out on the question if GCs increase bone resorption, the other key component to the development of osteoporosis, with studies both for and against (Tamura et al., 2004).

11.3. Cardiovascular disease: hypertension, heart attack, and stroke

11.3.1. Glucocorticoids

Prolonged elevations of circulating glucocorticoids promote hypertension and cardiovascular risk in a majority of patients with Cushing's Disease (Faggiano et al., 2003; Mancini et al., 2004). Furthermore, when prednisolone is taken for several years at doses >7.5 mg/day, there is a seven-fold increase in the risk of cardiovascular disease (Wei et al., 2004). The glucocorticoid effects appear to be directly on the vascular bed, as well as promoting abdominal obesity (Lohmeier et al., 2003) that also predicts cardiovascular disease (Davy and Hall, 2003; Faggiano et al., 2003; Mancini et al., 2004). Preclinical studies show direct effects of glucocorticoids on the nucleus of the tractus solitarius in the brainstem (Scheuer et al., 2003), and on the baroreflex (Scheuer and Mifflin, 2001) as well as on parts of brain that are activated by chronic stress, and feed into the premotor cardiovascular autonomic cell groups (Li and Sawchenko, 1998; Shepard et al., 2003). Moreover, chronic glucocorticoid treatment increases blood pressure and the size of experimental infarcts (Scheuer and Mifflin, 1997). Thus, in the absence of stressors, elevated glucocorticoids affect cardiovascular function through actions on both brain and body.

11.3.2. Chronic stress and cardiovascular disease (CVD)

The evidence that chronic stress in people, with elevated glucocorticoid concentrations, affects cardiovascular function is less clear, although provocative (Hemingway and Marmot, 1999; Soufer, 2004; Soufer et al., 2002, 1998). There is evidence to support a causal relationship between chronic stress, socioeconomic status, depression and social support and development of coronary artery disease (CAD) (Strike and Steptoe, 2004). However, in most human studies there is a chicken and egg problem because there are very few longitudinal studies that can unequivocally demonstrate that the specific stressor precedes the development of CAD, although this has been shown for certain types of job stress in men (Landbergis et al., 2003). Because both CAD (Stubbs et al., 1999) and stroke (Ahmed et al., 2004; Christensen et al., 2004a,b; Marklund et al., 2004) are strong stressors that activate the HPA axis, it is difficult to determine whether antecedent stress is in any way causal to the pathology that is acutely obvious. However, postmortem studies of CRF expression in hypertensive individuals show that hypothalamic CRF mRNA and peptide expression is greatly increased compared with carefully matched controls (Goncharuk et al., 2002), suggesting either that hypertension per se stimulates activity in the HPA axis or that these hypertensive patients were chronically stressed.

Depression, a condition that is frequently associated with elevated glucocorticoid secretion, and which may be considered a chronic stressor, again is associated with elevated hypothalamic CRF mRNA and peptide expression (Claes, 2004a,b; Raadsheer et al., 1994a), and is also associated with the subsequent development of CVD (Brown et al., 2004; Hemingway and Marmot, 1999; Miller et al., 2002; Musselman et al., 1998; Wassertheil-Smoller et al., 2004); however, the reverse process is also well known; a frequent sequela of acute myocardial infarction is development of depression (Frasure-Smith et al., 1993; Hemingway and Marmot, 1999; Otte et al., 2004; Strik et al., 2004; Williams et al., 2004). Preclinical studies make it clear that chronic stress, with elevated

corticosteroids, has cardiovascular sequelae (Scheuer and Mifflin, 1998; Sgoifo et al., 1999; Shively et al., 1997).

It is clear that GCs negatively affect cardiovascular function and cause hypertension and CVD in both man and animals. Although studies in man for the most part do not show causality between chronic stress and CVD, some studies suggest strongly that at least some CVD is mediated by stress-induced elevations in glucocorticoid concentrations. In animal studies, it is clear that chronic stressors elevate blood pressure, increase vessel disease and augment damage caused by experimental infarction. Furthermore, the glucocorticoids act directly on receptors in sites in brain that regulate pre-autonomic outflow.

Hypertension, dyslipidemia and a reduced fibrinolytic potential are the main adverse effects of GCs on the cardiovascular system (Sholter and Armstrong, 2000). These conditions can predispose the patient to atherosclerosis, coronary heart disease and a high cardiovascular morbidity and mortality (Nashel, 1986). GC-induced hypertension is caused by an increase in systemic vascular resistance, increased extracellular volume and increased cardiac contractility. The α-epithelial Na^+ channel and serum- and GC-regulated kinase genes appear to be important targets of GC action (Schacke et al., 2002). GCs also contribute to endothelial dysfunction, which frequently precedes the development of atherosclerosis. This is associated with impaired nitric oxide generation, as well as perturbed interactions between platelets, leukocytes and the vessel wall, in addition to alterations in thrombosis and thrombolysis (Girod and Brotman, 2004).

12. The hungry, impending doom

The HPA axis is a key mechanism through which the body adjusts to environmental demand. Although the final pathway of secretion is relatively simple, it must be viewed in the context of its integrative complexity and the diversity of its driving inputs. Major HPA axis drivers include the LEO and FEO controlling daily circadian cycles of energy balance, bottom-up inputs responding to systemic homeostatic pressures, such as the ascending medullary systems and melanocortin system within the arcuate complex, top-down influences involving complex cortico-striato-pallidal-hypothalamic projections that control HPA axis responses to adventitious psychogenic or predicted threats, and an intra-hypothalamic network strongly implicated in being a visceromotor pattern generator that coordinates neuroendocrine and autonomic outflows. These major drivers of the HPA axis are indeed as diverse as environmental demands themselves.

The flexible operating characteristics also reflect the diversity of function of the HPA axis. Under conditions of normal food availability and light cycles, the LEO gracefully controls secretion in a manner reflecting decreased glycogen reserves and anticipated foraging sessions, ceding that control to a secondary oscillator, the FEO, when food supplies become short and cyclical. The HPA axis is capable of gradually upregulating its function as starvation proceeds, and this capability appears to reflect species-specific abilities to proceed to inanition. The HPA axis can also respond acutely to challenges in both systemic and psychogenic realms, and tailors that response accordingly. Following a psychogenic threat, such as restraint, the response is rapid and robust, but quickly trimmed by fast feedback without further threat, thus avoiding excessive anti-inflammatory actions, alterations in metabolism, or feedforward effects in brain. A slowly acting systemic event, such as PEG-induced hypovolemia, not only appears to override such fast feedback, but sustains the response by upregulating transcription and translation of CRF mRNA as the hypovolemia proceeds. In addition, the HPA axis is well designed for responding to repeated stressors, in that it may habituate to a known or practiced threat, while at the same time upregulating central networks that allow renewed, and even enhanced responding to an unexpected heterotypic challenge.

This review has promoted and provided evidence for the view that the HPA axis can be profitably viewed in terms of two primary functions, namely, correcting peripheral energetic derangements and mounting, amplifying, and remembering central incentive states that promote adaptive responding to stress. Although the HPA axis has other critical roles in the periphery, e.g., anti-inflammatory actions, its primary function appears to be energy management, acting on metabolic processes primarily in liver to promote gluconeogenesis, while suppressing energetically expensive or non-essential processes in somatic growth and immune systems to remodel the body toward greater relative adiposity, particularly in mesenteric depots having access to the liver, but perhaps promoting specific depots depending on feeding status. In the absence of GCs, metabolic derangements ensue, and key nodes of the central stress networks are disinhibited, and the HPA axis becomes hyper-responsive. Because metabolic derangement, central stress network disinhibition, and HPA axis hyper-responding following the loss of GC can be corrected by high energy foods, it would appear that it is the management of metabolic fluxes by GCs that provide central inhibitory feedback. The actual metabolic signals, if they are indeed peripheral in origin, are unknown. However, GCs do not provide this inhibitory feedback chronically to brain, as they are excitatory to central stress networks.

Several caveats are in order regarding metabolic feedback. First, there are significant differences in the phenotypes produced by different rodent vendors, particularly with respect to growth rates, adiposity, body temperature regulation metabolic utilization, and HPA responses under various diets. In our experience, palatable, calorically dense food inhibits central HPA axis drive in Charles River (Raleigh, NC), Simonsen (Gilroy, CA), and some Harlan rats (Bantin & Kingman), but not in other Harlan rats (Seattle, WA). The second significant caveat, which may explain discrepancies in the literature, is that free choice appears to be critical to obtain the effect. Why this is true, and whether it obtains beyond vendors of the rats tested is unknown. Overall, the metabolic feedback aspect of the hypothesis is largely supported. The final critical caveat is that the feedback signal may not be of peripheral origin after all, and could reflect an upregulation, for example, of central opioid signaling interacting with palatable feeding and stress.

Being smartly designed by natural selection, the HPA system does not merely act in reactive fashion to repeated stressors and energy deficits, but rather mounts counter-regulatory systems in brain to meet repeated demands, including arousal, attentional, aversive, appetitive, opponent limbs and memorial systems of central incentive states as needed. These adjustments include upregulating and inducing plasticity in motivational systems involving CRF, NE, DA, and the EOPs. Amplification of the appetitive phenotype involves the upregulation of attention, global seach or migratory modes (as in wheel running), enhanced focal search (as on a maze), enhanced preference for high-energy foods, possibly through a more generally discriminative comparison process. Amplification of the aversive phenotype includes upregulating attention, anxiety, fear, anger, and depressive moods.

In addition, GCs are involved in consolidating memory for emotional events, encoding the value of significant biological events for later retrieval. This is relevant because GCs themselves do not appear to have intrinsic valence, and remain ambiguous in the absence of disambiguating cues or a predisposed phenotype. One of the key systems in brain involved in encoding valences is the fronto-temporal system, involving BLA and orbital/insular cortices. Prefrontal networks can then act through the mPFC to influence visceromotor output, whereas the BLA can act rather directly on striatal output areas such as CeA or NACC to influence motor output. In addition, GCs can affect glutamatergic-mediated plasticity within the DA system directly, by amplifying CRF signaling, or both. GCs also appear to sculpt memorial systems in terms of inhibiting hippocampal and enhancing amygdalar LTP. GCs literally and broadly sculpt neuronal architecture in the same regions, in ways that are consistent with the psychological side-effects of GC excess.

The evidence reviewed overwhelmingly commends the view that GCs remodel the brain in a feedforward fashion, yoking the needs of the body to the wants of the brain. Considering the manifold temporal dimensions of HPA function, from circadian control over energetic and motivational fluxes to gene transcription events to moment to moment variations in HPA output that clearly involve rapid and potent membrane-mediated effects on central incentive networks, the HPA axis constantly acts as a remodeling agent with respect to peripheral energetics, central incentive systems, memorial processes, and brain architecture.

A developmental analogy may be useful for understanding the function of these manifold forms of stress-induced phenotypic plasticity in adults. Consider the effects of stress on life history transitions in the amphibian. Within the extremely variable developmental environment of ephemeral desert ponds in the American Southwest, various species of desert amphibians, such as the spadefoot toad, breed explosively after rainfall, and exhibit extreme variability in the timing of developmental transitions, e.g., the timing of metamorphsis, that are triggered by stressors (Denver, 1997). After a critical post-hatching developmental stage, various stressors, such as overcrowding, food and water availability, predators, and other critical biotic factors (Crespi and Denver, 2005), accelerate the tadpole's transition to adulthood through major changes in physiology and morphology, including a reduction in ponderal growth and body size, decreased time to hindlimb and forelimb growth, and a shift from a small-headed morph specialized for omnivorous feeding on detritus to a large-headed morph specialized for carnivory (Denver, 1997; Frankino and Raff, 2004; Pfennig and Murphy, 2000).

Developmental phenotypic plasticity in amphibians is centrally mediated by GCs and central CRF stress pathways acting on both the somatotropic and HPA axes (Crespi and Denver, 2005; Crespi et al., 2004; Glennemeier and Denver, 2002). The stress-induced phenotype allows the animal to cope with changing conditions and escape to more favorable habitats more quickly, but has long-lasting consequences for overall growth and reproductive timing. Essentially, the accelerated transition functions to shunt energy into immediate coping responses that are critical for survival, but at the expense of long-term reproductive success. Similar, if somewhat less dramatic accelerations occur in reponse to stress in rodent, sheep, and human fetal development. In humans, stress-induced acceleration in development is also associated with trade-offs, such as reduced body size and increased increased risk for hypertension, type II diabetes, and obesity (Barker and Clark, 1997; Barker, 1994; Matthews, 2002). Maternal corticosteroids and CRF appear to be causative in stimulating mammalian fetal development (Crespi and Denver, 2005; McLean et al., 1995). Stress-modulated developmental clocks may further elaborate on Selye's (Selye, 1956) original observation on the adaptive function and costs of the stress response:

> Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older.

At least in the case of the desert amphibian, getting older faster is not merely payment for surviving the stressor—it is part of the survival plan. Such grossly plastic stages of ontogeny are similar to the finer scales of stress-induced tunings of the adult phenotype. By analogy, the role of HPA function in development might be thought of as a kind of Cantor set of life history strategies, wherein an interval of life may be divided in two, and each resulting subset of intervals are further divided in two to some arbitary extent, such that the system exhibits the self-similarity of being divided by two at all levels as one travels from macroscopic to finer levels. The HPA axis and central stress pathways appear to have very similar, if somewhat proportionally scaled effects on phenotypic plasticity within life history stages as they have across life history transitions. Over many time scales (e.g., over the course of chronic stress, circadian cycles, minute to hour length intervals, etc.), fluctuations in HPA activity frequently molds the phenotype toward responses that favor coping at the level of the time-scale in question, and frequently at the expense of later fitness (McEwen, 2000a,b, 2001; McEwen and Stellar, 1993; Sapolsky, 1987a,b, 1992).

Adverse effects of chronically elevated GCs on long-term fitness are abundant, but in a pre-agricultural state of nature, or during war, famine, or under conditions of carrying capacity,

when life is ''nasty, brutish, and short,'' such a fundamental yoking of needs and wants seems appropriate. As an environment becomes more extreme, the phenotype should also become more extreme, both physically and psychologically. For humans in relatively peaceful industrialized societies having a surfeit of inexpensive food, tonnages of drugs, and complex mechanisms of psycho-social stress, faults in the system are revealed, insofar as GCs promote many maladaptive behaviors, such as over-eating and drug abuse, directly in relation to these surfeits.

Even a cursory glance at the ''dismal science'' indicates that any afflictions of relative affluence could be temporary. Aside from the fact that massively interconnected consumer-based economies using currencies based on perceived value and controlled by insular, unchecked international organizations can and do collapse catastrophically and contagiously (Krugman, 1999; Stiglitz, 2000), more basic issues of population sustainability reveal disturbing trends. Between 1900 and 2000, the United Nations' estimates for world population were 1.6 billion in 1900 compared to more than 6 billion today. Populations of less-developed countries are projected to account for 87% of world population by 2050. In the early 1990s, 800 million humans were estimated to be undernourished (Organisation, 1992). Current wage gaps between countries have already resulted in the inevitable outsourcing of jobs to less-developed countries, which along with massive migrations to richer countries, act as great leveling forces for all but the wealthiest. Per capita grain production peaked in the mid 1980s. Fertilizer use is increased, along with ''algal blooms,'' ''dead zones,'' ''brown slime'' and ''mahogany tides,'' whereas crop yield is down. Within any reasoned approximation, the age of Peak Oil has arrived, and supplies are dwindling while demand is accelerating, which could carry a silver environmental lining were sweet crude not to be replaced by sulphurous sludges and coal (Simmons, 2005). Average sunlight hitting the earth is down 15% since 1950, dropping as much as 37% in Hong Kong, whereas sulphur, carbon, and nitrogen emissions are trending up (Roderick and Farquhar, 2002; Stanhill and Cohen, 2001; Wild et al., 2005). Climate change, destruction of forests, oceans, and fisheries are all present. The leading industrial nation refuses to acknowledge global warming, even as giant polar ice shelves fall into the sea, large glaciers exhibit surprising velocity doublings, and killer hurricanes destroy whole coastlines, and rather than adopting conservation as a mitigating strategy, has instead opted for perhaps the most common evolutionary strategy to resource shortages: exercising resource holding potential. Population declines in the closest human relatives, the chimpanzees and other great apes, are critical (Walsh et al., 2003). The human population is rapidly approaching, or has already exceeded carrying capacity, and the effects are being felt. Whatever the most precise scientific evidence indicates for any specific trend, many parts of the world are headed minimally for increased volatility directly as a result of human population growth (Dyson, 1999a,b, 2001). Nearly two millennia ago, similarly bleak Malthusian observations were made by the theologian Tertullian, who also noted the marked psychological changes accompanying the stresses of pre-technological carrying capacity:

> What most frequently meets our view (and occasions complaint), is our teeming population: our numbers are burdensome to the world, which can hardly supply us from its natural elements; our wants grow more and more keen, and our complaints more bitter in all mouths, whilst Nature fails in affording us her usual sustenance. In very deed, pestilence, and famine, and wars, and earthquakes have to be regarded as a remedy for nations, as the means of pruning the luxuriance of the human race ...
>
> Tertullian (De Anima)

As humans increasingly feel the crush of asymptotic growth, some will be infinitesimally better-suited to the the rigors of resource competition, and thus selected for reproductive success, no doubt due to a superior yoking of needs and wants by the HPA axis—provided any survive the impending doom (Kerr, 1999).

References

Abe, M., Saito, M., Ikeda, H., Shimazu, T., 1991. Increased neuropeptide Y content in the arcuato-paraventricular hypothalamic neuronal system in both insulin-dependent and non-insulin-dependent diabetic rats. Brain Res. 539, 223–227.

Abercrombie, E.D., Jacobs, B.L., 1987a. Microinjected clonidine inhibits noradrenergic neurons of the locus coeruleus in freely moving cats. Neurosci. Lett. 76, 203–208.

Abercrombie, E.D., Jacobs, B.L., 1987b. Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. I. Acutely presented stressful and nonstressful stimuli. J. Neurosci. 7, 2837–2843.

Abercrombie, E.D., Jacobs, B.L., 1987c. Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. II. Adaptation to chronically presented stressful stimuli. J. Neurosci. 7, 2844–2848.

Abercrombie, E.D., Jacobs, B.L., 1988. Systemic naloxone administration potentiates locus coeruleus noradrenergic neuronal activity under stressful but not non-stressful conditions. Brain Res. 441, 362–366.

Abercrombie, E.D., Levine, E.S., Jacobs, B.L., 1988. Microinjected morphine suppresses the activity of locus coeruleus noradrenergic neurons in freely moving cats. Neurosci. Lett. 86, 334–339.

Abrahamsen, G.C., Carr, K.D., 1997. Effect of adrenalectomy on cocaine facilitation of lateral hypothalamic self-stimulation. Brain Res. 755, 156–161.

Aghajanian, G.K., Wang, Y.Y., 1987. Common alpha 2- and opiate effector mechanisms in the locus coeruleus: intracellular studies in brain slices. Neuropharmacology 26, 793–799.

Ahmed, N., De la Torre, B., Wahlgren, N.G., 2004. Salivary cortisol, a biological marker of stress, is positively associated with 24-hour systolic blood pressure in patients with acute ischemic strokes. Cerebrovasc. Dis. 18, 206–213.

Aja, S., Sahandy, S., Ladenheim, E.E., Schwartz, G.J., Moran, T.H., 2001. Intracerebroventricular CART peptide reduces food intake and alters motor behavior at a hindbrain site. Am. J. Physiol. Regul. Integr. Comp. Physiol. 281, R1862–R1867.

Akabayashi, A., Watanabe, Y., Wahlestedt, C., McEwen, B.S., Paez, X., Leibowitz, S.F., 1994. Hypothalamic neuropeptide Y, its gene expression and receptor activity: relation to circulating corticosterone in adrenalectomized rats. Brain Res. 665, 201–212.

Akana, S.F., Cascio, C.S., Shinsako, J., Dallman, M.F., 1985. Corticosterone: narrow range required for normal body and thymus weight and ACTH. Am. J. Physiol. 249, R527–R532.

Akana, S.F., Chu, A., Soriano, L., Dallman, M.F., 2001. Corticosterone exerts site-specific and state-dependent effects in prefrontal cortex and amygdala

on regulation of adrenocorticotropic hormone, insulin and fat depots. J. Neuroendocrinol. 13, 625–637.
Akana, S.F., Dallman, M.F., 1992. Feedback and facilitation in the adrenocortical system: unmasking facilitation by partial inhibition of the glucocorticoid response to prior stress. Endocrinology 131, 57–68.
Akana, S.F., Hanson, E.S., Horsley, C.J., Strack, A.M., Bhatnagar, S., Bradbury, M.J., Milligan, E.D., Dallman, M.F., 1996. Clamped corticosterone (B) reveals the effect of endogenous B on both facilitated responsivity to acute restraint and metabolic responses to chronic stress. Stress 1, 33–49.
Akaoka, H., Aston-Jones, G., 1991. Opiate withdrawal-induced hyperactivity of locus coeruleus neurons is substantially mediated by augmented excitatory amino acid input. J. Neurosci. 11, 3830–3839.
Akil, H., Mayer, D.J., Liebeskind, J.C., 1976. Antagonism of stimulation-produced analgesia by naloxone, a narcotic antagonist. Science 191, 961–962.
Al-Damluji, S., Iveson, T., Thomas, J.M., Pendlebury, D.J., Rees, L.H., Besser, G.M., 1987. Food-induced cortisol secretion is mediated by central alpha-1 adrenoceptor modulation of pituitary ACTH secretion. Clin. Endocrinol. (Oxf.) 26, 629–636.
Albeck, D.S., McKittrick, C.R., Blanchard, D.C., Blanchard, R.J., Nikulina, J., McEwen, B.S., Sakai, R.R., 1997. Chronic social stress alters levels of corticotropin-releasing factor and arginine vasopressin mRNA in rat brain. J. Neurosci. 17, 4895–4903.
Albert, D.J., Walsh, M.L., White, R., 1985. Mouse killing induced by para-chlorophenylalanine injections or septal lesions but not olfactory bulb lesions is similar to that of food-deprived spontaneous killers. Behav. Neurosci. 99, 546–554.
Almeida, O.F., Nikolarakis, K.E., Herz, A., 1986. Regulation of hypothalamic beta-endorphin and dynorphin release by corticotropin-releasing factor (CRF). NIDA Res. Monogr. 75, 401–402.
Alvarez, C.V., Mallo, F., Burguera, B., Cacicedo, L., Dieguez, C., Casanueva, F.F., 1991. Evidence for a direct pituitary inhibition by free fatty acids of in vivo growth hormone responses to GHRH in the rat. Neuroendocrinology 53, 185–189.
Amir, S., Lamont, E.W., Robinson, B., Stewart, J., 2004. A circadian rhythm in the expression of PERIOD2 protein reveals a novel SCN-controlled oscillator in the oval nucleus of the bed nucleus of the stria terminalis. J. Neurosci. 24, 781–790.
Amorapanth, P., LeDoux, J.E., Nader, K., 2000. Different lateral amygdala outputs mediate reactions and actions elicited by a fear-arousing stimulus. Nat. Neurosci. 3, 74–79.
Anagnostaras, S.G., Gale, G.D., Fanselow, M.S., 2001. Hippocampus and contextual fear conditioning: recent controversies and advances. Hippocampus 11, 8–17.
Andrew, R., Phillips, D.I., Walker, B.R., 1998. Obesity and gender influence cortisol secretion and metabolism in man. J. Clin. Endocrinol. Metab. 83, 1806–1809.
Appleyard, S.M., Bailey, T.W., Doyle, M.W., Jin, Y.H., Smart, J.L., Low, M.J., Andresen, M.C., 2005. Proopiomelanocortin neurons in nucleus tractus solitarius are activated by visceral afferents: regulation by cholecystokinin and opioids. J. Neurosci. 25, 3578–3585.
Arase, K., York, D.A., Shimizu, H., Shargill, N., Bray, G.A., 1988. Effects of corticotropin-releasing factor on food intake and brown adipose tissue thermogenesis in rats. Am. J. Physiol. 255, E255–E259.
Arbisi, P.A., Billington, C.J., Levine, A.S., 1999. The effect of naltrexone on taste detection and recognition threshold. Appetite 32, 241–249.
Argaud, D., Zhang, Q., Pan, W., Maitra, S., Pilkis, S.J., Lange, A.J., 1996. Regulation of rat liver glucose-6-phosphatase gene expression in different nutritional and hormonal states: gene structure and 5′-flanking sequence. Diabetes 45, 1563–1571.
Arimura, A., Schally, A.V., Bowers, C.Y., 1969. Corticotropin releasing activity of lysine vasopressin analogues. Endocrinology 84, 579–583.
Armario, A., Lopez-Calderon, A., Jolin, T., Balasch, J., 1986. Response of anterior pituitary hormones to chronic stress. Neurosci. Biobehav. Rev. 10, 245–250.
Arnaldi, G., Angeli, A., Atkinson, A.B., Bertagna, X., Cavagnini, F., Chrousos, G.P., Fava, G.A., Findling, J.W., Gaillard, R.C., Grossman, A.B., Kola, B., Lacroix, A., Mancini, T., Mantero, F., Newell-Price, J., Nieman, L.K., Sonino, N., Vance, M.L., Giustina, A., Boscaro, M., 2003. Diagnosis and complications of Cushing's syndrome: a consensus statement. J. Clin. Endocrinol. Metab. 88, 5593–5602.
Asbach, S., Schulz, C., Lehnert, H., 2001. Effects of corticotropin-releasing hormone on locus coeruleus neurons in vivo: a microdialysis study using a novel bilateral approach. Eur. J. Endocrinol. 145, 359–363.
Asensio, C., Muzzin, P., Rohner-Jeanrenaud, F., 2004. Role of glucocorticoids in the physiopathology of excessive fat deposition and insulin resistance. Int. J. Obes. Relat. Metab. Disord. 28, S45–S52.
Askenazy, F., Candito, M., Caci, H., Myquel, M., Chambon, P., Darcourt, G., Puech, A.J., 1998. Whole blood serotonin content, tryptophan concentrations, and impulsivity in anorexia nervosa. Biol. Psychiatry 43, 188–195.
Association, A.P., 1994. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Association, Washington, DC.
Aston-Jones, G., Harris, G.C., 2004. Brain substrates for increased drug seeking during protracted withdrawal. Neuropharmacology 47 (Suppl. 1), 167–179.
Aston-Jones, G., Rajkowski, J., Cohen, J., 1999. Role of locus coeruleus in attention and behavioral flexability. Biol. Psychiatry 46, 1309–1320.
Avena, N.M., Carrillo, C.A., Needham, L., Leibowitz, S.F., Hoebel, B.G., 2004. Sugar-dependent rats show enhanced intake of unsweetened ethanol. Alcohol 34, 203–209.
Avena, N.M., Long, K.A., Hoebel, B.G., 2005. Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. Physiol. Behav. 84, 359–362.
Azrin, N.H., Hutchinson, R.R., 1967. Conditioning of the aggressive behavior of pigeons by a fixed-interval schedule of reinforcement. J. Exp. Anal. Behav. 10, 395–402.
Azrin, N.H., Rubin, H.B., Hutchinson, R.R., 1968. Biting attack by rats in response to aversive shock. J. Exp. Anal. Behav. 11, 633–639.
Badiani, A., Anagnostaras, S.G., Robinson, T.E., 1995a. The development of sensitization to the psychomotor stimulant effects of amphetamine is enhanced in a novel environment. Psychopharmacology (Berl.) 117, 443–452.
Badiani, A., Browman, K.E., Robinson, T.E., 1995b. Influence of novel versus home environments on sensitization to the psychomotor stimulant effects of cocaine and amphetamine. Brain Res. 674, 291–298.
Badiani, A., Morano, M.I., Akil, H., Robinson, T.E., 1995c. Circulating adrenal hormones are not necessary for the development of sensitization to the psychomotor activating effects of amphetamine. Brain Res. 673, 13–24.
Bailey, T.W., Dimicco, J.A., 2001. Chemical stimulation of the dorsomedial hypothalamus elevates plasma ACTH in conscious rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 280, R8–R15.
Baldwin, H.A., Rassnick, S., Rivier, J., Koob, G.F., Britton, K.T., 1991. CRF antagonist reverses the "anxiogenic" response to ethanol withdrawal in the rat. Psychopharmacology (Berl.) 103, 227–232.
Balleine, B.W., Dickinson, A., 1998. Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. Neuropharmacology 37, 407–419.
Balleine, B.W., Dickinson, A., 2000. The effect of lesions of the insular cortex on instrumental conditioning: evidence for a role in incentive memory. J. Neurosci. 20, 8954–8964.
Balleine, B.W., Killcross, S., 2006. Parallel incentive processing: an integrated view of amygdala function. Trends Neurosci. 29, 272–279.
Balsalobre, A., Brown, S.A., Marcacci, L., Tronche, F., Kellendonk, C., Reichardt, H.M., Schutz, G., Schibler, U., 2000. Resetting of circadian time in peripheral tissues by glucocorticoid signaling. Science 289, 2344–2347.
Balsalobre, A., Damiola, F., Schibler, U., 1998. A serum shock induces circadian gene expression in mammalian tissue culture cells. Cell 93, 929–937.
Barker, D.J., Clark, P.M., 1997. Fetal undernutrition and disease in later life. Rev. Reprod. 2, 105–112.
Barker, D.J.P., 1994. Mothers, Babies and Disease in Later Life. British Medical Journal Publishing, London.
Barnett, O.W., Fagan, R.W., Booker, J.M., 1991. Hotility and stress as mediators of aggression in violent men. J. Family Violence 6, 217–241.
Barr, A.M., Brotto, L.A., Phillips, A.G., 2000. Chronic corticosterone enhances the rewarding effect of hypothalamic self-stimulation in rats. Brain Res. 875, 196–201.

Barrot, M., Abrous, D.N., Marinelli, M., Rouge-Pont, F., Le Moal, M., Piazza, P.V., 2001. Influence of glucocorticoids on dopaminergic transmission in the rat dorsolateral striatum. Eur. J. Neurosci. 13, 812–818.

Barrot, M., Marinelli, M., Abrous, D.N., Rouge-Pont, F., Le Moal, M., Piazza, P.V., 1999. Functional heterogeneity in dopamine release and in the expression of Fos-like proteins within the rat striatal complex. Eur J. Neurosci. 11, 1155–1166.

Barrot, M., Marinelli, M., Abrous, D.N., Rouge-Pont, F., Le Moal, M., Piazza, P.V., 2000. The dopaminergic hyper-responsiveness of the shell of the nucleus accumbens is hormone-dependent. Eur. J. Neurosci. 12, 973–979.

Bassareo, V., De Luca, M.A., Di Chiara, G., 2002. Differential expression of motivational stimulus properties by dopamine in nucleus accumbens shell versus core and prefrontal cortex. J. Neurosci. 22, 4709–4719.

Bastard, J.P., Jardel, C., Bruckert, E., Blondy, P., Capeau, J., Laville, M., Vidal, H., Hainque, B., 2000. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J. Clin. Endocrinol. Metab. 85, 3338–3342.

Beaulieu, J., Champagne, D., Drolet, G., 1996. Enkephalin innervation of the paraventricular nucleus of the hypothalamus: distribution of fibers and origins of input. J. Chem. Neuroanat. 10, 79–92.

Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50, 7–15.

Bechara, A., Harrington, F., Nader, K., Van der Kooy, D., 1992. Neurobiology of motivation: double dissociation of two motivational mechanisms mediating opiate reward in drug-naive versus drug-dependent animals. Behav. Neurosci. 106, 798–807.

Bechara, A., Nader, K., Van der Kooy, D., 1998. A two-separate-motivational-systems hypothesis of opioid addiction. Pharmacol. Biochem. Behav. 59, 1–17.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., Damasio, A.R., 1995. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science 269, 1115–1118.

Beck, C.H., Fibiger, H.C., 1995. Conditioned fear-induced changes in behavior and in the expression of the immediate early gene *c*-fos: with and without diazepam pretreatment. J. Neurosci. 15, 709–720.

Beitner-Johnson, D., Guitart, X., Nestler, E.J., 1991. Dopaminergic brain reward regions of Lewis and Fischer rats display different levels of tyrosine hydroxylase and other morphine- and cocaine-regulated phosphoproteins. Brain Res. 561, 147–150.

Beitner-Johnson, D., Guitart, X., Nestler, E.J., 1992. Neurofilament proteins and the mesolimbic dopamine system: common regulation by chronic morphine and chronic cocaine in the rat ventral tegmental area. J. Neurosci. 12, 2165–2176.

Bell, M.E., Bhatnagar, S., Liang, J., Soriano, L., Nagy, T.R., Dallman, M.F., 2000. Voluntary sucrose ingestion, like corticosterone replacement, prevents the metabolic deficits of adrenalectomy. J. Neuroendocrinol. 12, 461–470.

Benedek, G., Szikszay, M., 1985. Sensitization or tolerance to morphine effects after repeated stresses. Prog. Neuropsychopharmacol. Biol. Psychiatry 9, 369–380.

Beninger, R.J., Hanson, D.R., Phillips, A.G., 1981. The acquisition of responding with conditioned reinforcement: effects of cocaine, (+)-amphetamine and pipradrol. Br. J. Pharmacol. 74, 149–154.

Berridge, C.W., Dunn, A.J., 1986. Corticotropin-releasing factor elicits naloxone sensitive stress-like alterations in exploratory behavior in mice. Regul. Peptides 16, 83–93.

Berridge, C.W., Foote, S.L., 1991. Effects of locus coeruleus activation on electroencephalographic activity in neocortex and hippocampus. J. Neurosci. 11, 3135–3145.

Berridge, C.W., Page, M.E., Valentino, R.J., Foote, S.L., 1993. Effects of locus coeruleus inactivation on electroencephalographic activity in neocortex and hippocampus. Neuroscience 55, 381–393.

Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res. Rev. 28, 309–369.

Berthoud, H.R., Powley, T.L., 1991. Morphology and distribution of efferent vagal innervation of rat pancreas as revealed with anterograde transport of Dil. Brain Res. 553, 336–341.

Berthoud, H.R., Powley, T.L., 1992. Vagal afferent innervation of the rat fundic stomach: morphological characterization of the gastric tension receptor. J. Comp. Neurol. 319, 261–276.

Bevins, R.A., Ayres, J.J., 1992. One-trial backward excitatory fear conditioning transfers across contexts. Behav. Res. Ther. 30, 551–554.

Bhatnagar, S., Bell, M.E., Liang, J., Soriano, L., Nagy, T.R., Dallman, M.F., 2000. Corticosterone facilitates saccharin intake in adrenalectomized rats. Does corticosterone increase stimulus salience? J. Neuroendocrinol. 12, 453–460.

Bhatnagar, S., Dallman, M.F., 1998. Neuroanatomical basis for facilitation of hypothalamic–pituitary–adrenal responses to a novel stressor after chronic stress. Neuroscience 84, 1025–1039.

Bhatnagar, S., Dallman, M.F., 1999. The paraventricular nucleus of the thalamus alters rhythms in core temperature and energy balance in a state-dependent manner. Brain Res. 851 (1–2), 66–75.

Bhatnagar, S., Huber, R., Nowak, N., Trotter, P., 2002. Lesions of the paraventricular thalamus block adaptation of hypothalamic–pituitary–adrenal (HPA) responses to repeated restraint. J. Neuroendocrinol. 14, 403–410.

Bhatnagar, S., Mitchell, J.B., Betito, K., Boksa, P., Meaney, M.J., 1995. Effects of chronic intermittent cold stress on pituitary adrenocortical and sympathetic adrenomedullary functioning. Physiol. Behav. 57, 633–639.

Bindra, D., Campbell, J.F., 1967. Motivational effects of rewarding intracranial stimulation. Nature 215, 375–376.

Bjorntorp, P., 1996. The regulation of adipose tissue distribution in humans. Int. J. Obes. 20, 291–302.

Bjorntorp, P., 1997. Hormonal control of regional fat distribution. Hum. Reprod. 12, 21–25.

Blackard, W.G., Boylen, C.T., Hinson, T.C., Nelson, N.C., 1969. Effect of lipid and ketone infusions on insulin-induced growth hormone elevations in rhesus monkeys. Endocrinology 85, 1180–1185.

Blair, H.T., Schafe, G.E., Bauer, E.P., Rodrigues, S.M., LeDoux, J.E., 2001. Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. Learn Mem. 8, 229–242.

Blanchard, R.J., Flannelly, K.J., Blanchard, D.C., 1986. Defensive behavior of laboratory and wild Rattus norvegicus. J. Comp. Psychol. 100, 101–107.

Blanchard, R.J., Mast, M., Blanchard, D.C., 1975. Stimulus control of defensive reactions in the albino rat. J. Comp. Physiol. Psychol. 88, 81–88.

Blatteis, C.M., 2006. Endotoxic fever: new concepts of its regulation suggest new approaches to its management. Pharmacol. Ther. 111 (1), 194–223.

Blundell, J.E., Herberg, L.J., 1968. Relative effects of nutritional deficit and deprivation period on rate of electrical self-stimulation of lateral hypothalamus. Nature 219, 627–628.

Bolles, R., Petrinovich, L., 1956. Bodyweight changes and behavioral attributes. J. Comp. Physiol. Psychol. 49, 177–180.

Bolles, R.C., 1963. Effect of food deprivation upon the rat's behavior in its home cage. J. Comp. Physiol. Psychol. 56, 456–460.

Bolles, R.C., De Lorge, J., 1962. Effect of hunger on exploration in a familiar locale. Psychol. Reports 10, 54.

Borrell, J., De Kloet, E.R., Versteeg, D.H., Bohus, B., 1983. Inhibitory avoidance deficit following short-term adrenalectomy in the rat: the role of adrenal catecholamines. Behav. Neural. Biol. 39, 241–258.

Boudaba, C., Schrader, L.A., Tasker, J.G., 1997. Physiological evidence for local excitatory synaptic circuits in the rat hypothalamus. J. Neurophysiol. 77, 3396–3400.

Bouret, S.G., Draper, S.J., Simerly, R.B., 2004a. Formation of projection pathways from the arcuate nucleus of the hypothalamus to hypothalamic regions implicated in the neural control of feeding behavior in mice. J. Neurosci. 24, 2797–2805.

Bouret, S.G., Draper, S.J., Simerly, R.B., 2004b. Trophic action of leptin on hypothalamic neurons that regulate feeding. Science 304, 108–110.

Bouret, S.G., Simerly, R.B., 2004. Minireview: leptin and development of hypothalamic feeding circuits. Endocrinology 145, 2621–2626.

Bouton, M.E., 2000. A learning theory perspective on lapse, relapse, and the maintenance of behavior change. Health Psychol. 19, 57–63.

Bouton, M.E., 2002. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol. Psychiatry 52, 976–986.

Bouton, M.E., Bolles, R.C., 1979. Role of conditioned contextual stimuli in reinstatement of extinguished fear. J. Exp. Psychol. Anim. Behav. Process 5, 368–378.

Bozarth, M.A., Wise, R.A., 1981a. Heroin reward is dependent on a dopaminergic substrate. Life Sci. 29, 1881–1886.

Bozarth, M.A., Wise, R.A., 1981b. Intracranial self-administration of morphine into the ventral tegmental area in rats. Life Sci. 28, 551–555.

Bradbury, M., Akana, S., Cascio, C., Levin, N., Jacobson, L., Dallman, M., 1991a. Regulation of basal ACTH secretion by corticosterone is mediated by both type I (MR) and type II (GR) receptors in rat brain. J. Steroid. Biochem. Mol. Biol. 40, 133–142.

Bradbury, M.J., Cascio, C.S., Scribner, K.A., Dallman, M.F., 1991b. Stress-induced adrenocorticotropin secretion: diurnal responses and decreases during stress in the evening are not dependent on corticosterone. Endocrinology 128, 680–688.

Bradbury, M., Akana, S., Dallman, M., 1994. Roles of type I and II corticosteroid receptors in regulation of basal activity in the hypothalamo–pituitary–adrenal axis during the diurnal trough and the peak: evidence for a nonadditive effect of combined receptor occupation. Endocrinology 134, 1286–1296.

Bradbury, M.J., Strack, A.M., Dallman, M.F., 1993. Lesions of the hippocampal efferent pathway (Fimbria-fornix) do not alter sensitivity of adrenocorticotropin to feedback inhibition by corticosterone in rats. Neuroendocrinology 58, 396–407.

Brady, L.S., Smith, M.A., Gold, P.W., Herkenham, M., 1990. Altered expression of hypothalamic neuropeptide mRNAs in food-restricted and food-deprived rats. Neuroendocrinology 52, 441–447.

Brandenberger, G., Follenius, M., Hietter, B., 1982. Feedback from meal-related peaks determines diurnal changes in cortisol response to exercise. J. Clin. Endocrinol. Metab. 54, 592–596.

Breese, G.R., Chu, K., Dayas, C.V., Funk, D., Knapp, D.J., Koob, G.F., Le, D.A., O'Dell, L.E., Overstreet, D.H., Roberts, A.J., Sinha, R., Valdez, G.R., Weiss, F., 2005a. Stress enhancement of craving during sobriety: a risk for relapse. Alcohol Clin. Exp. Res. 29, 185–195.

Breese, G.R., Overstreet, D.H., Knapp, D.J., 2005b. Conceptual framework for the etiology of alcoholism: a ''kindling''/stress hypothesis. Psychopharmacology (Berl.) 178, 367–380.

Breese, G.R., Knapp, D.J., Overstreet, D.H., 2004. Stress sensitization of ethanol withdrawal-induced reduction in social interaction: inhibition by CRF-1 and benzodiazepine receptor antagonists and a 5-HT1A-receptor agonist. Neuropsychopharmacology 29, 470–482.

Breland, K., Breland, M., 1961. The misbehavior of organisms. Am. Psychologist 16, 681–684.

Brett, L.P., Levine, S., 1979. Schedule-induced polydipsia suppresses pituitary–adrenal activity in rats. J. Comp. Physiol. Psychol. 93, 946–956.

Britton, D.R., Hoffman, D.K., Lederis, K., Rivier, J., 1984. A comparison of the behavioral effects of CRF, sauvagine, and urotensin I. Brain Res. 304, 201–205.

Brog, J.S., Salyapongse, A., Deutch, A.Y., Zahm, D.S., 1993. The patterns of afferent innervation of the core and shell in the ''accumbens'' part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. J. Comp. Neurol. 338, 255–278.

Brown, E.S., Varghese, F.P., McEwen, B.S., 2004. Association of depression with medical illness: does cortisol play a role? Biol. Psychiatry 55, 1–9.

Brown, J.S., Kalish, H.I., Farber, I.E., 1951. Conditioned fear as revealed by magnitude of startle response to an auditory stimulus. J. Exp. Psychol. 41, 317–328.

Brown, M.R., Fisher, L.A., 1986. Glucocorticoid suppression of the sympathetic nervous system and adrenal medulla. Life Sci. 39, 1003–1012.

Brown, P.L., Jenkins, H.M., 1968. Auto-shaping of the pigeon's key-peck. J. Exp. Anal. Behav. 11, 1–8.

Bubser, M., Deutch, A.Y., 1998. Thalamic paraventricular nucleus neurons collateralize to innervate the prefrontal cortex and nucleus accumbens. Brain Res. 787, 304–310.

Buckingham, J.C., Cooper, T.A., 1986. Effect of naloxone on hypothalamo–pituitary–adrenocortical activity in the rat. Neuroendocrinology 42, 421–426.

Bugarith, K., Dinh, T.T., Li, A.-J., Speth, R.C., Ritter, S., 2005. Basomedial hypothalamic injections of neuropeptide Y conjugated to saporin selectively disrupt hypothalamic controls of food intake. Endocrinology 146, 1179–1191.

Buijs, R.M., Hermes, M.H., Kalsbeek, A., 1998. The suprachiasmatic nucleus-paraventricular nucleus interactions: a bridge to the neuroendocrine and autonomic nervous system. Prog. Brain Res. 119, 365–382.

Buijs, R.M., Kalsbeek, A., 2001. Hypothalamic integration of central and peripheral clocks. Nat. Rev. Neurosci. 2, 521–526.

Buijs, R.M., Van Eden, C.G., 2000. The integration of stress by the hypothalamus, amygdala and prefrontal cortex: balance between the autonomic nervous system and the neuroendocrine system. Prog. Brain Res. 126, 117–132.

Buijs, R.M., Wortel, J., Van Heerikhuize, J.J., Feenstra, M.G., Ter Horst, G.J., Romijn, H.J., Kalsbeek, A., 1999. Anatomical and functional demonstration of a multisynaptic suprachiasmatic nucleus adrenal (cortex) pathway. Eur. J. Neurosci. 11, 1535–1544.

Bujalska, I.J., Kumar, S., Stewart, P.M., 1997. Does central obesity reflect ''Cushing's disease of the omentum''? Lancet 349, 1210–1213.

Buller, K.M., Smith, D.W., Day, T.A., 1999a. Differential recruitment of hypothalamic neuroendocrine and ventrolateral medulla catecholamine cells by non-hypotensive and hypotensive hemorrhages. Brain Res. 834, 42–54.

Buller, K.M., Smith, D.W., Day, T.A., 1999b. NTS catecholamine cell recruitment by hemorrhage and hypoxia. Neuroreport 10, 3853–3856.

Burgess, M.L., Davis, J.M., Wilson, S.P., Borg, T.K., Burgess, W.A., Buggy, J., 1993. Effects of intracranial self-stimulation on selected physiological variables in rats. Am. J. Physiol. 264, R149–R155.

Butler, P.D., Weiss, J.M., Stout, J.C., Nemeroff, C.B., 1990. Corticotropin-releasing factor produces fear-enhancing and behavioral activating effects following infusion into the locus coeruleus. J. Neurosci. 10, 176–183.

Buttgereit, F., Burmester, G.R., Lipworth, B.J., 2005. Optimised glucocorticoid therapy: the sharpening of an old spear. Lancet 365, 801–803.

Cabeza de Vaca, S., Carr, K.D., 1998. Food restriction enhances the central rewarding effect of abused drugs. J. Neurosci. 18, 7502–7510.

Cabeza De Vaca, S., Holiman, S., Carr, K.D., 1998. A search for the metabolic signal that sensitizes lateral hypothalamic self-stimulation in food-restricted rats. Physiol. Behav. 64, 251–260.

Cabib, S., Kempf, E., Schleef, C., Mele, A., Puglisi-Allegra, S., 1988a. Different effects of acute and chronic stress on two dopamine-mediated behaviors in the mouse. Physiol. Behav. 43, 223–227.

Cabib, S., Kempf, E., Schleef, C., Oliverio, A., Puglisi-Allegra, S., 1988b. Effects of immobilization stress on dopamine and its metabolites in different brain areas of the mouse: role of genotype and stress duration. Brain Res. 441, 153–160.

Cabib, S., Puglisi-Allegra, S., 1994. Opposite responses of mesolimbic dopamine system to controllable and uncontrollable aversive experiences. J. Neurosci. 14, 3333–3340.

Cador, M., Ahmed, S.H., Koob, G.F., le Moal, M., Stinus, L., 1992. Corticotropin-releasing factor induces a place aversion independent of its neuroendocrine role. Brain Res. 597, 304–309.

Campbell, B.A., Sheffield, F.D., 1953. Relation of random activity to food deprivation. J. Comp. Physiol. Psychol. 46, 320–322.

Campbell, U.C., Carroll, M.E., 2001. Effects of ketoconazole on the acquisition of intravenous cocaine self-administration under different feeding conditions in rats. Psychopharmacology (Berl.) 154, 311–318.

Canteras, N.S., Simerly, R.B., Swanson, L.W., 1994. Organization of projections from the ventromedial nucleus of the hypothalamus: a phaseolus vulgaris-leucoagglutinin study in the rat. J. Comp. Neurol. 348, 41–79.

Cappendijk, S.L., Hurd, Y.L., Nylander, I., Van Ree, J.M., Terenius, L., 1999. A heroin-but not a cocaine-expecting, self-administration state preferentially alters endogenous brain peptides. Eur. J. Pharmacol. 365, 175–182.

Carr, K.D., 2002. Augmentation of drug reward by chronic food restriction: behavioral evidence and underlying mechanisms. Physiol. Behav. 76, 353–364.

Carr, K.D., Abrahamsen, G.C., 1998. Effect of adrenalectomy on cocain facilitation of medial prefrontal cortex self-stimulation. Brain Res. 787, 321–327.

Carrive, P., Bandler, R., Dampney, R.A., 1989a. Somatic and autonomic integration in the midbrain of the unanesthetized decerebrate cat: a distinctive pattern evoked by excitation of neurones in the subtentorial portion of the midbrain periaqueductal grey. Brain Res. 483, 251–258.

Carrive, P., Bandler, R., Dampney, R.A., 1989b. Viscerotopic control of regional vascular beds by discrete groups of neurons within the midbrain periaqueductal gray. Brain Res. 493, 385–390.

Carroll, M.E., 1985. The role of food deprivation in the maintenance and reinstatement of cocaine-seeking behavior in rats. Drug Alcohol Depend. 16, 95–109.

Carroll, M.E., Campbell, U.C., Heideman, P., 2001. Ketoconazole suppresses food restriction-induced increases in heroin self-administration in rats: sex differences. Exp. Clin. Psychopharmacol. 9, 307–316.

Carroll, M.E., France, C.P., Meisch, R.A., 1979. Food deprivation increases oral and intravenous drug intake in rats. Science 205, 319–321.

Carroll, M.E., Lac, S.T., 1993. Autoshaping i.v. cocaine self-administration in rats: effects of nondrug alternative reinforcers on acquisition. Psychopharmacology (Berl.) 110, 5–12.

Carroll, M.E., Stotz, D.C., Kliner, D.J., Meisch, R.A., 1984. Self-administration of orally-delivered methohexital in rhesus monkeys with phencyclidine or pentobarbital histories: effects of food deprivation and satiation. Pharmacol. Biochem. Behav. 20, 145–151.

Carter-Su, C., Okamoto, K., 1987. Effect of insulin and glucocorticoids on glucose transporters in rat adipocytes. Am. J. Physiol. 252, E441–E453.

Cascio, C.S., Shinsako, J., Dallman, M.F., 1987. The suprachiasmatic nuclei stimulate evening ACTH secretion in the rat. Brain Res. 423, 173–179.

Ceccatelli, S., Orazzo, C., 1993. Effect of different types of stressors on peptide messenger ribonucleic acids in the hypothalamic paraventricular nucleus. Acta Endocrinol. (Copenh.) 128, 485–492.

Ceccatelli, S., Villar, M.J., Goldstein, M., Hokfelt, T., 1989. Expression of *c*-Fos immunoreactivity in transmitter-characterized neurons after stress. Proc. Natl. Acad. Sci. U.S.A. 86, 9569–9573.

Cechetto, D.F., 1987. Central representation of visceral function. Federation Proc. 46, 17–23.

Cechetto, D.F., Saper, C.B., 1987. Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. J. Comp. Neurol. 262, 27–45.

Cerri, M., Morrison, S.F., 2006. Corticotropin releasing factor increases in brown adipose tissue thermogenesis and heart rate through dorsomedial hypothalamus and medullary raphe pallidus. J. Neurosci. 140 (2), 711–721.

Chandola, T., Brunner, E.J., Marmot, M., 2006. Chronic stress at work and the metabolic syndrome: prospective study. BMJ 332, 521–525.

Chang, D.J., Ji, C., Kim, K.K., Casinghino, S., McCarthy, T.L., Centrella, M., 1998. Reduction in transforming growth factor beta receptor I expression and transcription factor CBFa1 on bone cells by glucocorticoid. J. Biol. Chem. 273, 4892–4896.

Chapman, P.F., Ramsay, M.F., Krezel, W., Knevett, S.G., 2003. Synaptic plasticity in the amygdala: comparisons with hippocampus. Ann. N.Y. Acad. Sci. 985, 114–124.

Chen, Y., Brunson, K.L., Muller, M.B., Cariaga, W., Baram, T.Z., 2000. Immunocytochemical distribution of corticotropin-releasing hormone receptor type-1 (CRF(1))-like immunoreactivity in the mouse brain: light microscopy analysis using an antibody directed against the C-terminus. J. Comp. Neurol. 420, 305–323.

Cho, K., Little, H.J., 1999. Effects of corticosterone on excitatory amino acid responses in dopamine-sensitive neurons in the ventral tegmental area. Neuroscience 88, 837–845.

Choi, S., Wong, L.S., Yamat, C., Dallman, M.F., 1998. Hypothalamic ventromedial nuclei amplify circadian rhythms: do they contain a food-entrained endogenous oscillator? J. Neurosci. 18, 3843–3852.

Christensen, H., Boysen, G., Johannesen, H.H., 2004a. Serum cortisol reflects severity and mortality in acute stroke. J. Neurol. Sci. 217, 175–180.

Christensen, H., Johannesen, H.H., Christensen, A.F., Bendtzen, K., Boysen, G., 2004b. Serum cardiac troponin I in acute stroke is related to serum cortisol and TNF-alpha. Cerebrovasc. Dis. 18, 194–199.

Christie, M.J., Trisdikoon, P., Chesher, G.B., 1982. Tolerance and cross tolerance with morphine resulting from physiological release of endogenous opiates. Life Sci. 31, 839–845.

Church, W.H., Justice Jr., J.B., Neill, D.B., 1987. Detecting behaviorally relevant changes in extracellular dopamine with microdialysis. Brain Res. 412, 397–399.

Ciccocioppo, R., Economidou, D., Feedeli, A., Massi, M., 2003a. The nociceptin/orphanin FQ/NOP receptor system as a target for treatment of alcohol abuse: a review of recent work in alcohol-preferring rats. Physiol. Behav. 79, 121–128.

Ciccocioppo, R., Lin, D., Martin-Fardon, R., Weiss, F., 2003b. Reinstatement of ethanol-seeking behavior by drug cues following single versus multiple ethanol intoxication in the rat: effects of naltrexone. Psychopharmacology (Berl.) 168, 208–215.

Cirulli, F., Van Oers, H., de Kloet, E.R., Levine, S., 1994. Differential influence of corticosterone and dexamethasone on schedule-induced polydipsia in adrenalectomized rats. Behav. Brain Res. 65, 33–39.

Claes, S.J., 2004a. Corticotropin-releasing hormone (CRH) in psychiatry: from stress to psychopathology. Ann. Med. 36, 50–61.

Claes, S.J., 2004b. CRH, stress and major depression: a psychobiological interplay. Vitam. Horm. 69, 117–150.

Clark, H.W., Masson, C.L., Delucchi, K.L., Hall, S.M., Sees, K.L., 2001. Violent traumatic events and drug abuse severity. J. Subst. Abuse. Treat. 20, 121–127.

Clark, K.B., Smith, D.C., Hassert, D.L., Browning, R.A., Naritoku, D.K., Jensen, R.A., 1998. Posttraining electrical stimulation of vagal afferents with concomitant vagal efferent inactivation enhances memory storage processes in the rat. Neurobiol. Learn. Mem. 70, 364–373.

Clement, L., Cruciani-Guglielmacci, C., Magnan, C., Vincent, M., Douared, L., Orosco, M., Assimacopoulos-Jeannet, F., Penicaud, L., Ktorza, A., 2002. Intracerebroventricular infusion of a triglyceride emulsion leads to both altered insulin secretion and hepatic glucose production in rats. Pflugers Arch. 445, 375–380.

Colantuoni, C., Rada, P.V., McCarthy, J., Patten, C., Avena, N.M., Chadeayne, A., Hoebel, B.G., 2002. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. Obes. Res. 10, 478–488.

Colantuoni, C., Schwenker, J., McCarthy, J., Rada, P., Ladenheim, B., Cadet, J.L., Schwartz, G.J., Moran, T.H., Hoebel, B.G., 2001. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. Neuroreport 12, 3549–3552.

Cole, B.J., Koob, G.F., 1988. Propranolol antagonizes the enhanced conditioned fear produced by corticotropin releasing factor. J. Pharmacol. Exp. Ther. 247, 902–910.

Cole, B.J., Koob, G.F., 1994. Corticotropin-releasing factor and schedule-induced polydipsia. Pharmacol. Biochem. Behav. 47, 393–398.

Cole, M., Kalman, B., Pace, T., Topczewski, F., Lowrey, M., Spencer, R., 2000. Selective blockade of the mineralocorticoid receptor impairs hypothalamic–pituitary–adrenal axis expression of habituation. J. Neuroendocrinol. 12, 1034–1042.

Collier, G., Levitsky, D.A., 1968. Operant running as a function of deprivation and effort. J. Comp. Physiol. Psychol. 66, 522–523.

Cone, R.D., 2005. Anatomy and regulation of the central melanocortin system. Nat. Neurosci. 8, 571–578.

Conrad, C.D., LeDoux, J.E., Magarinos, A.M., McEwen, B.S., 1999. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behav. Neurosci. 113, 902–913.

Cook, C.J., 2001. Measuring of extracellular cortisol and corticotropin-releasing hormone in the amygdala using immunosensor coupled microdialysis. J. Neurosci. Methods 110, 95–101.

Cook, C.J., 2002. Glucocorticoid feedback increases the sensitivity of the limbic system to stress. Physiol. Behav. 75, 455–464.

Cook, C.J., 2004. Stress induces CRF release in the paraventricular nucleus, and both CRF and GABA release in the amygdala. Physiol. Behav. 82, 751–762.

Cooper, K., Carmody, J., 1982. The characteristics of the opioid-related analgesia induced by the stress of swimming in the mouse. Neurosci. Lett. 31, 165–170.

Coover, G., Ursin, H., Levine, S., 1973a. Corticosterone and avoidance in rats with basolateral amygdala lesions. J. Comp. Physiol. Psychol. 85, 111–122.

Coover, G.D., Ursin, H., Levine, S., 1973b. Plasma-corticosterone levels during active-avoidance learning in rats. J. Comp. Physiol. Psychol. 82, 170–174.

Coover, G., Ursin, H., Levine, S., 1974. Corticosterone levels during avoidance learning in rats with cingulate lesions suggest an instrumental reinforcement deficit. J. Comp. Physiol. Psychol. 87, 970–977.

Coover, G.D., 1983. Positive and negative expectancies: the rat's reward environment and pituitary–adrenal activity. In: Ursin, H., Murison, R.C. (Eds.), Biological and Psychological Basis of Psychosomatic Disease. Pergamon Press, Inc., Elmsford, NY, USA, pp. 45–60.

Coover, G.D., 1984. Plasma corticosterone and meal expectancy in rats: effects of low probability cues. Physiol. Behav. 33, 179–184.

Coover, G.D., Goldman, L., Levine, S., 1971a. Plasma corticosterone increases produced by extinction of operant behavior in rats. Physiol. Behav. 6, 261–263.

Coover, G.D., Goldman, L., Levine, S., 1971b. Plasma corticosterone levels during extinction of a lever-press response in hippocampectomized rats. Physiol. Behav. 7, 727–732.

Coover, G.D., Sutton, B.R., Heybach, J.P., 1977. Conditioning decreases in plasma corticosterone level in rats by pairing stimuli with daily feedings. J. Comp. Physiol. Psychol. 91, 716–726.

Coover, G.D., Welle, S., Hart, R.P., 1980. Effects of eating, meal cues and ventromedial hypothalamic lesions on serum corticosterone, glucose and free fatty acid concentrations. Physiol. Behav. 25, 641–651.

Cordero, M.I., Merino, J.J., Sandi, C., 1998. Correlational relationship between shock intensity and corticosterone secretion on the establishment and subsequent expression of contextual fear conditioning. Behav. Neurosci. 112, 885–891.

Cordero, M.I., Sandi, C., 1998. A role for brain glucocorticoid receptors in contextual fear conditioning: dependence upon training intensity. Brain Res. 786, 11–17.

Cordero, M.I., Venero, C., Kruyt, N.D., Sandi, C., 2003. Prior exposure to a single stress session facilitates subsequent contextual fear conditioning in rats. Evidence for a role of corticosterone. Horm. Behav. 44, 338–345.

Corodimas, K.P., LeDoux, J.E., Gold, P.W., Schulkin, J., 1994. Corticosterone potentiation of conditioned fear in rats. Ann. N.Y. Acad. Sci. 746, 392–393.

Cover, P.O., Buckingham, J.C., 1989. Effects of selective opioid-receptor blockade on the hypothalamo–pituitary–adrenocortical responses to surgical trauma in the rat. J. Endocrinol. 121, 213–220.

Cowley, M.A., Smart, J.L., Rubinstein, M., Cerdain, M., Diano, S., Horvath, T.L., Cone, R.D., Low, M.J., 2001. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature 411, 480–484.

Crespi, E.J., Denver, R.J., 2005. Ancient origins of human developmental plasticity. Am. J. Hum. Biol. 17, 44–54.

Crespi, E.J., Vaudry, H., Denver, R.J., 2004. Roles of corticotropin-releasing factor, neuropeptide Y and corticosterone in the regulation of food intake in Xenopus laevis. J. Neuroendocrinol. 16, 279–288.

Crumpton, E., Wine, D.B., Drenick, E.J., 1966. Starvation: stress or satisfaction? JAMA 196, 394–396.

Cuadra, G., Zurita, A., Lacerra, C., Molina, V.A., 1999. Chronic stress sensitizes frontal cortex dopamine release in response to a subsequent novel stressor: reversal by naloxone. Brain Res. Bull. 48, 303–308.

Cullinan, W.E., Herman, J.P., Battaglia, D.F., Akil, H., Watson, S.J., 1995. Pattern and time course of immediate early gene expression in rat brain following acute stress. Neuroscience 64, 477–505.

Cullinan, W.E., Herman, J.P., Watson, S.J., 1993. Ventral subicular interaction with the hypothalamic paraventricular nucleus: evidence for a relay in the bed nucleus of the stria terminalis. J. Comp. Neurol. 332, 1–20.

Cunningham Jr., E.T., Sawchenko, P.E., 1988. Anatomical specificity of noradrenergic inputs to the paraventricular and supraoptic nuclei of the rat hypothalamus. J. Comp. Neurol. 274, 60–76.

Curtis, A.L., Bello, N.T., Connolly, K.R., Valentino, R.J., 2002. Corticotropin-releasing factor neurones of the central nucleus of the amygdala mediate locus coeruleus activation by cardiovascular stress. J. Neuroendocrinol. 14, 667–682.

Curtis, A.L., Bello, N.T., Valentino, R.J., 2001. Evidence for functional release of endogenous opioids in the locus coeruleus during stress termination. J. Neurosci. 21 (1–5), RC152.

Curtis, A.L., Lechner, S.M., Pavcovich, L.A., Valentino, R.J., 1997. Activation of the locus coeruleus noradrenergic system by intracoerulear microinfusion of corticotropin-releasing factor: effects on discharge rate, cortical norepinephrine levels and cortical electroencephalographic activity. J. Pharmacol. Exp. Ther. 281, 163–172.

Czeh, B., Michaelis, T., Watanabe, T., Frahm, J., de Biurrun, G., Van Kampen, M., Bartolomucci, A., Fuchs, E., 2001. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc. Natl. Acad. Sci. U.S.A. 98, 12796–12801.

Czyrak, A., Chocyk, A., 2001. Search for the presence of glucocorticoid receptors in dopaminergic neurons of rat ventral tegmental area and substantia nigra. Pol. J. Pharmacol. 53, 681–684.

Czyrak, A., Chocyk, A., Mackowiak, M., Fijal, K., Wedzony, K., 2000. Distribution of dopamine D1 receptors in the nucleus paraventricularis of the hypothalamus in rats: an immunohistochemical study. Brain Res. Mol. Brain Res. 85, 209–217.

Czyrak, A., Mackowiak, M., Chocyk, A., Fijal, K., Wedzony, K., 2003. Role of glucocorticoids in the regulation of dopaminergic neurotransmission. Pol. J. Pharmacol. 55, 667–674.

Czyrak, A., Mackowiak, M., Fijal, K., Chocyk, A., Wedzony, K., 1997a. Impact of metyrapone on MK-801-induced alterations in the rat dopamine D1 receptors. Pol. J. Pharmacol. 49, 305–316.

Czyrak, A., Wedzony, K., Michalska, B., Fijal, K., Dziedzicka-Wasylewska, M., Mackowiak, M., 1997b. The corticosterone synthesis inhibitor metyrapone decreases dopamine D1 receptors in the rat brain. Neuroscience 79, 489–495.

Daftary, S.S., Boudaba, C., Tasker, J.G., 2000. Noradrenergic regulation of parvocellular neurons in the rat hypothalamic paraventricular nucleus. Neuroscience 96, 743–751.

Dallman, M., Akana, S., Cascio, C., Darlington, D., Jacobson, L., Levin, N., 1987a. Regulation of ACTH secretion: variations on a theme of B. Recent Prog. Horm. Res. 43, 113–173.

Dallman, M.F., Akana, S.F., Jacobson, L., Levin, N., Cascio, C.S., Shinsako, J., 1987b. Characterization of corticosterone feedback regulation of ACTH secretion. Ann. N.Y. Acad. Sci. 512, 402–414.

Dallman, M., Levin, N., Cascio, C., Akana, S., Jacobson, L., Kuhn, R., 1989a. Pharmacological evidence that the inhibition of diurnal adrenocorticotropin secretion by corticosteroids is mediated via type I corticosterone-preferring receptors. Endocrinology 124, 2844–2850.

Dallman, M.F., Darlington, D.N., Suemaru, S., Cascio, C.S., Levin, N., 1989b. Corticosteroids in homeostasis. Acta Physiol. Scand. Suppl. 583, 27–34.

Dallman, M.F., Pecoraro, N.C., laFleur, S.E., 2005. Chronic stress and comfort foods: self-medication and abdominal obesity. Brain Behav. Immunol. 19 (4), 275–280.

Dallman, M.F., Akana, S.F., Bell, M.E., Bhatnagar, S., Choi, S., Chu, A., Horsley, C., Levin, N., Meijer, O.C., Strack, A.M., Soriano, L., Viau, V., 1999. Starvation: early signals, sensors, and sequelae. Endocrinology 140, 4015–4023.

Dallman, M.F., Akana, S.F., Bradbury, M.J., Strack, A.M., Hanson, E.S., Scribner, K.A., 1994. Regulation of the hypothalamo–pituitary–adrenal axis during stress: feedback, facilitation and feeding. Semin. Neurosci. 6, 205–213.

Dallman, M.F., Akana, S.F., Strack, A.M., Scribner, K.S., Pecoraro, N., La Fleur, S.E., Houshyar, H., Gomez, F., 2004. Chronic stress-induced effects of corticosterone on brain: direct and indirect. Ann. N.Y. Acad. Sci. 1018, 141–150.

Dallman, M.F., Bhatnagar, S., 2001. Chronic Stress and Energy Balance: Role of the Hypothalamo–Pituitary–Adrenal Axis. Oxford University Press, New York.

Dallman, M.F., Engeland, W.C., Rose, J.C., Wilkinson, C.W., Shinsako, J., Siedenburg, F., 1978. Nycthemeral rhythm in adrenal responsiveness to ACTH. Am. J. Physiol. R210–R218.

Dallman, M.F., Jones, M.T., 1973. Corticosteroid feedback control of ACTH secretion: effect of stress-induced corticosterone ssecretion on subsequent stress responses in the rat. Endocrinology 92, 1367–1375.

Dallman, M.F., Pecoraro, N., Akana, S.F., La Fleur, S.E., Gomez, F., Houshyar, H., Bell, M.E., Bhatnagar, S., Laugero, K.D., Manalo, S., 2003. Chronic stress and obesity: a new view of "comfort food". Proc. Natl. Acad. Sci. U.S.A. 100, 11696–11701.

Damasio, A.R., 1994. Decartes' Error: Emotion, Reason, and the Human Brain. Grosset/Putnam, New York.

Darlington, D.N., Barraclough, C.A., Gann, D.S., 1992. Hypotensive hemorrhage elevates corticotropin-releasing hormone messenger ribonucleic acid (mRNA) but not vasopressin mRNA in the rat hypothalamus. Endocrinology 130, 1281–1288.

Darlington, D.N., Keil, L.B., Dallman, M.F., 1989. Potentiation of hormonal responses to hemorrhage and fasting but not hypoglycemia in conscious ADX rats. Endocrinology 125, 1398–1406.

Davidson, A.J., Cappendijk, S.L., Stephan, F.K., 2000. Feeding-entrained circadian rhythms are attenuated by lesions of the parabrachial region in rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 278, R1296–R1304.

Davidson, A.J., Stephan, F.K., 1999. Feeding-entrained circadian rhythms in hypophysectomized rats with suprachiasmatic nucleus lesions. Am. J. Physiol. 277, R1376–R1384.

Davis, M., 1979. Morphine and naloxone: effects on conditioned fear as measured with the potentiated startle paradigm. Eur. J. Pharmacol. 54, 341–347.

Davis, M., 1998. Are different parts of the extended amygdala involved in fear versus anxiety? Biol. Psychiatry 44, 1239–1247.

Davis, M., Falls, W.A., Campeau, S., Kim, M., 1993. Fear-potentiated startle: a neural and pharmacological analysis. Behav. Brain Res. 58, 175–198.

Davis, M., Redmond Jr., D.E., Baraban, J.M., 1979. Noradrenergic agonists and antagonists: effects on conditioned fear as measured by the potentiated startle paradigm. Psychopharmacology (Berl.) 65, 111–118.

Davy, K.P., Hall, J.E., 2003. Obesity and hypertension: two epidemics or one? Am. J. Physiol. 286, R803–R813.

Day, H.E.W., Vittoz, N.M., Oates, M.M., Badiani, A., Watson Jr., S.J., Robinson, T.E., Akil, H., 2002. A 6-hydroxydopamine lesion of the mesostriatal dopamine system decreases the expression of corticotropin releasing hormone and neurotensin mRNAs in the amygdala and bed nucleus of the stria terminalis. Brain Res. 945, 151–159.

Day, T.A., 2005. Defining stress as a prelude to mapping its neurocircuitry: no help from allostasis. Prog. Neuropsychopharmacol. Biol. Psychiatry 29 (8), 1195–1200.

de Boer, S., Koopmans, S., Slangen, J., Van der Gugten, J., 1990. Plasma catecholamine, corticosterone and glucose responses to repeated stress in rats: effect of interstressor interval length. Physiol. Behav. 47, 1117–1124.

de Kloet, E.R., Oitzl, M.S., Joels, M., 1999. Stress and cognition: are corticosteroids good or bad guys? TINS 22, 422–426.

de Kloet, E.R., Vereugdenhil, E., Oitzl, M.S., Joels, M., 1998. Brain corticosteroid receptor balance in health and disease. Endocr. Rev. 19, 269–301.

De Novellis, V., Stotz-Potter, E.H., Morin, S.M., Rossi, F., DiMicco, J.A., 1995. Hypothalamic sites mediating cardiovascular effects of microinjected bicuculline and EAAs in rats. Am. J. Physiol. 269, R131–R140.

De Pedro, N., Alonso-Gomez, A.L., Gancedo, B., Delgado, M.J., Alonso-Bedate, M., 1993. Role of corticotropin-releasing factor (CRF) as a food intake regulator in goldfish. Physiol. Behav. 53, 517–520.

de Quervain, E.-F., Roozendaal, B., McGaugh, J.L., 1998. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 394, 787–790.

De Souza, E.B., Van Loon, G.R., 1982. Stress-induced inhibition of the plasma corticosterone response to a subsequent stress in rats: a nonadrenocorticotropin-mediated mechanism. Endocrinology 110, 23–33.

De Vos, P., Saladin, R., Auwerx, J., Staels, B., 1995. Induction of ob gene expression by corticosteroids is acompanied by weight loss and reduced food intake. J. Biol. Chem. 270, 15958–15961.

De Vry, J., Donselaar, I., Van Ree, J.M., 1989. Food deprivation and acquisition of intravenous cocaine self-administration in rats: effect of naltrexone and haloperidol. J. Pharmacol. Exp. Ther. 251, 735–740.

de Wit, H., Stewart, J., 1981. Reinstatement of cocaine-reinforced responding in the rat. Psychopharmacology (Berl.) 75, 134–143.

Delany, A.M., Gabbitas, B.Y., Canalis, E., 1995. Cortisol downregulates osteoblast alpha 1 (I) procollagen mRNA by transcriptional and posttranscriptional mechanisms. J. Cell Biochem. 57, 488–494.

Delfs, J.M., Zhu, Y., Druhan, J.P., Aston-Jones, G., 2000. Noradrenaline in the ventral forebrain is critical for opiate withdrawal-induced aversion. Nature 403, 430–434.

Delfs, J.M., Zhu, Y., Druhan, J.P., Aston-Jones, G.S., 1998. Origin of noradrenergic afferents to the shell subregion of the nucleus accumbens: anterograde and retrograde tract-tracing studies in the rat. Brain Res. 806, 127–140.

Delgado, J.M., 1960. Circulatory effects of cortical stimulation. Physiol. Rev. 40 (Suppl. 4), 146–178.

Delgado, J.M., Livingston, R.B., 1955. Motor representation in the frontal sulci of the cat. Yale J. Biol. Med. 28, 245–252.

Denver, R.J., 1997. Environmental stress as a developmental cue: corticotropin-releasing hormone is a promiximate mediator of adaptive phenotypic plasticity in amphibian metamorphosis. Horm. Behav. 31, 169–179.

Deroche, V., Marinelli, M., Le Moal, M., Piazza, P.V., 1997. Glucocorticoids and behavioral effects of psychostimulants. II: cocaine intravenous self-administration and reinstatement depend on glucocorticoid levels. J. Pharmacol. Exp. Ther. 281, 1401–1407.

Deroche, V., Marinelli, M., Maccari, S., Le Moal, M., Simon, H., Piazza, P.V., 1995. Stress-induced sensitization and glucocorticoids. I. Sensitization of dopamine-dependent locomotor effects of amphetamine and morphine depends on stress-induced corticosterone secretion. J. Neurosci. 15, 7181–7188.

Deroche, V., Piazza, P.V., Casolini, P., Le Moal, M., Simon, H., 1993. Sensitization to the psychomotor effects of amphetamine and morphine induced by food restriction depends on corticosterone secretion. Brain Res. 611, 352–356.

Deroche, V., Piazza, P.V., Casolini, P., Maccari, S., Le Moal, M., Simon, H., 1992. Stress-induced sensitization to amphetamine and morphine psychomotor effects depend on stress-induced corticosterone secretion. Brain Res. 598, 343–348.

Deroche, V., Piazza, P.V., Le Moal, M., Simon, H., 1994. Social isolation-induced enhancement of the psychomotor effects of morphine depends on corticosterone secretion. Brain Res. 640, 136–139.

Deroche-Gamonet, V., Sillaber, I., Aouizerate, B., Izawa, R., Jaber, M., Ghozland, S., Kellendonk, C., Le Moal, M., Spanagel, R., Schutz, G., Tronche, F., Piazza, P.V., 2003. The glucocorticoid receptor as a potential target to reduce cocaine abuse. J. Neurosci. 23, 4785–4790.

Deutch, A.Y., Cameron, D.S., 1992. Pharmacological characterization of dopamine systems in the nucleus accumbens core and shell. Neuroscience 46, 49–56.

Deutch, A.Y., Elsworth, J.D., Roth, R.H., Goldstein, M., 1990. 3-Acetylpyridine results in degeneration of the extrapyramidal and cerebellar motor systems: loss of the dorsolateral striatal dopamine innervation. Brain Res. 527, 96–102.

Di Chiara, G., Acquas, E., Tanda, G., Cadoni, C., 1993. Drugs of abuse: biochemical surrogates of specific aspects of natural reward? Biochem. Soc. Symp. 59, 65–81.

Di Chiara, G., Bassareo, V., Fenu, S., De Luca, M.A., Spina, L., Cadoni, C., Acquas, E., Carboni, E., Valentini, V., Lecca, D., 2004. Dopamine and drug addiction: the nucleus accumbens shell connection. Neuropharmacology 47 (Suppl. 1), 227–241.

Di Chiara, G., Loddo, P., Tanda, G., 1999a. Reciprocal changes in prefrontal and limbic dopamine responsiveness to aversive and rewarding stimuli after chronic mild stress: implications for the psychobiology of depression. Biol. Psychiatry 46, 1624–1633.

Di Chiara, G., Tanda, G., Bassareo, V., Pontieri, F., Acquas, E., Fenu, S., Cadoni, C., Carboni, E., 1999b. Drug addiction as a disorder of associative learning. Role of nucleus accumbens shell/extended amygdala dopamine. Ann. N.Y. Acad. Sci. 877, 461–485.

Diamant, M., Croiset, G., de Wied, D., 1992a. The effect of corticotropin-releasing factor (CRF) on autonomic and behavioral responses during shock-prod burying test in rats. Peptides 13, 1149–1158.

Diamant, M., Kashtanov, S.I., Fodor, M., de Wied, D., 1992b. Corticotropin-releasing factor induces differential behavioral and cardiovascular effects after intracerebroventricular and lateral hypothalamic/perifornical injections in rats. Neuroendocrinology 56, 750–760.

Diamond, D.M., Bennett, M.C., Fleshner, M., Rose, G.M., 1992. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. Hippocampus 2, 421–430.

Diamond, D.M., Campbell, A., Park, C.R., Vouimba, R.M., 2004. Preclinical research on stress, memory, and the brain in the development of pharmacotherapy for depression. Eur. Neuropsychopharmacol. 14 (Suppl. 5), S491–S495.

Diaz-Munoz, M., Vasques-Martinez, O., Aguilar-Roblero, R., Escobar, C., 2000. Anticipatory changes in liver metabolism and entrainment of insulin, glucagon and corticosterone in food-restricted rats. Am. J. Physiol. 279, R2048–R2056.

DiMicco, J.A., Abshire, V.M., Hankins, K.D., Sample, R.H., Wible Jr., J.H., 1986. Microinjection of GABA antagonists into posterior hypothalamus elevates heart rate in anesthetized rats. Neuropharmacology 25, 1063–1066.

DiMicco, J.A., Samuels, B.C., Zaretskaia, M.V., Zaretsky, D.V., 2002. The dorsomedial hypothalamus and the response to stress. Part renaissance, part revolution. Pharmacol. Biochem. Behav. 71, 469–480.

Diorio, D., Viau, V., Meaney, M.J., 1993. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic–pituitary–adrenal responses to stress. J. Neurosci. 13, 3839–3847.

Dobrakovova, M., Kvetnansky, R., Oprsalova, Z., Jezova, D., 1993. Specificity of the effect of repeated handling on sympathetic–adrenomedullary and pituitary–adrenocortical activity in rats. Psychoneuroendocrinology 18, 163–174.

Doerr, P., von Zerssen, D., Fischler, M., Schulz, H., 1979. Relationship between mood changes and adrenal cortical activity in a patient with 48-hour unipolar-depressive cycles. J. Affect Disord. 1, 93–104.

Domanski, E., Romanowicz, K., Kerdelhue, B., 1993. Enhancing effect of intracerebrally infused beta-endorphin antiserum on the secretion of cortisol in foot-shocked sheep. Neuroendocrinology 57, 127–131.

Dove, L.D., 1976. Relation between level of food deprivation and rate of schedule-induced attack. J. Exp. Anal. Behav. 25, 63–68.

Drolet, G., Dumont, E.C., Gosselin, I., Kinkead, R., LaForest, S., Trottier, J.-F., 2001. Role of endogenous opioid system in the regulation of the stress resposne. Prog. Neuropsychopharmacol. Biol. Psychiatry 25, 729–741.

Drolet, G., Van Bockstaele, E.J., Aston-Jones, G., 1992. Robust enkephalin innervation of the locus coeruleus from the rostral medulla. J. Neurosci. 12, 3162–3174.

Duclos, M., Bouchet, M., Vettier, A., Richard, D., 2005a. Genetic differences in hypothalamic–pituitary–adrenal axis activity and food restriction-induced hyperactivity in three inbred strains of rats. J. Neurendocrinol. 17, 740–752.

Duclos, M., Timofeeva, E., Michel, C., Richard, D., 2005b. Corticosterone-dependent metabolic and neuroendocrine abnormalities in obese Zucker rats in relation to feeding. Am. J. Physiol. Endocrinol. Metab. 288, E254–E266.

Duka, T., Townshend, J.M., Collier, K., Stephens, D.N., 2002. Kindling of withdrawal: a study of craving and anxiety after multiple detoxifications in alcoholic inpatients. Alcohol Clin. Exp. Res. 26, 785–795.

Duman, R.S., Tallman, J.F., Nestler, E.J., 1988. Acute and chronic opiate-regulation of adenylate cyclase in brain: specific effects in locus coeruleus. J. Pharmacol. Exp. Ther. 246, 1033–1039.

Dumont, E.C., Kinkead, R., Trottier, J.-F., Gosselin, I., Drolet, G., 2000. Effect of chronic psychogenic stress exposure on enkephalin neuronal activity and expression in the rat hypothalamic paraventricular nucleus. J. Neurochem. 75, 2200–2211.

Dunn, A.J., Berridge, C.W., 1990. Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? Brain Res. Rev. 15, 71–100.

Dunn, A.J., Swiergiel, A.H., Palamarchouk, V., 2004. Brain circuits involved in corticotropin-releasing factor-norepinephrine interactions during stress. Ann. N.Y. Acad. Sci. 1018, 25–34.

Dunn, J.D., 1987a. Differential plasma corticosterone responses to electrical stimulation of the medial and lateral septal nuclei. Neuroendocrinology 46, 406–411.

Dunn, J.D., 1987b. Plasma corticosterone responses to electrical stimulation of the bed nucleus of the stria terminalis. Brain Res. 407, 327–331.

Durrant, E.P., 1924. Studies on vigor. 1. Affect of adrenalin extirpation on activity of the albino rat. Am. J. Physiol. 70, 344–350.

Dyson, T., 1999a. Prospects for feeding the world. BMJ 319, 988–990 discussion 991.

Dyson, T., 1999b. World food trends and prospects to 2025. Proc. Natl. Acad. Sci. U.S.A. 96, 5929–5936.

Dyson, T., 2001. World food trends: a neo-Malthusian prospect? Proc. Am. Philos. Soc. 145, 438–455.

Eaton, M.J., Cheung, S., Moore, K.E., Lookingland, K.J., 1996. Dopamine receptor-mediated regulation of corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus. Brain Res. 738, 60–66.

Egawa, M., Yoshimatsu, H., Bray, G.A., 1991. Neuropeptide Y suppresses sympathetic activity to interscapular brown adipose tissue in rats. Am. J. Physiol. 260, R328–R334.

Ehlers, C.L., Henriksen, S.J., Wang, M., Rivier, J., Vale, W., Bloom, F.E., 1983. Corticotropin releasing factor produces increases in brain excitability and convulsive seizures in rats. Brain Res. 278, 332–336.

Ehrman, R., Ternes, J., O'Brien, C.P., McLellan, A.T., 1992. Conditioned tolerance in human opiate addicts. Psychopharmacology (Berl.) 108, 218–224.

Eichenbaum, H., 2003. How does the hippocampus contribute to memory? Trends Cogn. Sci. 7, 427–429.

Eichenbaum, H., Stewart, C., Morris, R.G., 1990. Hippocampal representation in place learning. J. Neurosci. 10, 3531–3542.

Eikelboom, R., Stewart, J., 1981. Conditioned temperature effects using amphetamine as the unconditioned stimulus. Psychopharmacology (Berl.) 75, 96–97.

Eikelboom, R., Stewart, J., 1982. Conditioning of drug-induced physiological responses. Psychol. Rev. 89, 507–528.

Eisenberg, R.M., 1985. Effects of chronic treatment with diazepam, phenobarbital, or amphetamine on naloxone-precipitated morphine withdrawal. Drug Alcohol Depend. 15, 375–381.

Elias, C.F., Aschkenasi, C., Lee, C., Kelly, J., Ahima, R.S., Bjorbaek, C., Flier, J.S., Saper, C.B., Elmquist, J.K., 1999. Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. Neuron 23, 775–786.

Emmert, M.H., Herman, J.P., 1999. Differential forebrain *c*-fos mRNA induction by ether inhalation and novelty: evidence for distinctive stress pathways. Brain Res. 845, 60–67.

Erb, S., Salmaso, N., Rodaros, D., Stewart, J., 2001. A role for the CRF-containing pathway from central neucleus of the amygdala to bed nucleus of the stria terminalis in the stress-induced reinstatement of cocaine seeking in rats. Psychopharmacology 158, 360–365.

Erb, S., Shaham, Y., Stewart, J., 1996. Stress reinstates cocaine-seeking behavior after prolonged extinction and a drug-free period. Psychopharmacology (Berl.) 128, 408–412.

Erb, S., Shaham, Y., Stewart, J., 1998. The role of corticotropin-releasing factor and corticosterone in stress- and cocaine-induced relapse to cocaine seeking in rats. J. Neurosci. 18, 5529–5536.

Erickson, K., Drevets, W.C., Schulkin, J., 2003. Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. Neurosci. Biobehav. Rev. 27, 233–246.

Everitt, B.J., Parkinson, J.A., Olmstead, M.C., Arroyo, M., Robledo, P., Robbins, T.W., 1999. Associative processes in addiction and reward. The role of amygdala- ventral striatal subsystems. Ann. N.Y. Acad. Sci. 877, 412–438.

Faggiano, A., Pivonello, R., Spiezia, S., de Martino, M.C., Filippella, M.d.S.C., Lombardi, G., Colao, A., 2003. Cardiovascular risk factors and common carotid arter caliber and stiffness in patients with Cushing's Disease during active disease and 1 year after disease remission. J. Clin. Endocrinol. Metab. 88, 2527–2533.

Fahlke, C., Hansen, S., 1999. Effect of local intracerebral corticosterone implants on alcohol intake in the rat. Alcohol Alcohol. 34, 851–861.

Fahlke, C., Hard, E., Hansen, S., 1996. Facilitation of ethanol consumption by intracerebroventricular infusions of corticosterone. Psychopharmacology (Berl.) 127, 133–139.

Fahlke, C., Hard, E., Thomasson, R., Engel, J.A., Hansen, S., 1994. Metyrapone-induced suppression of corticosterone synthesis reduces ethanol consumption in high-preferring rats. Pharmacol. Biochem. Behav. 48, 977–981.

Falk, J.L., 1961. Production of polydipsia in normal rats by an intermittent food schedule. Science 133, 195–196.

Falk, J.L., 1966a. Addictive behavior with and without pharmacologic action: critical role of stimulus control. NIDA Res. Monogr. 169, 134–153.

Falk, J.L., 1966b. The motivational properties of schedule-induced polydipsia. J. Exp. Anal. Behav. 9, 19–25.
Falk, J.L., 1969. Conditions producing psychogenic polydipsia in animals. Ann. N.Y. Acad. Sci. 157, 569–593.
Falk, J.L., 1971. The nature and determinants of adjunctive behavior. Physiol. Behav. 6, 577–588.
Fanselow, M.S., 1994. Neural organization of the defensive behavior system responsible for fear. Psychonom. Bull. Rev. 1, 429–438.
Fanselow, M.S., 2000. Contextual fear, gestalt memories, and the hippocampus. Behav. Brain Res. 110, 73–81.
Fanselow, M.S., LeDoux, J.E., 1999. Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. Neuron 23, 229–232.
Fanselow, M.S., Lester, L.S., Helmstetter, F.J., 1988. Changes in feeding and foraging patterns as an antipredator defensive strategy: a laboratory simulation using aversive stimulation in a closed economy. J. Exp. Anal. Behav. 50, 361–374.
Fanselow, M.S., Sigmundi, R.A., 1986. Species-specific danger signals, endogenous opioid analgesia, and defensive behavior. J. Exp. Psychol. Anim. Behav. Process 12, 301–309.
Fantino, M., Hosotte, J., Apfelbaum, M., 1986. An opioid antagonist, naltrexone, reduces preference for sucrose in humans. Am. J. Physiol. 251, R91–R96.
Fava, M., Rappe, S.M., West, J., Herzog, D.B., 1995. Anger attacks in eating disorders. Psychiatry Res. 56, 205–212.
Feldman, S., Conforti, N., 1985. Modifications of adrenocortical responses following frontal cortex simulation in rats with hypothalamic deafferentations and medial forebrain bundle lesions. Neuroscience 15, 1045–1047.
Feldman, S., Saphier, D., Weidenfeld, J., 1992. Corticosterone implants in the paraventricular nucleus inhibit ACTH and corticosterone responses and the release of corticotropin-releasing factor following neural stimuli. Brain Res. 578, 251–255.
Fendt, M., Fanselow, M.S., 1999. The neuroanatomical and neurochemical basis of conditioned fear. Neurosci. Biobehav. Rev. 23, 743–760.
Ferry, B., Roozendaal, B., McGaugh, J.L., 1999. Role of norepinephrine in mediating stress hormone regulation of long-term memory storage: a critical involvement of the amygdala. Biol. Psychiatry 46, 1140–1152.
Fessler, D.M., 2003. The implications of starvation induced psychological changes for the ethical treatment of hunger strikers. J. Med. Ethics 29, 243–247.
Fichter, M.M., Pirke, K.M., 1984. Hypothalamic pituitary function in starving healthy subjects. In: Pirke, K.M., Ploog, D. (Eds.), The Psychobiology of Anorexia Nervosa. Springer-Verlag, Berlin, pp. 124–135.
Figlewicz, D.P., 1999a. Endocrine regulation of neurotransmitter transporters. Epilepsy Res. 37, 203–210.
Figlewicz, D.P., 1999b. Endocrine regulation of the neurotransmitter transporters. Epilepsy Res. 37, 203–210.
Filibeck, U., Cabib, S., Castellano, C., Puglisi-Allegra, S., 1988. Chronic cocaine enhances defensive behaviour in the laboratory mouse: involvement of D2 dopamine receptors. Psychopharmacology (Berl.) 96, 437–441.
Filliol, D., Ghozland, S., Chluba, J., Martin, M., Matthes, H.W., Simonin, F., Befort, K., Gaveriaux-Ruff, C., Dierich, A., LeMeur, M., Valverde, O., Maldonado, R., Kieffer, B.L., 2000. Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. Nat. Genet. 25, 195–200.
Finlay, J.M., Zigmond, M.J., Abercrombie, E.D., 1995. Increased dopamine and norepinephrine release in medial prefrontal cortex induced by acute and chronic stress: effects of diazepam. Neuroscience 64, 619–628.
Fiserova, M., Consolo, S., Krsiak, M., 1999. Chronic morphine induces long-lasting changes in acetylcholine release in rat nucleus accumbens core and shell: an in vivo microdialysis study. Psychopharmacology (Berl.) 142, 85–94.
Flaherty, C.F., 1996. Incentive Relativity. Cambridge University Press, New York, NY, US.
Flaherty, C.F., Becker, H.C., Porhorecky, L., 1985. Correlation of corticosterone elevation and negative contrast varies as a function of postshift day. Anim. Learn. Behav. 13, 309–314.
Fleischer, N., Vale, W., 1968. Inhibition of vasopressin-induced ACTH release from the pituitary by glucocorticoids in vitro. Endocrinology 83, 1232–1236.
Flier, J.S., 2004. Obesity wars: molecular progress confronts an expanding epidemic. Cell 116, 337–350.
Flood, J.F., Vidal, D., Bennett, E.L., Orme, A.E., Vasquez, S., Jarvik, M.E., 1978. Memory facilitating and anti-amnesic effects of corticosteroids. Pharmacol. Biochem. Behav. 8, 81–87.
Flory, R.K., Smith, C.T., 1983. Effects of limited-target availability on schedule-induced attack. Physiol. Behav. 30, 11–18.
Follenius, M., Brandenberger, G., Hietter, B., 1982. Diurnal cortisol peaks and their relationships to meals. J. Clin. Endocrinol. Metab. 55, 757–761.
Fontes, M.A., Tagawa, T., Polson, J.W., Cavanagh, S.J., Dampney, R.A., 2001. Descending pathways mediating cardiovascular response from dorsomedial hypothalamic nucleus. Am. J. Physiol. Heart Circ. Physiol. 280, H2891–H2901.
Foote, S.L., Berridge, C.W., Adams, L.M., Pineda, J.A., 1991. Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. Prog. Brain Res. 88, 521–532.
Fox, E.A., Powley, T.L., 1992. Morphology of identified preganglionic neurons in the dorsal motor nucleus of the vagus. J. Comp. Neurol. 322, 79–98.
Foy, M.R., Stanton, M.E., Levine, S., Thompson, R.F., 1987. Behavioral stress impairs long-term potentiation in rodent hippocampus. Behav. Neural. Biol. 48, 138–149.
Frankino, W.A., Raff, R.A., 2004. Evolutionary importance and pattern of phenotypic plasticity: insights gained from development. In: De Witt, T.J., Scheiner, S.M. (Eds.), Phenotypic Plasticity: Functional and Conceptual Approaches. Oxford University Press, New York, pp. 64–81.
Frasure-Smith, N., Lespereance, F., Talajic, M., 1993. Depression following myocardial infarction. Impact on 6-month survival. JAMA 270, 1819–1825.
Fredricksen, L.W., Peterson, G.L., 1977. Schedule-induced aggression in humans and animalas: a comparative parametric review. Aggressive Behav. 3, 57–75.
Freedman, M.K., Horwitz, B.A., Stern, J.S., 1986. Effect of adrenalectomy and glucocorticoid replacement on the development of obesity. Am. J. Physiol. 250, R595–R607.
Fried, S.K., Bunkin, D.A., Greenberg, A.S., 1998. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J. Clin. Endocrinol. Metab. 83, 847–850.
Fried, S.K., Russell, C.D., Grauso, N.L., Brolin, R.E., 1993. Lipoprotein lipase regulation by insulin and glucocorticoid in subcutaneous and omental adipose tissues of obese women and men. J. Clin. Invest. 92, 2191–2198.
Friedman, J.E., Yun, J.S., Patel, Y.M., McGrane, M.M., Hanson, R.W., 1993. Glucocorticoids regulate the induction of phosphoenolpyruvate carboxykinase (GTP) gene transcription during diabetes. J. Biol. Chem. 268, 12952–12957.
Friedman, M.I., 1997. An energy sensor for control of energy intake. Proc. Nutr. Soc. 56, 41–50.
Frisina, P.G., Sclafani, A., 2002. Naltrexone suppresses the late but not early licking response to a palatable sweet solution: opioid hedonic hypothesis reconsidered. Pharmacol. Biochem. Behav. 74, 163–172.
Gaillet, S., Alonso, G., Le Borgne, R., Barbanel, G., Malaval, F., Assenmacher, I., Szafarczyk, A., 1993. Effects of discrete lesions in the ventral noradrenergic ascending bundle on the corticotropic stress response depend on the site of the lesion and on the plasma levels of adrenal steroids. Neuroendocrinology 58, 408–419.
Gallagher, M., Kapp, B.S., Pascoe, J.P., 1982. Enkephalin analogue effects in the amygdala central nucleus on conditioned heart rate. Pharmacol. Biochem. Behav. 17, 217–222.
Gallistel, C., 1990. The Organization of Learning. MIT Press, Cambridge, MA.
Galvez, R., Mesches, M.H., McGaugh, J.L., 1996. Norepinephrine release in the amygdala in response to footshock stimulation. Neurobiol. Learn. Mem. 66, 253–257.
Gardner, R.A., Gardner, B.T., 1988. Feedforward versus feedbackward: an ethological alternative to the law of effect. Behav. Brain Sci. 11, 429–447.
Ghitza, U.E., Gray, S.M., Epstein, D.H., Rice, K.C., Shaham, Y., 2005. The anxiogenic drug yohimbine reinstates palatable food seeking in a rat relapse

model: a role of CRF1 receptors. Neuropsychopharmacology, doi:10.1038/sj.npp.1300964.

Giacchino, J.L., Henriksen, S.J., 1996. Systemic morphine and local opioid effects on neuronal activity in the medial prefrontal cortex. Neuroscience 70, 941–949.

Giacchino, J.L., Henriksen, S.J., 1998. Opioid effects on activation of neurons in the medial prefrontal cortex. Prog. Neuropsychopharmacol. Biol. Psychiatry 22, 1157–1178.

Gilad, G.M., Rabey, J.M., Gilad, V.H., 1987. Presynaptic effects of glucocorticoids on dopaminergic and cholinergic synaptosomes. Implications for rapid endocrine-neural interactions in stress. Life Sci. 40, 2401–2408.

Gillies, G.E., Linton, E.A., Lowry, P.J., 1982. Corticotropin releasing activity of the new CRF is potentiated several times by vasopressin. Nature 299, 355–357.

Ginsberg, A.B., Frank, M.G., Francis, A.B., Rubin, B.A., O'Connor, K.A., Spencer, R.L., 2006. Specific and time-dependent effects of glucocorticoid receptor agonist RU28362 on stress-induced pro-opiomelanocortin hnRNA, c-fos mRNA and zif268 mRNA in the pituitary. J. Neuroendocrinol. 18 (2), 129–138.

Ginsberg, A., O'Connor, K.A., Spencer, R.L., 2003. Negative feedback effects of glucocortioid receptor agonist RU28362 on stress-induced gene expression in the PVN and pituitary. Abstract Viewer/Itinerary Planner. Society for Neuroscience, Washington, DC, 2003, Program No. 282.17.

Giralt, M., Armario, A., 1989. Individual housing does not influence the adaptation of the pituitary–adrenal axis and other physiological variables to chronic stress in adult male rats. Physiol. Behav. 45, 477–481.

Giraudo, S.Q., Grace, M.K., Billington, C.J., Levine, A.S., 1999. Differential effects of neuropeptide Y and the u-agonist DAMGO on 'palatability' vs. 'energy' Brain Res. 834, 160–163.

Giraudo, S.Q., Kotz, C.M., Billington, C.J., Levine, A.S., 1998. Association between the amygdala and the nucleus of the solitary tract in u-opioid induced feeding in the rat. Brain Res. 802, 184–188.

Girod, J.P., Brotman, D.J., 2004. Does altered glucocorticoid homeostasis increase cardiovascular risk? Cardiovasc. Res. 64, 217–226.

Glass, M.J., Billington, C.J., Levine, A.S., 1999. Opioids and food intake: distributed functional neural pathways? Neuropeptides 33, 360–368.

Glass, M.J., Billington, C.J., Levine, A.S., 2000. Opioids, food reward and macronutrient selection. In: Berthoud, H.-R., Seeley, R.J. (Eds.), Neural and Metabolic Control of Macronutrient Selection. CRC Press, Boca Raton, pp. 407–423.

Glennemeier, K.A., Denver, R.J., 2002. Small changes in whole-body corticosterone content affect larval Rana pipiens fitness components. Gen. Comp. Endocrinol. 127, 16–25.

Glick, S.D., Cox, R.S., Crane, A.M., 1975. Changes in morphine self-administration and morphine dependence after lesions of the caudate nucleus in rats. Psychopharmacologia 41, 219–224.

Goeders, N.E., 1997. A neuroendocrine role in cocaine reinforcement. Psychoneuroendocrinology 22, 237–259.

Goeders, N.E., Guerin, G.F., 1994. Non-contingent electric footshock facilitates the acquisition of intravenous cocaine self-administration in rats. Psychopharmacology (Berl.) 114, 63–70.

Goeders, N.E., Guerin, G.F., 1996a. Effects of surgical and pharmacological adrenalectomy on the initiation and maintenance of intravenous cocaine self-administration in rats. Brain Res. 722, 145–152.

Goeders, N.E., Guerin, G.F., 1996b. Role of corticosterone in intravenous cocaine self-administration in rats. Neuroendocrinology 64, 337–348.

Goff, S., 2006. In: Huffington, A. (Ed.), KIA in Alabama. The Huffington Post.

Gold, P.W., Chrousos, G.P., 2002. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs. low CRH/NE states. Mol. Psychiatry 7, 254–275.

Gold, P.W., Gabry, K.E., Yasuda, M.R., Chrousos, G.P., 2002. Divergent endocrine abnormalities in melancholic and atypical depression: clinical and pathophysiologic implications. Endocrinol. Metab. Clin. North Am. 31, 37–62 vi.

Gold, P.W., Goodwin, F.K., Chrousos, G.P., 1988a. Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (1). N. Engl. J. Med. 319, 348–353.

Gold, P.W., Goodwin, F.K., Chrousos, G.P., 1988b. Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (2). N. Engl. J. Med. 319, 413–420.

Gold, P.W., Gwittsman, H.E., Aveignie, P.C., Nieman, L.K., Galluci, W.T., Kaye, W.H., Jimerson, D., Ebert, M., Rittmaster, R., Loriaux, D.L., Chrousos, G.P., 1986. Abnormal hypothalamic–pituitary–adrenal function in anorexia nervosa: pathophysiologic mechanisms in underweight and weight corrected patients. N. Engl. J. Med. 314, 1335–1342.

Goldman, L., Coover, G.O., Levine, S., 1973. Bidirectional effects of reinforcement shifts on pituitary adrenal activity. Physiol. Behav. 10, 209–214.

Goldman-Rakic, P.S., 1987a. Circuitry of the frontal association cortex and its relevance to dementia. Arch. Gerontol. Geriatr. 6, 299–309.

Goldman-Rakic, P.S., 1987b. Development of cortical circuitry and cognitive function. Child Dev. 58, 601–622.

Gomez, F., Leo, N.A., Grigson, P.S., 2000. Morphine-induced suppression of saccharin intake is correlated with elevated corticosterone levels. Brain Res. 863, 52–58.

Goncharuk, V.D., Van Heerikhuize, J., Swaab, D.F., Buijs, R.M., 2002. Paraventricular nucleus of the human hypothalamus in primary hypertension: activation of corticotropin-releasing hormone neurons. J. Comp. Neurol. 443, 321–331.

Good, A.J., Westbrook, R.F., 1995. Effects of a microinjection of morphine into the amygdala on the acquisition and expression of conditioned fear and hypoalgesia in rats. Behav. Neurosci. 109, 631–641.

Goodwin, G.M., Muir, W.J., Seckl, J.R., Bennie, J., Carroll, S., Dick, H., Fink, G., 1992. The effects of cortisol infusion upon hormone secretion from the anterior pituitary and subjective mood in depressive illness and in controls. J. Affect. Disord. 26, 73–83.

Gooley, J., Schomer, A., Saper, C.B., 2006. The dorsomedial hypothalamic nucleus is critical for the expression of food-entrainable circadian rhythms. Nat. Neurosci. 398–407.

Goosens, K.A., Maren, S., 2002. Long-term potentiation as a substrate for memory: evidence from studies of amygdaloid plasticity and Pavlovian fear conditioning. Hippocampus 12, 592–599.

Gosnell, B.A., Krahn, D.D., Majchrzak, M.J., 1990a. The effects of morphine on diet selection are dependent upon baseline diet preferences. Pharmacol. Biochem. Behav. 37, 207–212.

Gosnell, B.A., Majchrzak, M.J., Krahn, D.D., 1990b. Effects of preferential delta and kappa opioid receptor agonists on the intake of hypotonic saline. Physiol. Behav. 47, 601–603.

Goto, M., Swanson, L.W., 2004. Axonal projections from the parasubthalamic nucleus. J. Comp. Neurol. 469, 581–607.

Gould, E., Tanapat, P., Rydel, T., Hastings, N., 2000. Regulation of hippocampal neurogenesis in adulthood. Biol. Psychiatry 48, 715–720.

Gould, E., Woolley, C.S., McEwen, B.S., 1990. Short-term glucocorticoid manipulations affect neuronal morphology and survival in the adult dentate gyrus. Neuroscience 37, 367–375.

Grace, A.A., Rosenkranz, J.A., 2002. Regulation of conditioned responses of basolateral amygdala neurons. Physiol. Behav. 77, 489–493.

Graham, J.C., Hoffman, G.E., Sved, A.F., 1995. *c*-Fos expression in brain in response to hypotension and hypertension in conscious rats. J. Auton. Nerv. Syst. 55, 92–104.

Gray, G.D., Bergfors, A.M., Levin, R., Levine, S., 1978. Comparison of the effects of restricted morning or evening water intake on adrenocortical activity in female rats. Neuroendocrinology 25, 236–246.

Gray, T.S., 1993. Amygdaloid CRF pathways Role in autonomic, neuroendocrine, and behavioral responses to stress. In: Tache, Y., Rivier, C. (Eds.), Corticotropin-Releasing Factor and Cytokines: Role in the Stress Response, vol. 697. New York Academy of Sciences, New York, pp. 53–60.

Gray, T.S., Bingaman, E.W., 1996. The amygdala: corticotropin-releasing fator, steroids and stress. Crit. Rev. Neurobiol. 10, 155–168.

Greenwood-Van Meerveld, B., Gibson, M., Gunter, W., Shepard, J., Foreman, R., Myers, D., 2001. Stereotaxic delivery of corticosterone to the amygdala modulates colonic sensitivity in rats. Brain Res. 893, 135–142.

Greenwood-Van Meerveld, B., Johnson, A.C., Cochrane, S., Schulkin, J., Myers, D.A., 2005. Corticotropin-releasing factor 1 receptor-mediated mechanisms inhibit colonic hypersensitivity in rats. Neurogastroenterol. Motil. 17, 415–422.

Gresch, P.J., Sved, A.F., Zigmond, M.J., Finlay, J.M., 1995. Local influence of endogenous norepinephrine on extracellular dopamine in rat medial prefrontal cortex. J. Neurochem. 65, 111–116.

Grigson, P.S., Twining, R.C., 2002. Cocaine-induced suppression of saccharin intake: a model of drug-induced devaluation of natural rewards. Behav. Neurosci. 116, 321–333.

Grigson, P.S., Twining, R.C., Carelli, R.M., 2000. Heroin-induced suppression of saccharin intake in water-deprived and water-replete rats. Pharmacol. Biochem. Behav. 66, 603–608.

Grill, H.J., Norgren, R., 1978. The taste reactivity test. II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. Brain Res. 143, 281–297.

Grinevich, V., Ma, X.M., Verbalis, J., Aguilera, G., 2001. Hypothalamic pituitary adrenal axis and hypothalamic-neurohypophyseal responsiveness in water-deprived rats. Exp. Neurol. 171, 329–341.

Grinker, R.R., Spiegel, J.P., 1945. Men Under Stress. Blakiston, Philadelphia, PA.

Grizzle, W.E., Dallman, M.F., Schramm, L.P., Gann, D.S., 1974. Inhibitory and facilitatory hypothalamic areas mediating ACTH release in the cat. Endocrinology 95, 1450–1461.

Groenewegen, H.J., Wright, C.I., Beijer, A.V., 1996. The nucleus accumbens: gateway for limbic structures to reach the motor system? Prog. Brain Res. 107, 485–511.

Groop, L.C., Widen, E., Ferrannini, E., 1993. Insulin resistance and insulin deficiency in the pathogenesis of type 2 (non-insulin-dependent) diabetes mellitus: errors of metabolism or of methods? Diabetologia 36, 1326–1331.

Guillaume, V., Conte-Devolx, B., Szafarczyk, A., Malaval, F., Pares-Herbute, N., Grino, M., Alonso, G., Assenmacher, I., Oliver, C., 1987. The corticotropin-releasing factor release in rat hypophysial portal blood is mediated by brain catecholamines. Neuroendocrinology 46, 143–146.

Guthrie, E.R., 1938. The Psychology of Human Conflict: The Clash of Motives within the Individual. Harper, Oxford, UK.

Guthrie, E.R., 1953. The Psychology of Learning. Harper, Oxford, UK.

Gwynne, D., Rentz, D., 1983. Beetles on the bottle: male bupestrids mistake stubbies for females. J. Entomol. Soc. Aust. 22, 79–80.

Hagan, M.M., Moss, D.E., 1991. An animal model of bulimia nervosa: opioid sensitivity to fasting episodes. Pharmacol. Biochem. Behav. 39, 421–422.

Hakim, H., DeBernardo, A.P., Silver, R., 1991. Circadian locomotor rhythms, but not photoperiodic responses, survive surgical isolation of the SCN in hamsters. J. Biol. Rhythms 6, 97–113.

Haley, S.A., 1974. When the patient reports atrocities. Arch. Gen. Psychiatry 30, 191–196.

Hall, R.C., Popkin, M.K., Stickney, S.K., Gardner, E.R., 1979. Presentation of the steroid psychoses. J. Nerv. Ment. Dis. 167, 229–236.

Haller, J., Kiem, D.T., Makara, G.B., 1996. The physiology of social conflict in rats: what is particularly stressful? Behav. Neurosci. 110, 353–359.

Handa, R.J., Nunley, K.M., Bollnow, M.R., 1993. Induction of *c*-fos mRNA in the brain and anterior pituitary gland by a novel environment. Neuroreport 4, 1079–1082.

Haney, M., Maccari, S., Le Moal, M., Simon, H., Piazza, P.V., 1995. Social stress increases the acquisition of cocaine self-administration in male and female rats. Brain Res. 698, 46–52.

Hansen, S., Fahlke, C., Soderpalm, A.H., Hard, E., 1995. Significance of adrenal corticosteroid secretion for the food restriction-induced enhancement of alcohol drinking in the rat. Psychopharmacology (Berl.) 121, 213–221.

Hanson, E.S., Levin, N., Dallman, M.F., 1997. Elevated corticosterone is not required for the rapid induction of NPY gene expression by an overnight fast. Endocrinology 138, 1041–1047.

Harbuz, M.S., Lightman, S.L., 1989. Responses of hypothalamic and pituitary mRNA to physical and psychological stress in the rat. J. Endocrinology 122, 705–711.

Harfstrand, A., Fuxe, K., Cintra, A., Agnati, L.F., Zini, I., Wikstrom, A.-C., Okret, S., Yu, Z.-Y., Goldstein, M., Steinbusch, H., Verhofstad, A., Gustafsson, J.-Å., 1986. Glucocorticoid receptor immunoreactivity in monoaminergic neurons of rat brain. Proc. Natl. Acad. Sci. U.S.A. 83, 9779–9783.

Harris, G.C., Wimmer, M., Byrne, R., Aston-Jones, G., 2004. Glutamate-associated plasticity in the ventral tegmental area is necessary for conditioning environmental stimuli with morphine. Neuroscience 129, 841–847.

Haskell-Luevano, C., Chen, P., Li, C., Chang, K., Smith, M.S., Cameron, J.L., Cone, R.D., 1999. Characterization of the neuroanatomical distribution of agouti-related protein immunoreactivity in the Rhesus monkey and the rat. Endocrinology 140, 1408–1415.

Hasue, R.H., Shammah-Lagnado, S.J., 2002. Origin of the dopaminergic innervation of the central extended amygdala and accumbens shell: a combined retrograde tracing and immunohistochemical study in the rat. J. Comp. Neurol. 454, 15–33.

Hauger, R.L., Lorang, M., Irwin, M., Aguilera, G., 1990. CRF receptor regulation and sensitization of ACTH responses to acute ether stress during chronic intermittent immobilization stress. Brain Res. 532, 34–40.

Hauser, M.D., 1999. Perseveration, inhibition and the prefrontal cortex: a new look. Curr. Opin. Neurobiol. 9, 214–222.

Hautanen, A., Adlercreutz, H., 1993. Altered adrenocorticotropin and cortisol secretion in abdominal obesity: implications for the insulin resistance syndrome. J. Intern. Med. 234, 461–469.

He, B., White, B.D., Edwards, G.L., Martin, R.J., 1998. Longer-term fourth ventricular 5-thioglucose infusion increases body fat in the rat. Proc. Soc. Exp. Biol. Med. 217, 168–172.

Hearst, E., Jenkins, H.M., 1974. Sign-Tracking: The Stimulus-Reinforcer Relation and Directed Action. Psychonomic Society, Austin, TX.

Hebb, D.O., 1949. The Organization of Behavior: A Neuropsychological Theory. John Wiley and Sons, New York, NY.

Hecaen, H., Albert, M.L., 1978. Human Neuropsychology. John Wiley, New York, NY.

Heiman, M.L., Ahima, R.S., Craft, L.S., Schoner, B., Stephens, T.W., Flier, J.S., 1997. Leptin inhibition of the hypothalamic–pituitary–adrenal axis in response to stress. Endocrinology 138, 3859–3863.

Heinrichs, S.C., Britton, K.T., Koob, G.F., 1991. Both conditioned taste preference and aversion induced by corticotropin-releasing factor. Pharmacol. Biochem. Behav. 40, 717–721.

Helm, K.A., Rada, P.V., Hoebel, B.G., 2003. Cholecystokinin combined with serotonin in the hypothalamus limits accumbens dopamine release while increasing acetylcholine: a possible satiation mechanism. Brain Res. 963, 290–297.

Hemingway, H., Marmot, M., 1999. Psychosocial factors in the aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies. BMJ 318, 1460–1467.

Hench, P.S., 1950. The reversibility of certain rheumatic and non-rheumatic conditions by the use of cortisone or of the pituitary adrenocorticotropic hormone. In: Nobel Lectures, Physiology or Medicine 1942–1962, Elsevier, Amsterdam, Netherlands.

Hench, P.S., Slocumb, C.H., Barnes, A.R., Smith, H.L., Polley, H.F., Kendall, E.C., 1949. The effect of the hormone of the adrenal cortex, 17-hydroxy-11-dehydrocorticosterone (compound E), on the acute phase of rheumatic fevers. Mayo Clin. Proc. 24, 277–279.

Hendry, D., Rasche, R.H., 1961. Analysis of a new nonnutritive positive reinforcer based on thirst. J. Comp. Physiol. Psychol. 54, 477–483.

Herman, J.P., Cullinan, W.E., Morano, M.I., Akil, H., Watson, S.J., 1995. Contribution of the ventral subiculum to inhibitory regulation of the hypothalamo–pituitary–adrenocortical axis. J. Neuroendocrinol. 7, 475–482.

Herman, J.P., Dolgas, C.M., Carlson, S.L., 1998. Ventral subiculum regulates hypothalamo–pituitary–adrenocortical and behavioral responses to cognitive stressors. Neuroscience 86, 449–459.

Herman, J.P., Figueriedo, H.F., Mueller, N.K., Ulrich-Lai, Y., Ostrander, M.M., Choi, D.C., Culinan, W.E., 2003. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo–pituitary–adrenocortical responsiveness. Front. Neuroendocrinol. 24, 151–180.

Herman, J.P., Tasker, J.G., Ziegler, D.R., Cullinan, W.E., 2002. Local circuit regulation of paraventricular nucleus stress integration. Glutamate-GABA connections. Pharmacol. Biochem. Behav. 71, 457–468.

Hernandez, L., Hoebel, B.G., 1988a. Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. Physiol. Behav. 44, 599–606.

Hernandez, L., Hoebel, B.G., 1988b. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci. 42, 1705–1712.

Herzog, D.B., Keller, M.B., Lavori, P.W., Kenny, G.M., Sacks, N.R., 1992a. The prevalence of personality disorders in 210 women with eating disorders. J. Clin. Psychiatry 53, 147–152.

Herzog, D.B., Keller, M.B., Sacks, N.R., Yeh, C.J., Lavori, P.W., 1992b. Psychiatric comorbidity in treatment-seeking anorexics and bulimics. J. Am. Acad. Child Adolesc. Psychiatry 31, 810–818.

Heyser, C.J., Moc, K., Koob, G.F., 2003. Effects of naltrexone alone and in combination with acamprosate on the alcohol deprivation effect in rats. Neuropsychopharmacology 28, 1463–1471.

Heyser, C.J., Schulteis, G., Koob, G.F., 1997. Increased ethanol self-administration after a period of imposed ethanol deprivation in rats trained in a limited access paradigm. Alcohol Clin. Exp. Res. 21, 784–791.

Higgins, G.A., Sellers, E.M., 1994. Antagonist-precipitated opioid withdrawal in rats: evidence for dissociations between physical and motivational signs. Pharmacol. Biochem. Behav. 48, 1–8.

Hilton, S.M., Spyer, K.M., Timms, R.J., 1979. The origin of the hind limb vasodilatation evoked by stimulation of the motor cortex in the cat. J. Physiol. 287, 545–557.

Hinson, R.E., Siegel, S., 1983. Anticipatory hyperexcitability and tolerance to the narcotizing effect of morphine in the rat. Behav. Neurosci. 97, 759–767.

Hiroshige, T., Honma, K., Honma, S., 1991. SCN-independent circadian oscillators in the rat. Brain Res. Bull. 27, 441–445.

Hitchcock, F.A., 1928. The effect of low protein and protein-free diets and starvation on the activity of the albino rat. Am. J. Physiol. 84, 410–416.

Hochberg, Z., Pacak, K., Chrousos, G.P., 2003. Endocrine withdrawal syndromes. Endocr. Rev. 24, 523–538.

Hoebel, B.G., 1985. Brain neurotransmitters in food and drug reward. Am. J. Clin. Nutr. 42, 1133–1150.

Hoebel, B.G., Rada, P., Mark, G.P., Hernandez, L., 1994. The power of integrative peptides to reinforce behavior by releasing dopamine. Ann. N.Y. Acad. Sci. 739, 36–41.

Hollingdal, M., Juhl, C.B., Dall, R., Sturis, J., Veldhuis, J.D., Schmitz, O., Porksen, N., 2002. Glucocorticoid induced insulin resistance impairs basal but not glucose entrained high-frequency insulin pulsatility in humans. Diabetologia 45, 49–55.

Holstege, G., 1991. Descending motor pathways and the spinal motor system: limbic and non-limbic components. Prog. Brain Res. 87, 307–421.

Honma, K., Honma, S., Hiroshige, T., 1984. Feeding-associated corticosterone peak in rats under various feeding cycles. Am. J. Physiol. 246, R721–R726.

Honma, K., Noe, Y., Honma, S., Katsuno, Y., Hiroshige, T., 1992. Roles of paraventricular catecholamines in feeding-associated corticosterone rhythm in rats. Am. J. Physiol. 262, E948–E955.

Honma, S., Honma, K.-I., Nagasaka, T., Hiroshige, T., 1987. The ventromedial hypothalamic nucleus is not essential for the prefeeding corticosterone peak in rats under restricted daily feeding. Physiol. Behav. 39, 211–215.

Horger, B.A., Shelton, K., Schenk, S., 1990. Preexposure sensitizes rats to the rewarding effects of cocaine. Pharmacol. Biochem. Behav. 37, 707–711.

Horvath, T.L., 2005. The hardship of obesity: a soft-wired hypothalamus. Nat. Neurosci. 8, 561–565.

Houshyar, H., Galigniana, M.D., Pratt, W.B., Woods, J.H., 2001. Differential responsivity of the hypothalamic–pituitary–adrenal axis to glucocorticoid negative-feedback and corticotropin releasing hormone in rats undergoing morphine withdrawal: possible mechanisms involved in facilitated and attenuated stress responses. J. Neuroendocrinol. 13, 875–886.

Houshyar, H., Gomez, F., Manalo, S., Bhargava, A., Dallman, M.F., 2003. Intermittent morphine administration induces dependence and is a chronic stress in rats. Neuropsychopharmacology 28, 1960–1972.

Houshyar, H., Manalo, S., Dallman, M.F., 2004. Time-dependent alterations in mRNA expression of brain neuropeptides regulating energy balance and hypothalamo–pituitary–adrenal activity after withdrawal from intermittent morphine treatment. J. Neurosci. 24, 9414–9424.

Hsu, D.T., Chen, F.-L., Takahashi, L.K., Kalin, N.H., 1998. Rapid stress-induced elevations in corticotropin-releasing hormone mRNA in rat central amygdala nucleus and hypothalamic paraventricular nucleus: an in situ hybridization analysis. Brain Res. 788, 305–310.

Hui, G.K., Figueroa, I.R., Poytress, B.S., Roozendaal, B., McGaugh, J.L., Weinberger, N.M., 2004. Memory enhancement of classical fear conditioning by post-training injections of corticosterone in rats. Neurobiol. Learn. Mem. 81, 67–74.

Hunt, W.A., Barnett, L.W., Branch, L.G., 1971. Relapse rates in addiction programs. J. Clin. Psychol. 27, 455–456.

Hutchinson, R.R., Azrin, N.H., Hunt, G.M., 1968a. Attack produced by intermittent reinforcement of a concurrent operant response. J. Exp. Anal. Behav. 11, 489–495.

Hutchinson, R.R., Azrin, N.H., Renfrew, J.W., 1968b. Effects of shock intensity and duration on the frequency of biting attack by squirrel monkeys. J. Exp. Anal. Behav. 11, 83–88.

Ikemoto, S., Panksepp, J., 1999. The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res. Brain Res. Rev. 31, 6–41.

Imaki, T., Shibasaki, T., Demura, H., 1995. Regulation of gene expression in the central nervous system by stress: molecular pathways of stress responses. Endocr. J. 42, 121–130.

Imaki, T., Shibasaki, T., Masuda, A., Demura, H., Shizume, K., Ling, N., 1987. Effects of adrenergic blockers on corticotropin-releasing factor-induced behavioral changes in rats. Regul. Pept. 19, 243–251.

Imaki, T., Shibasaki, T., Shizume, K., Masuda, A., Hotta, M., Kiyosawa, Y., Jibiki, K., Demura, H., Tsushima, T., Ling, N., 1985. The effect of free fatty acids on growth hormone (GH)-releasing hormone-mediated GH secretion in man. J. Clin. Endocrinol. Metab. 60, 290–293.

Imperato, A., Puglisi-Allegra, S., Casolini, P., Zocchi, A., Angelucci, L., 1989. Stress-induced enhancement of dopamine and acetylcholine release in limbic structures: role of corticosterone. Eur. J. Pharmacol. 165, 337–338.

Iranmanesh, A., Lizarralde, G., Short, D., Veldhuis, J.D., 1990. Intensive venous sampling paradigms disclose high frequency adrenocorticotropin release episodes in normal men. J. Clin. Endocrinol. Metab. 71, 1276–1283.

Ishizaki, K., Honma, S., Katsuno, Y., Abe, H., Masubuchi, S., Namihira, M., Honma, K., 2003. Gene expression of neuropeptide Y in the nucleus of the solitary tract is activated in rats under restricted daily feeding but not under 48-h food deprivation. Eur. J. Neurosci. 17, 2097–2105.

Islam, A., Henriksson, B., Mohammed, A., Winblad, B., Adem, A., 1995. Behavioural deficits in adult rats following long-term adrenalectomy. Neurosci. Lett. 194, 49–52.

Ivanov, A., Aston-Jones, G., 2001. Local opiate withdrawal in locus coeruleus neurons in vitro. J. Neurophysiol. 85, 2388–2397.

Iwata, J., Chida, K., LeDoux, J.E., 1987. Cardiovascular responses elicited by stimulation of neurons in the central amygdaloid nucleus in awake but not anesthetized rats resemble conditioned emotional responses. Brain Res. 418, 183–188.

Iwata, J., LeDoux, J.E., Reis, D.J., 1986. Destruction of intrinsic neurons in the lateral hypothalamus disrupts the classical conditioning of autonomic but not behavioral emotional responses in the rat. Brain Res. 368, 161–166.

Jacobsen, L.K., Southwick, S.M., Kosten, T.R., 2001. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. Am. J. Psychiatry 158, 1184–1190.

Jacobson, L., Sapolsky, R., 1993. Augmented ACTH responses to stress in adrenalectomized rats replaced with constant physiological levels of corticosterone are partially normalized by acute increases in corticosterone. Neuroendocrinology 58, 420–429.

Jaferi, A., Nowak, N., Bhatnagar, S., 2006. Negative feedback functions in chronically stressed rats: role of the posterior paraventricular thalamus. Physiol. Behav. [Epub ahead of print].

Janssens, C.J., Helmond, F.A., Loyens, L.W., Schouten, W.G., Wiegant, V.M., 1995. Chronic stress increases the opioid-mediated inhibition of the pituitary–adrenocortical response to acute stress in pigs. Endocrinology 136, 1468–1473.

Jarvinen, M.K., Powley, T.L., 1999. Dorsal motor nucleus of the vagus neurons: a multivariate taxonomy. J. Comp. Neurol. 403, 359–377.

Jasper, M.S., Engeland, W.C., 1994. Splanchnic neural activity modulates ultradian and circadian rhythms in adrenocortical secretion in awake rats. Neuroendocrinology 59, 97–109.

Jedema, H.P., Finlay, J.M., Sved, A.F., Grace, A.A., 2001. Chronic cold exposure potentites CRF-evoked increases in electrophysiologic activity of locus coeruleus neurons. Biol. Psychiatry 49, 351–359.

Jedema, H.P., Sved, A.F., Zigmond, M.J., Finlay, J.M., 1999. Sensitization of norepinephrine release in medial prefrontal cortex: effect of different chronic stress protocols. Brain Res. 830, 211–217.

Joels, M., 2000. Modulatory actions of steroid hormones and neuropeptides on electrical activity in brain. Eur. J. Pharmacol. 405, 207–216.

Johnson, J.T., Levine, S., 1973. Influence of water deprivation on adrenocortical rhythms. Neuroendocrinology 11, 268–273.

Jouandet, M.L., Gazzaniga, M.S., 1979. Cortical field of origin of the anterior commissure of the rhesus monkey. Exp. Neurol. 66, 381–397.

Kalivas, P.W., Duffy, P., 1995. Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. Brain Res. 675, 325–328.

Kalivas, P.W., Duffy, P., Latimer, L.G., 1987. Neurochemical and behavioral effects of corticotropin-releasing factor in the ventral tegmental area of the rat. J. Pharmacol. Exp. Ther. 242, 757–764.

Kalivas, P.W., Nakamura, M., 1999. Neural systems for behavioral activation and reward. Curr. Opin. Neurobiol. 9, 223–227.

Kalivas, P.W., Stewart, J., 1991. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res. Rev. 16, 223–244.

Kalra, S.P., Dube, M.G., Pu, S., Xu, B., Horvath, T.L., Kalra, P.S., 1999. Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. Endocr. Rev. 20, 68–100.

Kalra, S.P., Dube, M.G., Sahu, A., Phelps, C.P., Kalra, P.S., 1991. Neuropeptide Y secretion increases in the paraventricular nucleus in association with increased appetite for food. Proc. Natl. Acad. Sci. U.S.A. 88, 10931–10935.

Kalsbeek, A., Buijs, R.M., 2002. Output pathways of the mammalian suprachiasmatic nucleus: coding circadian time by transmitter selection and specific targeting. Cell Tissue Res. 309, 109–118.

Kamara, K., Eskay, R., Castonguay, T., 1998. High-fat diets and stress responsivity. Physiol. Behav. 64, 1–6.

Kaneda, T., Makino, S., Nishiyama, M., Asaba, K., Hashimoto, K., 2001. Differential neuropeptide responses to starvation with aging. J. Neuroendocrinol. 13, 1066–1073.

Kaneko, M., Hiroshige, T., Shinsako, J., Dallman, M.F., 1980. Diurnal changes in amplification of hormone rhythms in the adrenocortical system. Am. J. Physiol. 239, R309–R316.

Kang, W., Wilson, S.P., Wilson, M.A., 2000. Overexpression of proenkephalin in the amygdala potentiates the anxiolytic effects of benzodiazepines. Neuropsychopharmacology 22, 77–88.

Kant, G.J., Eggleston, T., Landman-Robers, L., Kenion, C.C., Driver, G.C., Meyerhoff, J.L., 1985. Habituation to repeated stress is stressor specific. Pharmacol. Biochem. Behav. 22, 631–634.

Karteszi, M., Dallman, M.F., Makara, G.B., Stark, E., 1982. Regulation of the adrenocortical response to insulin-induced hypoglycemia. Endocrinology 111, 535–541.

Kawasaki, K., Iwasaki, T., 1997. Corticosterone levels during extinction of runway response in rats. Life Sci. 61, 1721–1728.

Keim, S.R., Shekhar, A., 1996. The effects of GABAA receptor blockade in the dorsomedial hypothalamic nucleus on corticotrophin (ACTH) and corticosterone secretion in male rats. Brain Res. 739, 46–51.

Keller-Wood, M.E., Dallman, M.F., 1984. Corticosteroid inhibition of ACTH secretion. Endocr. Rev. 5, 1–24.

Keller-Wood, M.E., Shinsako, J., Dallman, M.F., 1983. Integral as well as proportional adrenal responses to ACTH. Am. J. Physiol. 245, R53–R59.

Keller-Wood, M.E., Shinsako, J., Dallman, M.F., 1984. Interaction between stimulus intensity and corticosteroid feedback in control of ACTH. Am. J. Physiol. 247, E489–E494.

Kelley, A.E., Berridge, K.C., 2002. The neuroscience of natural rewards: relevance to addictive drugs. J. Neurosci. 22, 3306–3311.

Kelly, S.J., Franklin, K.B., 1987. Role of peripheral and central opioid activity in analgesia induced by restraint stress. Life Sci. 41, 789–794.

Kennedy, J.A., Hartman, N., Sbriglio, R., Khuri, E., Albeck, H., Kreek, M.J., 1991. Metyrapone-induced withdrawal symptoms: symptoms in methadone-maintained patients. NIDA Res. Monogr. 105, 416.

Kern, P.A., Di Gregorio, G., Lu, T., Rassouli, N., Ranganathan, G., 2004. Perilipin expression in human adipose tissue is elevated with obesity. J. Clin. Endocrinol. Metab. 89, 1352–1358.

Kerr, R.A., 1999. Climate change: a smoking gun for an ancient methane discharge. Science 286, 1465.

Kershaw, E.E., Morton, N.M., Dhillon, H., Ramage, L., Seckl, J.R., Flier, J.S., 2005. Adipocyte-specific glucocorticoid inactivation protects against diet-induced obesity. Diabetes 54, 1023–1031.

Kessing, L.V., Andersen, P.K., 2005. Predictive effects of previous episodes on the risk of recurrence in depressive and bipolar disorders. Curr. Psychiatry Rep. 7, 413–420.

Keys, A., 1950a. The Biology of Human Starvation. University of Minnesota Laboratory of Physical Hygeine. University of Minnesota Press.

Keys, A., 1950b. The residues of malnutrition and starvation. Science 112, 371–373.

Kim, J.J., Diamond, D.M., 2002. The stressed hippocampus, synaptic plasticity and lost memories. Nat. Rev. Neurosci. 3, 453–462.

Kivimaki, M., Head, J., Ferrie, J.E., Shipley, M.J., Brunner, E.J., Vahtera, J., Marmot, M.G., 2006. Work stress, weight gain and weight loss: evidence for bidirectional effects of job strain on body mass index in the Whitehall II study. Int. J. Obes. 30, 982–987.

Klein, J.F., 1992. Adverse psychiatric effects of systemic glucocorticoid therapy. Am. Fam. Physician 46, 1469–1474.

Knapp, D.J., Overstreet, D.H., Moy, S.S., Breese, G.R., 2004. SB242084, flumazenil, and CRA1000 block ethanol withdrawal-induced anxiety in rats. Alcohol 32, 101–111.

Koch, B., Bucher, B., Mialhe, C., 1974a. Pituitary nuclear retention of dexamethasone and ACTH biosynthesis. Neuroendocrinology 15, 365–375.

Koch, B., Lutz, B., Briaud, B., Bucher, B., Mialhe, C., 1974b. Mechanism of action of various secretagogues and glucocorticoids on regulation of pituitary corticotropin activity. Probl. Actuels Endocrinol. Nutr. Ser. 18, 157–175.

Koenig, H.N., Olive, M.F., 2004. The glucocorticoid receptor antagonist mifepristone reduces ethanol intake in rats under limited access conditions. Psychoneuroendocrinology 29, 999–1003.

Kollar, E.J., Atkinson, R.M., 1966. Responses of extremely obese patients to starvation. Psychosom. Med. 28, 227–246.

Komatsuzaki, Y., Murakami, G., Tsurugizawa, T., Mukai, H., Tanabe, N., Mitsuhashi, K., Kawata, M., Kimoto, T., Ooishi, Y., Kawato, S., 2005. Rapid spinogenesis of pyramidal neurons induced by activation of glucocorticoid receptors in adult male rat hippocampus. Biochem. Biophys. Res. Commun. 335, 1002–1007.

Konecka, A.M., Sroczynska, I., Przewlocki, R., 1985. The effect of food and water deprivation on post-stress analgesia in mice and levels of beta-endorphin and dynorphin in blood plasma and hypothalamus. Arch. Int. Physiol. Biochim. 93, 279–284.

Konig, M., Zimmer, A.M., Steiner, H., Holmes, P.V., Crawley, J.N., Brownstein, M.J., Zimmer, A., 1996. Pain responses, anxiety and aggression in mice deficient in pre-proenkephalin. Nature 383, 535–538.

Koob, G.F., 1992. Neural mechanisms of drug reinforcement. Ann. N.Y. Acad. Sci. 654, 171–191.

Koob, G.F., 1999. Corticotropin-releasing factor, norepinephrine and stress. Biol. Psychiatry 46, 1167–1180.

Koob, G.F., Heinrichs, S.C., 1999. A role for corticotropin releasing factor and urocortin in behavioral responses to stressors. Brain Res. 848, 141–152.

Koob, G.F., Le Moal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52–58.

Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24, 97–129.

Koob, G.F., Swerdlow, N., Seeligson, M., Eaves, M., Sutton, R., Rivier, J., Vale, W., 1984. Effects of alpha-flupenthixol and naloxone on CRF-induced locomotor activation. Neuroendocrinology 39, 459–464.

Koubi, H.E., Robin, J.P., Dewasmes, G., Lemaho, Y., Frutoso, J., Minaire, Y., 1991. Fasting-Induced Rise in Locomotor Activity in Rats Coincides With Increased Protein Utilization. Physiol. Behav. 50, 337–343.

Kovacs, K., Foldes, A., Sawchenko, P., 2000. Glucocorticoid negative feedback selectively targets vasopressin transcription in parvocellular neurosecretory neurons. J. Neurosci. 20, 3843–3852.

Kovacs, K., Kiss, J.Z., Makara, G.B., 1986. Glucocorticoid implants around the hypothalamic paraventricular nucleus prevent the increase of corticotropin-releasing factor and arginine vasopressin immunostaining induced by adrenalectomy. Neuroendocrinology 44, 229–234.

Kovacs, K., Makara, G.B., 1988. Corticosterone and dexamethasone act at different brain sites to inhibit adrenalectomy-induced adrenocorticotropin secretion. Brain Res. 474, 205–210.

Kovacs, K.J., Mezey, E., 1987. Dexamethasone inhibits corticotropin-releasing factor gene expression in the rat paraventricular nucleus. Neuroendocrinology 46, 365–368.

Krahn, D.D., Gosnell, B.A., Grace, M., Levine, A.S., 1986. CRF antagonist partially reverses CRF- and stress-induced behavioral effects. Brain Res. Bull. 17, 285–289.

Krank, M.D., 2003. Pavlovian conditioning with ethanol: sign-tracking (autoshaping), conditioned incentive, and ethanol self-administration. Alcohol Clin. Exp. Res. 27, 1592–1598.

Kreek, M.J., Koob, G.F., 1998. Drug dependence: stress and dysregulation of brain reward pathways. Drug Alcohol Depend. 51, 23–47.

Krieger, D.T., 1972. Circadian corticosteroid periodicity: critical period for abolition by neonatal injection of corticosteroid. Science 178, 1205–1207.

Krieger, D.T., 1974. Food and water restriction shifts corticosterone, temperature, activity and brain amine periodicity. Endocrinology 95, 1195–1201.

Krieger, D.T., Allen, W., Rizzo, F., Krieger, H.P., 1971. Characterization of the normal temporal pattern of plasma corticosteroid levels. J. Clin. Endocrinol. Metab. 32, 266–284.

Krieger, D.T., Hauser, H., Krey, L.C., 1977. Suprachiasmatic nuclear lesions do not abolish food-shifted circadian adrenal and temperature rhythmicity. Science 197, 398–399.

Kristensen, P., Judge, M.E., Thim, L., Ribel, U., Christjansen, K.N., Wulff, B.S., Clausen, J.T., Jensen, P.B., Madsen, O.D., Vrang, N., Larsen, P.J., Hastrup, S., 1998. Hypothalamic CART is a new anorectic peptide regulated by leptin. Nature 393, 72–76.

Krugman, P., 1999. The Return of Depression Economics. Norton Press.

Kruk, M.R., Halasz, J., Meelis, W., Haller, J., 2004. Fast positive feedback between the adrenocortical stress resposne and a brain mechanism involved in aggressive behavior. Behav. Neurosci. 118, 1062–1070.

Kuczenski, R., Segal, D.S., 2001. Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: relative roles of dopamine and norepinephrine. J. Pharmacol. Exp. Ther. 296, 876–883.

Kuczenski, R., Segal, D.S., Todd, P.K., 1997. Behavioral sensitization and extracellular dopamine responses to amphetamine after various treatments. Psychopharmacology (Berl.) 134, 221–229.

Kushner, M.G., Abrams, K., Borchardt, C., 2000. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. Clin. Psychol. Rev. 20, 149–171.

Kushner, M.G., Sher, K.J., Wood, M.D., Wood, P.K., 1994. Anxiety and drinking behavior: moderating effects of tension-reduction alcohol outcome expectancies. Alcohol Clin. Exp. Res. 18, 852–860.

Kushner, M.G., Thuras, P., Abrams, K., Brekke, M., Stritar, L., 2001. Anxiety mediates the association between anxiety sensitivity and coping-related drinking motives in alcoholism treatment patients. Addict. Behav. 26, 869–885.

La Fleur, S.E., Akana, S.F., Manalo, S.L., Dallman, M.F., 2004. Interaction between corticosterone and insulin in obesity: regulation of lard intake and fat stores. Endocrinology 145, 2174–2185.

la Fleur, S.E., Houshyar, H., Roy, M., Dallman, M.F., 2005. Choice of lard, but not total lard calories, damps ACTH responses to restraint. Endocrinology 146, 2193–2199.

Lafontan, M., Berlan, M., 1993. Fat cell adrenergic receptors and the control of white and brown fat cell function. J. Lipid. Res. 34, 1057–1091.

LaLumiere, R.T., Nawar, E.M., McGaugh, J.L., 2005. Modulation of memory consolidation by the basolateral amygdala or nucleus accumbens shell requires concurrent dopamine receptor activation in both brain regions. Learn Mem. 12, 296–301.

Lam, T.K., Pocai, A., Gutierrez-Juarez, R., Obici, S., Bryan, J., Aguilar-Bryan, L., Schwartz, G.J., Rossetti, L., 2005a. Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. Nat. Med. 11, 320–327.

Lam, T.K., Schwartz, G.J., Rossetti, L., 2005b. Hypothalamic sensing of fatty acids. Nat. Neurosci. 8, 579–584.

Lambert, P.D., Couceyro, P.R., McGirr, K.M., Dall Vechia, S.E., Smith, Y., Kuhar, M.J., 1998. CART peptides in the central control of feeding and interactions with neuropeptide Y. Synapse 29, 293–298.

Lambillotte, C., Gilon, P., Henquin, J.-C., 1997. Direct glucocorticoid inhibition of insulin secretion. J. Clin. Invest. 99, 414–423.

Lamblin, F., De Witte, P., 1996. Adrenalectomy prevents the development of alcohol preference in male rats. Alcohol 13, 233–238.

Lamont, E.W., Diaz, L.R., Barry-Shaw, J., Stewart, J., Amir, S., 2005a. Daily restricted feeding rescues a rhythm of period2 expression in the arrhythmic suprachiasmatic nucleus. Neuroscience 132, 245–248.

Lamont, E.W., Robinson, B., Stewart, J., Amir, S., 2005b. The central and basolateral nuclei of the amygdala exhibit opposite diurnal rhythms of expression of the clock protein Period2. Proc. Natl. Acad. Sci. U.S.A. 102, 4180–4184.

Landbergis, P.A., Schnall, P.L., Pickering, T.G., Warren, K., Schwartz, J.E., 2003. Life-course exposure to job strain and ambulatory blood pressure in men. Am. J. Epidemiol. 157, 998–1006.

Landry, G.J., Simon, M.M., Webb, I.C., Mistlberger, R.E., 2006. Persistence of a behavioral food-anticipatory circadian rhythm following dorsomedial hypothalamic ablation in rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 290, R1527–R1534.

Lanfranco, F., Giordano, R., Pellegrino, M., Gianotti, L., Ramunni, J., Picu, A., Baldi, M., Ghigo, E., Arvat, E., 2004. Free fatty acids exert an inhibitory effect on adrenocorticotropin and cortisol secretion in humans. J. Clin. Endocrinol. Metab. 89, 1385–1390.

Langley, K.M., 1982. Post-traumatic stress disorder among Vietnam combat veterans. Social Casework 63, 593–598.

Laorden, M.L., Castells, M.T., Martinez, M.D., Martinez, P.J., Milanes, M.V., 2000. Activation of *c-fos* expression in hypothalamic nuclei by mu- and kappa-receptor agonists: correlation with catecholaminergic activity in the hypothalamic paraventricular nucleus. Endocrinology 141, 1366–1376.

Laugero, K.D., 2001. A new perspective on glucocorticoid feedback: relation to stress, carbohydrate feeding and feeling better. J. Neuroendocrinol. 13, 827–835.

Laugero, K.D., 2004. Reinterpretation of basal glucocorticoid feedback: implications to behavioral and metabolic disease. Vitam. Horm. 69, 1–29.

Laugero, K.D., Bell, M.E., Bhatnagar, S., Soriano, L., Dallman, M.F., 2001a. Sucrose ingestion normalizes central expresion of corticotropin-releasing factor mRNA and energy balance in adrenalectomized rats: a glucocorticoid-metabolic-brain axis? Endocrinology 142, 2796–2804.

Laugero, K.D., Gomez, F., Dallman, M.F., 2001b. Sucrose ingestion, but not corticosterone infusion into brain, normalizes caloric intake and storage in ADX rats: a new view of glucocorticoid feedback. Society for Neuroscience 31st Meeting, Abstract #1820.

Laugero, K.D., Gomez, F., Siao, D., Dallman, M.F., 2002. Corticosterone infused intracerebroventricularly inhibits energy storage and stimulates the hypothalamo–pituitary axis in adrenalectomized rats. Endocrinology 143, 4552–4562.

Le, A.D., Harding, S., Juzytsch, W., Watchus, J., Shalev, U., Shaham, Y., 2000. The role of corticotrophin-releasing factor in stress-induced relapse to alcohol-seeking behavior in rats. Psychopharmacology (Berl.) 150, 317–324.

Lechner, S.M., Curtis, A.L., Brons, R., Valentino, R.J., 1997. Locus coeruleus activation by colon distention: role of corticotropin-releasing factor and excitatory amino acids. Brain Res. 756, 114–124.

Lechner, S.M., Valentino, R.J., 1999. Glucocorticoid receptor-immunoreactivity in corticotropin-releasing factor afferents to locus coeruleus. Brain Res. 816, 17–28.

LeDoux, J., 2003. The emotional brain, fear, and the amygdala. Cell Mol. Neurobiol. 23, 727–738.

LeDoux, J.E., 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. 23, 155–184.

LeDoux, J.E., Sakaguchi, A., Reis, D.J., 1984. Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned to acoustic stimuli. J. Neurosci. 4, 683–698.

Lee, Y., Schulkin, J., Davis, M., 1994. Effect of corticosterone on the enhancement of the acoustic startle reflex by corticotropin releasing factor (CRF). Brain Res. 666, 93–98.

Leibowitz, S.F., 1978. Paraventricular nucleus: a primary site mediating adrenergic stimulation of feeding and drinking. Pharmacol. Biochem. Behav. 8, 163–175.

Leibowitz, S.F., Diaz, S., Tempel, D., 1989. Norepinephrine in the paraventricular nucleus stimulates corticosterone release. Brain Res. 496, 219–227.

Leibowitz, S.F., Sladek, C., Spencer, L., Tempel, D., 1988. Neuropeptide Y, epinephrine and norepinephrine in the paraventricular nucleus: stimulation of feeding and the release of corticosterone, vasopressin and glucose. Brain Res. Bull. 21, 905–912.

Leshner, A.I., 1971. The adrenals and the regulatory nature of running wheel activity. Physiol. Behav. 6, 551–558.

Levin, E.R., Sharp, B., Meyer, N.V., Carlson, H.E., 1981. Morphine and naloxone: effects on beta-endorphin immunoreactivity in canine plasma and secretions from rat pituitaries. Endocrinology 109, 146–151.

Levine, A.S., Grace, M.K., Cleary, J.P., Billington, C.J., 2002. Naltrexone infusion inhibits the development of preference for a high sucrose diet. Am. J. Physiol. 283, R1149–R1154.

Levine, A.S., Kotz, C.M., Gosnell, B.A., 2003. Sugars and fats: the neurobiology of preferences. J. Nutr. 133, 831S–834S.

Levine, S., 2000. Influence of psychological variables on the activity of the hypothalamic–pituitary–adrenal axis. Eur. J. Pharmacol. 405, 149–160.

Levine, S., Coover, G.D., 1976. Environmental control of suppression of the pituitary–adrenal sysem. Physiol. Behav. 17, 35–37.

Levine, S., Goldman, L., Coover, G.D., 1972. Expectancy and the pituitary–adrenal system. Ciba Found. Symp. 8, 281–291.

Levine, S., Weinberg, J., Brett, L.P., 1979. Inhibition of pituitary–adrenal activity as a consequence of consummatory behavior. Psychoneuroendocrinology 4, 275–286.

Li, C.S., Davis, B.J., Smith, D.V., 2003. Opioid modulation of taste responses in the nucleus of the solitary tract. Brain Res. 965, 21–34.

Li, H.-Y., Ericsson, A., Sawchenko, P.E., 1996. Distinct mechanisms underlie activation of hypothalamic neurosecretory neurons and their medullary catecholaminergic afferents in categorically different stress paradigms. Proc. Natl. Acad. Sci. U.S.A. 93, 2359–2364.

Li, H.-Y., Sawchenko, P.E., 1998. Hypothalamic effector neurons and extended circuitries activated in "neurogenic" stress: a comparison of footshock effects exerted acutely, chornically, and in animals with controlled glucocorticoid levels. J. Comp. Neurol. 393, 244–266.

Li, Z., Perlik, V., Feleder, C., Tang, Y., Blatteis, C.M., 2006. Kupffer cell-generated PGE2 triggers the febrile response of guinea pigs to intravenously injected LPS. Am. J. Physiol. 290, R1262–R1270.

Liang, C.L., Kozlowski, G.P., Joseph, S.A., German, D.C., 1992a. ACTH1-39 inputs to mesocorticolimbic dopaminergic neurons: light and electron microscopic examination. Neurosci. Lett. 146, 79–83.

Liang, K.C., Melia, K.R., Miserendino, M.J., Falls, W.A., Campeau, S., Davis, M., 1992b. Corticotropin-releasing factor: long-lasting facilitation of the acoustic startle reflex. J. Neurosci. 12, 2303–2312.

Liang, K.C., Chen, H.C., Chen, D.Y., 2001. Posttraining infusion of norepinephrine and corticotropin releasing factor into the bed nucleus of the stria terminalis enhanced retention in an inhibitory avoidance task. Chin. J. Physiol. 44, 33–43.

Liang, K.C., Juler, R.G., McGaugh, J.L., 1986. Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. Brain Res. 368, 125–133.

Liang, K.C., Lee, E.H.Y., 1988. Intra-amygdala injections of corticotropin releasing factor facilitate inhibitory avoidance learning and reduce exploratory behavior in rats. Psychopharmacology 96, 232–236.

Licinio, J., Wong, M.L., Gold, P.W., 1996. The hypothalamic–pituitary–adrenal axis in anorexia nervosa. Psychiatry Res. 62, 75–83.

Lieberman, D.A., 1972. Secondary reinforcement and information as determinants of observing behavior in monkeys (Macaca mulatta). Learn Motiv. 3, 341–358.

Lightman, S.L., Young 3rd, W.S., 1987a. Changes in hypothalamic preproenkephalin A mRNA following stress and opiate withdrawal. Nature 328, 643–645.

Lightman, S.L., Young 3rd, W.S., 1987b. Vasopressin, oxytocin, dynorphin, enkephalin and corticotrophin-releasing factor mRNA stimulation in the rat. J. Physiol. 394, 23–39.

Ling, M.H., Perry, P.J., Tsuang, M.T., 1981. Side effects of corticosteroid therapy. Psychiatric aspects. Arch. Gen. Psychiatry 38, 471–477.

Liposits, Z., Sievers, L., Paull, W.K., 1988. Neuropeptide-Y and ACTH-immunoreactive innervation of corticotropin releasing factor (CRF)-synthesizing neurons in the hypothalamus of the rat. An immunocytochemical analysis at the light and electron microscopic levels. Histochemistry 88, 227–234.

Lisman, J.E., 1999. Relating hippocampal circuitry to function: recall of memory sequences by reciprocal dentate-CA3 interactions. Neuron 22, 233–242.

Liu, L., Tsuji, M., Takeda, H., Takada, K., Matsumiya, T., 1999. Adrenocortical suppression blocks the enhancement of memory storage produced by exposure to psychological stress in rats. Brain Res. 821, 134–140.

Liu, X., Weiss, F., 2002. Additive effect of stress and drug cues on reinstatement of ethanol seeking: exacerbation by history of dependence and role of concurrent activation of corticotropin-releasing factor and opioid mechanisms. J. Neurosci. 22, 7856–7861.

Lloyd, J., 1965. Aggressive mimicry in Photuris: firefly femmes fatales. Science 149, 653–654.

Lohmeier, T.E., Warren, S., Cunningham, J.T., 2003. Sustained activation of the central baroreceptor pathway in obesity hypertension. Hypertension 42, 96–102.

Lopez-Grancha, M., Lopez-Crespo, G., Venero, C., Canadas, F., Sanchez-Santed, F., Sandi, C., Flores, P., 2006. Differences in corticosterone level due to inter-food interval length: implications for schedule-induced polydipsia. Horm. Behav. 49 (2), 166–172.

Lore, R., Gottdiener, C., Delahunty, M.J., 1986. Lean and mean rats: some effects of acute changes in the food supply upon territorial aggression. Aggressive Behav. 12, 409–415.

Lorenz, K., 1950. The comparative method in studying innate behaviour patterns. In: Symposia for the Society of Experimental Biology, vol. 4. Cambridge University Press, Cambridge, UK, pp. 221–268.

Lowry, C.A., Plant, A., Shanks, N., Ingram, C.D., Lightman, S.L., 2003. Anatomical and functional evidence for a stress-responsive, monoamine-accumulating area in the dorsomedial hypothalamus of adult rat brain. Horm. Behav. 43, 254–262.

Lu, L., Zhang, B., Liu, Z., Zhang, Z., 2002. Reactivation of cocaine conditioned place preference induced by stress is reversed by cholecystokinin-B receptors antagonist in rats. Brain Res. 954, 132–140.

Lu, X.-Y., Barsh, G.S., Akil, H., Watson Jr., S.J., 2003. Interaction between α-melanocyte-stimulating hormone and corticotropin-releasing hormone in the regulation of feeding and hypothalamo–pituitary–adrenal responses. J. Neurosci. 23, 7863–7872.

Maccari, S., Piazza, P.V., Deminiere, J.M., Lemaire, V., Mormede, P., Simon, H., Angelucci, L., Le Moal, M., 1991. Life events-induced decrease of corticosteroid type I receptors is associated with reduced corticosterone feedback and enhanced vulnerability to amphetamine self-administration. Brain Res. 547, 7–12.

Makino, S., Gold, P.W., Schulkin, J., 1994a. Corticosterone effects on corticotropin-releasing hormone mRNA in the central nucleus of the amygdala and the parvocellular region of the paraventricular nucleus of the hypothalamus. Brain Res. 640, 105–112.

Makino, S., Gold, P.W., Schulkin, J., 1994b. Effects of corticosterone on CRH mRNA and content in bed nucleus of the stria terminalis; comparison with the effects in the bed nucleus of the amygdala and the paraventricular nucleus of the hypothalamus. Brain Res. 657, 141–149.

Makino, S., Hashimoto, K., Gold, P., 2002. Multiple feedback mechanisms activating corticotropin-releasing hormone systm in the brain during stress. Pharmacol. Biochem. Behav. 73, 147–158.

Makino, S., Kaneda, T., Nishiyama, M., Asaba, K., Hashimoto, K., 2001. Lack of decrease in hypothalamic and hippocampal glucocorticoid receptor mRNA during starvation. Neuroendocrinology 74, 120–128.

Makino, S., Schulkin, J., Smith, M.A., Pacâak, K., Palkovits, M., Gold, P.W., 1995a. Regulation of corticotropin-releasing hormone receptor messenger ribonucleic acid in the rat brain and pituitary by glucocorticoids and stress. Endocrinology 136, 4517–4525.

Makino, S., Smith, M.A., Gold, P.W., 1995b. Increased expression of corticotropin-releasing formone and vasopressin messenger ribonucleic acid (mRNA) in the hypothalamic paraventricular nucleus during repeated stress: association with reduction in glucocorticoid receptor mRNA levels. Endocrinology 136, 3299–3309.

Malick, J.B., 1975. Effects of age and food deprivation on the development of muricidal behavior in rats. Physiol. Behav. 14, 171–175.

Malinow, R., Malenka, R.C., 2002. AMPA receptor trafficking and synaptic plasticity. Annu. Rev. Neurosci. 25, 103–126.

Mancini, T., Kola, B., Mantero, F., Boscaro, M., Arnaldi, G., 2004. High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. Clin. Endocrinol. (Oxf.) 61, 768–777.

Mansi, J.A., Laforest, S., Drolet, G., 2000. Effect of stress exposure on the activation pattern of enkephalin-containing perikarya in the rat ventral medulla. J. Neurochem. 74, 2568–2575.

Mantsch, J.R., Goeders, N.E., 1999. Ketoconazole blocks the stress-induced reinstatement of cocaine-seeking behavior in rats: relationship to the discriminative stimulus effects of cocaine. Psychopharmacology (Berl.) 142, 399–407.

Marcus, M.M., Nomikos, G.G., Svensson, T.H., 1996. Differential actions of typical and atypical antipsychotic drugs on dopamine release in the core and shell of the nucleus accumbens. Eur. Neuropsychopharmacol. 6, 29–38.

Maren, S., 2001. Neurobiology of Pavlovian fear conditioning. Annu. Rev. Neurosci. 24, 597–931.

Maren, S., Fanselow, M.S., 1995. Synaptic plasticity in the basolateral amygdala induced by hippocampal formation stimulation in vivo. J. Neurosci. 15, 7548–7564.

Marinelli, M., Aouizerate, B., Barrot, M., Le Moal, M., Piazza, P.V., 1998a. Dopamine-dependent responses to morphine depend on glucocorticoid receptors. Proc. Natl. Acad. Sci. U.S.A. 95, 7742–7747.

Marinelli, M., Le Moal, M., Piazza, P.V., 1998b. Sensitization to the motor effects of contingent infusions of heroin but not of kappa agonist RU 51599. Psychopharmacology (Berl.) 139, 281–285.

Marinelli, M., Le Moal, M., Piazza, P.V., 1996. Acute pharmacological blockade of corticosterone secretion reverses food restriction-induced sensitization of the locomotor response to cocaine. Brain Res. 724, 251–255.

Marinelli, M., Piazza, P.V., Deroche, V., Maccari, S., Le Moal, M., Simon, H., 1994. Corticosterone circadian secretion differentially facilitates dopamine-mediated psychomotor effect of cocaine and morphine. J. Neurosci. 14, 2724–2731.

Marinelli, M., Rouge-Pont, F., Deroche, V., Barrot, M., de Jusus-Olivera, L., Le Moal, M., Piazza, P.V., 1997. Glucocorticoids and behavioral effects of psychostimulants. 1. Locomotor response to cocaine depends of basal levels of glucocorticoids. J. Pharmacol. Exp. Ther. 281, 1392–1400.

Mark, G.P., Rada, P., Pothos, E., Hoebel, B.G., 1992. Effects of feeding and drinking on acetylcholine release in the nucleus accumbens, striatum, and hippocampus of freely behaving rats. J. Neurochem. 58, 2269–2274.

Marklund, N., Peltonen, M., Nilsson, T.K., Olsson, T., 2004. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. J. Intern. Med. 256, 15–21.

Marrosu, F., Mereu, G., Fratta, W., Carcangiu, P., Camarri, F., Gessa, G.L., 1987. Different epileptogenic activities of murine and ovine corticotropin-releasing factor. Brain Res. 408, 394–398.

Mason, J.W., 1968. A review of psychoendocrine research on the pituitary–adrenal cortical system. Psychosom. Med. 30 (Suppl.), 576–607.

Mason, J.W., 1971. A re-evaluation of the concept of ''non-specificity'' in stress theory. J. Psychiatr. Res. 8, 323–333.

Mason, J.W., Brady, J.V., Sidman, M., 1957. Plasma 17-hydroxycorticosteroid levels and conditioned behavior in the Rhesus monkey. Endocrinology 60, 741–752.

Masoro, E.J., 2005. Overview of caloric restriction and ageing. Mech. Ageing Dev. 126, 913–922.

Masuzaki, H., Paterson, J., shinyama, H., Morton, N.M., Seckl, J.R., Flier, J.S., 2001. A transgenic model of viseral obesity and the metabolic syndrome. Science 94, 2166–2170.

Matsuzaki, I., Takamatsu, Y., Moroji, T., 1989. The effects of introcerebroventricularly injected corticotropin-releasing factor (CRF) on the central nervous system: behavioral and biochemical studies. Neuropeptides 13, 147–155.

Matthaei, S., Strumvoll, M., Kellerer, M., Haring, H.-U., 2000. Pathophysiology and pharmacological treatment of insulin resistance. Endocr. Rev. 21, 585–618.

Matthews, S.G., 2002. Early programming of the hypothalamo–pituitary–adrenal axis. Trends Endocrinol. Metab. 13, 373–380.

McBride, W.J., Murphy, J.M., Ikemoto, S., 1999. Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. Behav. Brain Res. 101, 129–152.

McCullough, L.D., Salamone, J.D., 1992. Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: a microdialysis and behavioral study. Brain Res. 592, 29–36.

McEwen, B.S., 1999a. Stress and hippocampal plasticity. Annu. Rev. Neurosci. 22, 105–122.

McEwen, B.S., 1999b. Stress and the aging hippocampus. Front. Neuroendocrinol. 20, 49–70.

McEwen, B.S., 2000a. Allostasis, allostatic load, and the aging nervous system: role of excitatory amino acids and neurotoxicity. Neurochem. Res. 25, 1219–1231.

McEwen, B.S., 2000b. The neurobiology of stress: from serendipity to clinical relevance. Brain Res. 886, 172–189.

McEwen, B.S., 2001. From molecules to mind. Stress, individual differences, and the social environment. Ann. N.Y. Acad. Sci 935, 42–49.

McEwen, B.S., 2003. Mood disorders and allostatic load. Biol. Psychiatry 54, 200–207.

McEwen, B.S., 2004. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann. N.Y. Acad. Sci. 1032, 1–7.

McEwen, B.S., Magarinos, A.M., 2001. Stress and hippocampal plasticity: implications for the pathophysiology of affective disorders. Hum. Psychopharmacol. 16, S7–S19.

McEwen, B.S., Magarinos, A.M., Reagan, L.P., 2002. Studies of hormone action in the hippocampal formation. Possible relevance to depression and diabetes. J. Psychosom. Res. 53, 883–890.

McEwen, B.S., Stellar, E., 1993. Stress and the individual: mechanisms leading to disease. Arch. Intern. Med. 153, 2093–2101.

McFarland, K., Davidge, S.B., Lapish, C.C., Kalivas, P.W., 2004. Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. J. Neurosci. 24, 1551–1560.

McGaugh, J.L., 2000. Memory—a century of consolidation. Science 287, 248–251.

McGaugh, J.L., 2002. Memory consolidation and the amygdala: a systems perspective. Trends Neurosci. 25, 456–461.

McGaugh, J.L., 2004. The amygdala modulates the consolidation of memories of emotionally arousing stimuli. Annu. Rev. Neurosci. 27, 1–28.

McGaugh, J.L., Cahill, L., Roozendaal, B., 1996. Involvement of the amygdala in memory storage: interaction with other brain systems. Proc. Natl. Acad. Sci. U.S.A. 93, 13508–13514.

McGaugh, J.L., Introini-Collison, I.B., Nagahara, A.H., Cahill, L., Brioni, J.D., Castellano, C., 1990. Involvement of the amygdaloid complex in neuromodulatory influences on memory storage. Neurosci. Biobehav. Rev. 14, 425–431.

McGaugh, J.L., McIntyre, C.K., Power, A.E., 2002. Amygdala modulation of memory consolidation: interaction with other brain systems. Neurobiol. Learn. Mem. 78, 539–552.

McKernan, M.G., Shinnick-Gallagher, P., 1997. Fear conditioning induces a lasting potentiation of synaptic currents in vitro. Nature 390, 607–611.

McKibbin, P.E., Cotton, S.J., McCarthy, H.D., Williams, G., 1992. The effect of dexamethasone on neuropeptide Y concentrations in specific hypothalamic regions. Life Sci. 51, 1301–1307.

McKinzie, D.L., Nowak, K.L., Yorger, L., McBride, W.J., Murphy, J.M., Lumeng, L., Li, T.K., 1998. The alcohol deprivation effect in the alcohol-preferring P rat under free-drinking and operant access conditions. Alcohol Clin. Exp. Res. 22, 1170–1176.

McKittrick, C.R., Magarinos, A.M., Blanchard, D.C., Blanchard, R.J., McEwen, B.S., Sakai, R.R., 2000. Chronic social stress reduces dendritic arbors

in CA3 of hippocampus and decreases binding to serotonin transporter sites. Synapse 36, 85–94.
McLean, M., Bisits, A., Davies, J., Woods, R., Lowry, P., Smith, R., 1995. A placental clock controlling the length of human pregnancy. Nat. Med. 1, 460–463.
Mendelson, J.H., Mello, N.K., Sholar, M.B., Siegel, A.J., Mutschler, N., Halpern, J., 2002. Temporal concordance of cocaine effects on mood states and neuroendocrine hormones. Psychoneuroendocrinology 27, 71–82.
Merali, Z., McIntosh, J., Kent, P., Michaud, D., Anisman, H., 1998. Aversive and appetitive events evoke the release of corticotropin-releasing hormone and bombesin-like peptides at the central nucleus of the amygdala. J. Neurosci. 18, 4758–4766.
Merchant, K.M., Dorsa, D.M., 1993. Differential induction of neurotensin and *c*-fos gene expression by typical versus atypical antipsychotics. Proc. Natl. Acad. Sci. U.S.A. 90, 3447–3451.
Mesches, M.H., Fleshner, M., Heman, K.L., Rose, G.M., Diamond, D.M., 1999. Exposing rats to a predator blocks primed burst potentiation in the hippocampus in vitro. J. Neurosci. 19, RC18.
Metcalfe, J., Jacobs, W.J., 1996. A ''hot-system/cool-system'' view of memory under stress. PTSD Res. Q. 7, 1–3.
Miczek, K.A., Thompson, M.L., Shuster, L., 1982. Opioid-like analgesia in defeated mice. Science 215, 1520–1522.
Mihaly, E., Fekete, C., Lechan, R.M., Liposits, Z., 2002. Corticotropin-releasing hormone-synthesizing neurons of the human hypothalamus receive neuropeptide Y-immunoreactive innervation from neurons residing primarily outside the infundibular nucleus. J. Comp. Neurol. 446, 235–243.
Mikics, E., Kruk, M.R., Haller, J., 2004. Genomic and non-genomic effects of glucocorticoids on aggressive behavior in male rats. Psychoneuroendocrinology 29, 618–635.
Milanes, M.V., Laorden, M.L., Chapleur-Chateau, M., 1997. Differential regulation of corticotropin-releasing factor and vasopressin in discrete brain regions after morphine adminmistration: correlations with hpothalamic noradrenergic activity and pituitary–adrenal response. Naunyn-Schmiedeberg's Arch. Pharmacol. 356, 603–610.
Milanes, M.V., Puig, M.M., Vargas, M.L., 1993. Simultaneous changes in hypothalamic catecholamine levels and plasma corticosterone concentration in the rat after acute morphine and during tolerance. Neuropeptides 24, 279–284.
Millenson, J.R., Leslie, J., 1974. The conditioned emotional response (CER) as a baseline for the study of anti-anxiety drugs. Neuropharmacology 13, 1–9.
Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.
Miller, G.E., Stetler, C.A., Carney, R.M., Freedland, K.E., Banks, W.A., 2002. Clinical depression and inflammatory risk markers for coronary heart disease. Am. J. Cardiol. 90, 1279–1283.
Miller, W.R., Sanchez-Craig, M., 1996. How to have a high success rate in treatment: advice for evaluators of alcoholism programs. Addiction 91, 779–785.
Mishkin, S., 1964. The interdependence of clinical neurology and neurophysiology. An historical review of the vestibulo-ocular reflex. Mcgill. Med. J. 33, 80–97.
Misra, M., Miller, K.K., Almazan, C., Worley, M., Herzog, D.B., Klibanski, A., 2005. Hormonal determinants of regional body composition in adolescent girls with anorexia nervosa and controls. J. Clin. Endocrinol. Metab. 90, 2580–2587 (Epub. February 15).
Mistlberger, R., 1994. Circadian food-anticipatory activity: formal models and physiological mechanisms. Neurosci. Biobehav. Rev. 18, 171–195.
Mistlberger, R., Rusak, B., 1987. Palatable daily meals entrain anticipatory activity rhythms in free-feeding rats: dependence on meal size and nutrient content. Physiol. Behav. 41, 219–226.
Mistlberger, R.E., Rechtschaffen, A., 1984. Recovery of anticipatory activity to restricted feeding in rats with ventromedial hypothalamic lesions. Physiol. Behav. 33, 227–235.
Mitchell, C., Flaherty, C.F., 1998. Temporal dynamics of corticosterone elevation in successive negative contrast. Physiol. Behav. 64, 287–292.
Mitra, R., Jadhav, S., McEwen, B.S., Vyas, A., Chattarji, S., 2005. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. Proc. Natl. Acad. Sci. U.S.A. 102, 9371–9376.
Mittleman, G., Blaha, C.D., Phillips, A.G., 1992. Pituitary–adrenal and dopaminergic modulation of schedule-induced polydipsia: behavioral and neurochemical evidence. Behav. Neurosci. 106, 408–420.
Mittleman, G., Brener, J., Robbins, T.W., 1990. Physiological correlates of schedule-induced activities in rats. Am. J. Physiol. 259, R485–R491.
Mittleman, G., Jones, G.H., Robbins, T.W., 1988. The relationship between schedule-induced polydipsia and pituitary–adrenal activity: pharmacological and behavioral manipulations. Behav. Brain Res. 28, 315–324.
Mizuno, T.M., Kleopoulos, S.P., Bergen, H.T., Roberts, J.L., Priest, C.A., Mobbs, C.V., 1998. Hypothalamic pro-opiomelanocortin mRNA is reduced by fasting and [corrected] in ob/ob and db/db mice, but is stimulated by leptin. Diabetes 47, 294–297.
Moga, M.M., Weis, R.P., Moore, R.Y., 1995. Efferent projections of the paraventricular thalamic nucleus of the rat. J. Comp. Neurol. 359, 221–238.
Mogenson, G.J., Jones, D.L., Yim, C.Y., 1980. From motivation to action: functional interface between the limbic system and the motor system. Prog. Neurobiol. 14, 69–97.
Moghaddam, B., 1993. Stress preferentially increases extraneuronal levels of excitatory amino acids in the prefrontal cortex: comparison to hippocampus and basal ganglia. J. Neurochem. 60, 1650–1657.
Moghaddam, B., Bolinao, M.L., Stein-Behrens, B., Sapolsky, R., 1994. Glucocorticoids mediate the stress-induced extracellular accumulation of glutamate. Brain Res. 655, 251–254.
Moorcroft, W.H., Lytle, L.D., Campbell, B.A., 1971. Ontogeny of starvation-induced behavioral arousal in the rat. J. Comp. Physiol. Psychol. 75, 59–67.
Moore, R.Y., Eichler, V.B., 1972. Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. Brain Res. 42, 201–206.
Moore-Ede, M.C., Sulzman, F.M., Fuller, C.A., 1982. The Clocks that Time Us: Physiology of the Circadian Timing System. Harvard University Press, Cambridge, MA.
Morilak, D.A., Garera, G., Echevarria, D.J., Garcia, A.S., Hernandez, A., Ma, S., Petre, C.O., 2005. Role of brain norepinephrine in the behavioral response to stress. Prog. Neuropsychopharmacol. Biol. Psychiatry 29, 1214–1224.
Morris, R.G., Garrud, P., Rawlins, J.N., O'Keefe, J., 1982. Place navigation impaired in rats with hippocampal lesions. Nature 297, 681–683.
Morrison, S.F., Sved, A.F., Passerin, A.M., 1999. GABA-mediated inhibition of raphe pallidus neurons regulates sympathetic outflow to brown adipose tissue. Am. J. Physiol. 276, R290–R297.
Morrow, B.A., Elsworth, J.D., Lee, E.J., Roth, R.H., 2000. Divergent effects of putative anxiolytics on stress-induced fos expression in the mesoprefrontal system of the rat. Synapse 36, 143–154.
Morse, W.H., Skinner, B.F., 1957. A second type of superstition in the pigeon. Am. J. Psychol. 70, 308–311.
Moskowitz, M.J., 1959. Running-wheel activity in the white rat as a function of combined food and water deprivation. J. Comp. Physiol. Psychol. 52, 621–625.
Mulders, W.H.A.M., Meek, J., Hafmans, T.G.M., Cools, A.R., 1997. Plasticity in the stress-regulating circuit: decreased input from the bed nucleus of the stria terminalis to the hypothalamic paraventricular nucleus in Wistar rats following adrenalectomy. Eur. J. Neurosci. 9, 2462–2471.
Musselman, D.L., Evans, D.L., Nemeroff, C.B., 1998. The relationship of depression and cardiovascular disease. Arch. Gen. Psychiatry 55, 580–592.
Myers, D.A., Gibson, M., Schulkin, J., Greenwood Van-Meerveld, B., 2005. Corticosterone implants to the amygdala and type 1 CRH receptor regulation: effects on behavior and colonic sensitivity. Behav. Brain Res. 161, 39–44.
Nader, K., Bechara, A., Roberts, D.C., Van der Kooy, D., 1994. Neuroleptics block high- but not low-dose heroin place preferences: further evidence for a two-system model of motivation. Behav. Neurosci. 108, 1128–1138.
Nashel, D.J., 1986. Is atherosclerosis a complication of long-term corticosteroid treatment? Am. J. Med. 80, 925–929.
Natelson, B., Ottenweller, J., Cook, J., Pitman, D., McCarty, R., Tapp, W., 1988. Effects of stressor intensity on habituation of the adrenocortical stress response. Physiol. Behav. 43, 41–46.
Nauta, W.J., 1971. The problem of the frontal lobe: a reinterpretation. J. Psychiatr. Res. 8, 167–187.

Neafsey, E.J., 1990. Prefrontal cortical control of the autonomic nervous system: anatomical and physiological observations. Prog. Brain Res. 85, 147–165.

Nemeroff, C.B., Widerlov, E., Bissette, G., Walleus, H.I.K., Eklund, K., Kilts, C.D., Loosen, P.T., Vale, W., 1984. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 226, 1342–1344.

Nestler, E.J., Alreja, M., Aghajanian, G.K., 1994. Molecular and cellular mechanisms of opiate action: studies in the rat locus coeruleus. Brain Res. Bull. 35, 521–528.

Nestler, E.J., Tallman, J.F., 1988. Chronic morphine treatment increases cyclic AMP-dependent protein kinase activity in the rat locus coeruleus. Mol. Pharmacol. 33, 127–132.

Nieto, M.M., Wilson, J., Cupo, A., Roques, B.P., Noble, F., 2002. Chronic morphine treatment modulates the extracellular levels of endogenous enkephalins in rat brain structures involved in opiate dependence: a microdialysis study. J. Neurosci. 22, 1034–1041.

Nikolarakis, K.E., Almeida, O.F., Herz, A., 1986. Stimulation of hypothalamic beta-endorphin and dynorphin release by corticotropin-releasing factor (in vitro). Brain Res. 399, 152–155.

Nikolarakis, K.E., Pfeiffer, A., Stalla, G.K., Herz, A., 1989. Facilitation of ACTH secretion by morphine is mediated by activation of CRF releasing neurons and sympathetic neuronal pathways. Brain Res. 498, 385–388.

North, R.A., Williams, J.T., 1983. Opiate activation of potassium conductance inhibits calcium action potentials in rat locus coeruleus neurones. Br. J. Pharmacol. 80, 225–228.

North, R.A., Williams, J.T., 1985. On the potassium conductance increased by opioids in rat locus coeruleus neurones. J. Physiol. 364, 265–280.

O'Brien, C., Childress, A.R., Ehrman, R., Robbins, S., McLellan, A.T., 1992a. Conditioning mechanisms in drug dependence. Clin. Neuropharmacol. 15 (Suppl. 1 Pt A), 66A–67A.

O'Brien, C.P., Childress, A.R., McLellan, A.T., Ehrman, R., 1992b. Classical conditioning in drug-dependent humans. Ann. N.Y. Acad. Sci. 654, 400–415.

O'Brien, C.P., Childress, A.R., McLellan, A.T., Ehrman, R., 1992c. A learning model of addiction. Res. Publ. Assoc. Res. Nerv. Ment. Dis. 70, 157–177.

O'Hare, E., Shaw, D.L., Tierney, K.J., Levine, A.S., Shephard, R.A., 2004. Behavioral and neurochemical mechanisms of the action of mild stress in the enhancement of feeding. Behav. Neurosci. 118, 173–177.

O'Hare, E.O., Cleary, J., Bartz, P.J., Weldon, D.T., Billington, C.J., Levine, A.S., 1997. Naloxone administration following operant training of sucrose/water discrimination in the rat. Psychopharmacology (Berl.) 129, 289–294.

Oda, N., Nakai, A., Mokuno, T., Sawai, Y., Nishida, Y., Mano, T., Asano, K., Itoh, Y., Kotake, M., Kato, S., et al., 1995. Dexamethasone-induced changes in glucose transporter 4 in rat heart muscle, skeletal muscle and adipocytes. Eur. J. Endocrinol. 133, 121–126.

Oitzl, M.S., de Kloet, E.R., 1992. Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. Behav. Neurosci. 106, 62–71.

Okuda, S., Roozendaal, B., McGaugh, J.L., 2004. Glucocorticoid effects on object recognition memory require training-associated emotional arousal. PNAS 101, 853–858.

Olds, J., 1976. Brain stimulation and the motivation of behavior. Prog. Brain Res. 45, 401–426.

Olds, J., Milner, P., 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J. Comp. Physiol. Psychol. 47, 419–427.

Olds, M.E., Fobes, J.L., 1981. The central basis of motivation: intracranial self-stimulation studies. Annu. Rev. Psychol. 32, 523–574.

Olefsky, J.M., 1975. Effect of dexamethasone on insulin binding, glucose transport, and glucose oxidation of isolated rat adipocytes. J. Clin. Invest. 56, 1499–1508.

Olive, M.F., Koenig, H.N., Nannini, M.A., Hodge, C.W., 2002. Elevated extracellular CRF levels in the bed nucleus of the stria terminalis during ethanol withdrawal and reduction by subsequent ethanol intake. Pharmacol. Biochem. Behav. 72, 213–220.

Oltmanns, K.M., Dodt, B., Schultes, B., Raspe, H.H., Schweiger, U., Born, J., Fehm, H.L., Peters, A., 2006. Cortisol correlates with metabolic disturbances in a population study of type 2 diabetic patients. Eur. J. Endocrinol. 154, 325–331.

Onn, S.P., Grace, A.A., 1995. Repeated treatment with haloperidol and clozapine exerts differential effects on dye coupling between neurons in subregions of striatum and nucleus accumbens. J. Neurosci. 15, 7024–7036.

Oomura, Y., Ono, T., Ooyama, H., Wayner, M.J., 1969. Glucose and osmosensitive neurones of the rat hypothalamus. Nature 222, 282–284.

Organisation, F.a.A., 1992. World food supplies and prevalence of chronic under-nutrition in developing regions as assessed in 1992. Food and Agriculture Organisation, vol. Document ESS/Misc/1/92, Rome.

Orth, D.N., 1995. Cushing's syndrome. N. Engl. J. Med. 332, 791–803.

Ortiz, J., Fitzgerald, L.W., Lane, S., Terwilliger, R., Nestler, E.J., 1996. Biochemical adaptations in the mesolimbic dopamine system in response to repeated stress. Neuropsychopharmacology 14, 443–452.

Ortiz, R.M., Wade, C.E., Ortiz, C.L., 2001. Effects of prolonged fasting in plasma cortisol and TH in postweaned northern elephant seal pups. Am. J. Physiol. 280, R790–R795.

Osborne, S.R., 1977. The free food (contrafreeloading) phenomenon: a review and analysis. Anim. Learn. Behav. 5, 221–235.

Otake, K., Nakamura, Y., 1995. Sites of origin of corticotropin-releasing factor-like immunoreactive projection fibers to the paraventricular thalamic nucleus in the rat. Neurosci. Lett. 201, 84–86.

Otte, C., Marmar, C.R., Pipkin, S.S., Moos, R., Browner, W.S., Whooley, M.A., 2004. Depression and 24-hour urinary cortisol in medical outpatients with coronary heart disease: the Heart and Soul study. Biol. Psychiatry 56, 241–247.

Ottosson, M., Lonnroth, P., Bjorntorp, P., Eden, S., 2000. Effects of cortisol and growth hormone on lipolysis in human adipose tissue. J. Clin. Endocrinol. Metab. 85, 799–803.

Overstreet, D.H., Knapp, D.J., Breese, G.R., 2002. Accentuated decrease in social interaction in rats subjected to repeated ethanol withdrawals. Alcohol Clin. Exp. Res. 26, 1259–1268.

Overstreet, D.H., Knapp, D.J., Breese, G.R., 2004. Modulation of multiple ethanol withdrawal-induced anxiety-like behavior by CRF and CRF1 receptors. Pharmacol. Biochem. Behav. 77, 405–413.

Overstreet, D.H., Knapp, D.J., Moy, S.S., Breese, G.R., 2003. A 5-HT1A agonist and a 5-HT2c antagonist reduce social interaction deficit induced by multiple ethanol withdrawals in rats. Psychopharmacology (Berl.) 167, 344–352.

Pacak, K., McCarty, R., Palkovits, M., Kopin, I.J., Goldstein, D.S., 1995a. Effects of immobilization on in vivo release of norepinephrine in the bed nucleus of the stria terminalis in conscious rats. Brain Res. 688, 242–246.

Pacak, K., Palkovits, M., Kopin, I.J., Goldstein, D.S., 1995b. Stress-induced norepinephrine release in hypothalamic paraventricular nucleus and pituitary–adrenocortical and sympathoadrenal activity: in vivo microdialysis studies. Front. Neuroendocrinol. 16, 89–150.

Pacak, K., Palkovits, M., Kvetnansky, R., Yadid, G., Kopin, I.J., Goldstein, D.S., 1995c. Effects of various stressors on in vivo norepinephrine release in the hypothalamic paraventricular nucleus and on the pituitary–adrenocortical axis. Ann. N.Y. Acad. Sci. 771, 115–130.

Pacak, K., Palkovits, M., 2001. Stressor specificity of central neuroendocrine responses: implications for stress-related disorders. Endocr. Rev. 22, 502–548.

Pacak, K., Palkovits, M., Makino, S., Kopin, I.J., Goldstein, D.S., 1996. Brainstem hemisection decreases corticotropin-releasing hormone mRNA in the paraventricular nucleus but not in the central amygdaloid nucleus. J. Neuroendocrinol. 8, 543–551.

Pacak, K., Palkovits, M., Yadid, G., Kvetnansky, R., Kopin, I.J., Goldstein, D.S., 1998. Heterogeneous neurochemical responses to different stressors: a test of Selye's doctrine of nonspecificity. Am. J. Physiol. 275, R1247–R1255.

Palkovits, M., Baffi, J., Toth, Z.E., Pacak, K., 1998. Brain catecholamine systems in stress. Adv. Pharmacol. 42, 572–575.

Palkovits, M., Baffi, J.S., Pacak, K., 1997. Stress-induced Fos-like Immunoreactivity in the Pons and the Medulla Oblongata of Rats. Stress 1, 155–168.

Palkovits, M., Baffi, J.S., Pacak, K., 1999. The role of ascending neuronal pathways in stress-induced release of norepinephrine in the hypothalamic-paraventricular nucleus of rats. J. Neuroendocrinol. 11, 529–539.

Parker, L.A., 1996. LSD produces place preference and flavor avoidance but does not produce flavor aversion in rats. Behav. Neurosci. 110, 503–508.

Parker, L.A., 2003. Taste avoidance and taste aversion: evidence for two different processes. Learn Behav. 31, 165–172.

Patterson, T.A., Brot, M.D., Zavosh, A., Schenk, J.O., Szot, P., Figlewicz, D.P., 1998. Food deprivation decreases mRNA and activity of the rat dopamine transporter. Neuroendocrinology 68, 11–20.

Patti, C.L., Kameda, S.R., Carvalho, R.C., Takatsu-Coleman, A.L., Lopez, G.B., Niigaki, S.T., Abilio, V.C., Frussa-Filho, R., Silva, R.H., 2006. Effects of morphine on the plus-maze discriminative avoidance task: role of state-dependent learning. Psychopharmacology 184, 1–12.

Pavcovich, L.A., Valentino, R.J., 1997. Regulation of a putative neurotransmitter effect of corticotropin-releasing factor: effects of adrenalectomy. J. Neurosci. 17, 401–408.

Pavlov, I.P., 1927. Conditional Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex. Oxford University Press, Oxford, UK.

Pecina, S., Schulkin, J., Berridge, K.C., 2006. Nucleus accumbens corticotropin-releasing factor increases cue-triggered motivation for sucrose reward: paradoxical positive incentive effects in stress? BMC Biol. 4, 8.

Pecoraro, N., Chou-Green, J., Dallman, M.F., 2003. *c*-Fos after incentive shifts: expectancy, incredulity, and recovery. Society for Neuroscience, vol. 292.15, New Orleans, LA.

Pecoraro, N., Dallman, M., 2005. *c*-Fos after incentive shifts: expectancy, incredulity, and recovery. Behav. Neurosci. 119, 366–387.

Pecoraro, N., Gomez, F., la Fleur, S., Roy, M., Dallman, M.F., 2005a. Single, but not multiple pairings of sucrose and corticosterone enhance memory for sucrose drinking and amplify remote reward relativity effects. Neurobiol. Learn. Mem. 83, 188–195.

Pecoraro, N., Gomez, F., Laugero, K., Dallman, M.F., 2002. Brief access to sucrose engages food-entrainable rhythms in food-deprived rats. Behav. Neurosci. 116, 757–776.

Pecoraro, N., Reyes, F., Gomez, F., Bhargava, A., Dallman, M.F., 2004. Chronic stress promotes palatable feeding, which reduces signs of stress: feedforward and feedback effects of chronic stress. Endocrinology 145, 3754–3762.

Pecoraro, N.C., Gomez, F., Dallman, M.F., 2005b. Glucocorticoids dose-dependently remodel energy stroes and amplify incentive reality effects. Psychoneuroendocrinology 30 (9), 815–825.

Pecoraro, N., Ginsberg, A.B., Warne, J.P., Gomez, F., la Fleur, S.E., Dallman, M.F., 2006. Diverse basal and stress-related phenotypes of Sprague Dawley rats from three vendors. Physiol Behav. [Epub ahead of print].

Pecoraro, N.C., Timberlake, W.D., Tinsley, M., 1999. Incentive downshifts evoke search repertoires in rats. J. Exp. Psychol. Anim. Behav. Process 25, 153–167.

Perreau-Lenz, S., Pevet, P., Buijs, R.M., Kalsbeek, A., 2004. The biological clock: the bodyguard of temporal homeostasis. Chronobiol. Int. 21, 1–25.

Pettit, H.O., Ettenberg, A., Bloom, F.E., Koob, G.F., 1984. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology (Berl.) 84, 167–173.

Pfennig, D.W., Murphy, P.J., 2000. Character displacement in polyphenic tadpoles. Evolution Int. J. Org. Evolution 54, 1738–1749.

Phillips, R.G., LeDoux, J.E., 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav. Neurosci. 106, 274–285.

Piazza, P.V., Barrot, M., Rouge-Pont, F., Marinelli, M., Maccari, S., Abrous, D.N., Simon, H., Le Moal, M., 1996a. Suppression of glucocorticoid secretion and antipsychotic drugs have similar effects on the mesolimbic dopaminergic transmission. Proc. Natl. Acad. Sci. U.S.A. 93 (26), 15445–15450.

Piazza, P.V., Deminiere, J.M., Le Moal, M., Simon, H., 1989. Factors that predict individual vulnerability to amphetamine self-administration. Science 245, 1511–1513.

Piazza, P.V., Deminiere, J.M., le Moal, M., Simon, H., 1990a. Stress- and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. Brain Res. 514, 22–26.

Piazza, P.V., Deminiere, J.M., Maccari, S., Mormede, P., Le Moal, M., Simon, H., 1990b. Individual reactivity to novelty predicts probability of amphetamine self-administration. Behav. Pharmacol. 1, 339–345.

Piazza, P.V., Deroche, V., Deminiere, J.-M., Maccari, S., Le Moal, M., Simon, H., 1993. Corticosterone in the range of stress-induced levels possesses reinforcing properties: implications for sensation-seeking behaviors. Proc. Natl. Acad. Sci. U.S.A. 90, 11738–11742.

Piazza, P.V., Le Moal, M., 1997. Glucocorticoids as a biological substrate of reward: physiological and pathophysiological implications. Brain Res. Rev. 25, 359–372.

Piazza, P.V., Le Moal, M., 1998. The role of stress in drug self-administration. TiPS 19, 67–74.

Piazza, P.V., Rouge-Pont, F., Derche, V., Maccari, S., Simon, H., Le Moal, M., 1996b. Glucocorticoids have state-dependent stimulant effects on the mesencephalic dopaminergic transmission. Proc. Natl. Acad. Sci. U.S.A. 93, 8716–8720.

Pierre, P.J., Vezina, P., 1997. Predisposition to self-administer amphetamine: the contribution of response to novelty and prior exposure to the drug. Psychopharmacology (Berl.) 129, 277–284.

Pinto, S., Roseberry, A.G., Liu, H., Diano, S., Shanabrough, M., Cai, X., Friedman, J.M., Horvath, T.L., 2004. Rapid rewiring of arcuate nucleus feeding circuits by leptin. Science 304, 110–115.

Pitman, D.L., Ottenweller, J.E., Natelson, B.H., 1988. Plasma corticosterone levels during repeated presentation of two intensities of restraint stress: chronic stress and habituation. Physiol. Behav. 43, 47–55.

Pitman, D.L., Ottenweller, J.E., Natelson, B.H., 1990. Effect of stressor intensity on habituation and sensitization of glucocorticoid responses in rats. Behav. Neurosci. 104, 28–36.

Plihal, W., Krug, R., Pietrowsky, R., Fehm, H.L., Born, J., 1996. Corticosteroid receptor mediated effects on mood in humans. Psychoneuroendocrinology 21, 515–523.

Plotsky, P.M., Cunningham Jr., E.T., Widmaier, E.P., 1989. Catecholaminergic modulation of corticotropin-releasing factor and adrenocorticotropin secretion. Endocr. Rev. 10, 437–458.

Pontieri, F.E., Colangelo, V., La Riccia, M., Pozzilli, C., Passarelli, F., Orzi, F., 1994. Psychostimulant drugs increase glucose utilization in the shell of the rat nucleus accumbens. Neuroreport 5, 2561–2564.

Pontieri, F.E., Tanda, G., Di Chiara, G., 1995. Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. Proc. Natl. Acad. Sci. U.S.A. 92, 12304–12308.

Pothos, E., Rada, P., Mark, G.P., Hoebel, B.G., 1991. Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. Brain Res. 566, 348–350.

Poulos, C.X., Hinson, R.E., Siegel, S., 1981. The role of Pavlovian processes in drug tolerance and dependence: implications for treatment. Addict. Behav. 6, 205–211.

Powley, T.L., 2000. Vagal circuitry mediating cephalic-phase responses to food. Appetite 34, 184–188.

Powley, T.L., Martinson, F.A., Phillips, R.J., Jones, S., Baronowsky, E.A., Swithers, S.E., 2001. Gastrointestinal projection maps of the vagus nerve are specified permanently in the perinatal period. Brain Res. Dev. Brain Res. 129, 57–72.

Prasad, C., Prasad, A., 1995. A relationship between increased voluntary alcohol preference and basal hypercorticosteronemia associated with an attenuated rise in corticosterone output during stress. Alcohol 12, 59–63.

Przegalinski, E., Filip, M., Siwanowicz, J., Nowak, E., 2000. Effect of adrenalectomy and corticosterone on cocaine-induced sensitization in rats. J. Physiol. Pharmacol. 51, 193–204.

Przekop, F., Mateusiak, K., Stupnicka, E., Romanowicz, K., Domanski, E., 1990. Suppressive effect of beta-endorphin and naloxone on the secretion of cortisol under stress conditions in sheep. Exp. Clin. Endocrinol. 95, 210–216.

Przewlocki, R., 2002. Stress, opioid peptides, and their receptors. In: Pfaff, D.W. (Ed.), Hormones, Brain, and Behavior, vol. 1. Academic Press, San Diego, CA, pp. 691–734.

Przewlocki, R., Hollt, V., Voigt, K.H., Herz, A., 1979. Modulation of in vitro release of beta-endorphin from the separate lobes of the rat pituitary. Life Sci. 24, 1601–1607.

Pugh, C.R., Tremblay, D., Fleshner, M., Rudy, J.W., 1997. A selective role for corticosterone in contextual-fear conditioning. Behav. Neurosci. 111, 503–511.

Quirarte, G.L., Galvez, R., Roozendaal, B., McGaugh, J.L., 1998. Norepinephrine release in the amygdala in response to footshock and opioid peptidergic drugs. Brain Res. 808, 134–140.

Quirarte, G.L., Roozendaal, B., McGaugh, J.L., 1997. Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. Proc. Natl. Acad. Sci. U.S.A. 94, 14048–14053.

Raadsheer, F.C., Hoogendijk, W.J.G., Stam, F.C., Tilders, F.H.J., Swaab, D.F., 1994a. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology 60, 433–436.

Raadsheer, F.C., Hoogendijk, W.J.G., Stam, F.C., Tilders, F.J.H., Swaab, D.F., 1994b. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology 60, 436–444.

Rada, P., Avena, N.M., Hoebel, B.G., 2005. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. Neuroscience 134, 737–744.

Rada, P., Mark, G.P., Pothos, E., Hoebel, B.G., 1991a. Systemic morphine simultaneously decreases extracellular acetylcholine and increases dopamine in the nucleus accumbens of freely moving rats. Neuropharmacology 30, 1133–1136.

Rada, P., Pothos, E., Mark, G.P., Hoebel, B.G., 1991b. Microdialysis evidence that acetylcholine in the nucleus accumbens is involved in morphine withdrawal and its treatment with clonidine. Brain Res. 561, 354–356.

Rada, P.V., Mark, G.P., Hoebel, B.G., 1998. Dopamine release in the nucleus accumbens by hypothalamic stimulation-escape behavior. Brain Res. 782, 228–234.

Radley, J.J., Morrison, J.H., 2005. Repeated stress and structural plasticity in the brain. Ageing Res. Rev. 4, 271–287.

Radley, J.J., Rocher, A.B., Janssen, W.G., Hof, P.R., McEwen, B.S., Morrison, J.H., 2005a. Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. Exp. Neurol. 196, 199–203.

Radley, J.J., Rocher, A.B., Miller, M., Janssen, W.G., Liston, C., Hof, P.R., McEwen, B.S., Morrison, J.H., 2005b. Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex. Cereb. Cortex.

Radley, J.J., Sisti, H.M., Hao, J., Rocher, A.B., McCall, T., Hof, P.R., McEwen, B.S., Morrison, J.H., 2004. Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. Neuroscience 125, 1–6.

Ramsay, T.G., 1996. Fat cells. Endocrinol. Metab. Clin. N. Am. 25, 847–870.

Rasmussen, K., Aghajanian, G.K., 1989. Withdrawal-induced activation of locus coeruleus neurons in opiate-dependent rats: attenuation by lesions of the nucleus paragigantocellularis. Brain Res. 505, 346–350.

Rassnick, S., Sved, A.F., Rabin, B.S., 1994. Locus coeruleus stimulation by corticotropin-releasing hormone suppresses in vitro cellular immune responses. J. Neurosci. 14, 6033–6040.

Ratka, A., Sutanto, W., Bloemers, M., de Kloet, E., 1989. On the role of brain mineralocorticoid (type I) and glucocorticoid (type II) receptors in neuroendocrine regulation. Neuroendocrinology 50, 117–123.

Redgate, E.S., Szechtman, H., Fahringer, E.E., 1974. The effect of plasma cortisol concentration on the pituitary adrenal response elicited by electrical stimulation of the infundibular area of the awake unrestrained cat. Horm. Res. 5, 173–181.

Reid, S.L., Finger, F.W., 1955. The rat's adjustment to 23-hour food deprivation cycles. J. Comp. Physiol. Psychol. 48, 110–113.

Reilly, S., Trifunovic, R., 1999. Gustatory thalamus lesions eliminate successive negative contrast in rats. Behav. Neurosci. 113, 1242–1248.

Renaud, L.P., Tang, M., McCann, M.J., Stricker, E.M., Verbalis, J.G., 1987. Cholecystokinin and gastric distension activate oxytocinergic cells in rat hypothalamus. Am. J. Physiol. 253, R661–R665.

Reyes, B.A., Valentino, R.J., Xu, G., Van Bockstaele, E.J., 2005. Hypothalamic projections to locus coeruleus neurons in rat brain. Eur. J. Neurosci. 22, 93–106.

Richter, C.P., 1927. Animal behavior and internal drives. Q. Rev. Biol. II (3), 307–343.

Rinaman, L., Stricker, E.M., Hoffman, G.E., Verbalis, J.G., 1997. Central *c*-Fos expression in neonatal and adult rats after subcutaneous injection of hypertonic saline. Neuroscience 79, 1165–1175.

Ritter, S., Bugarith, K., Dinh, T.T., 2001. Immunotoxic destruction of distinct catecholamine subgroups produces selective impairment of glucoregulatory responses and neuronal activation. J. Comp. Neurol. 432, 197–216.

Ritter, S., Watts, A.G., Dinh, T.T., Sanchez-Watts, G., Pedrow, C., 2003. Immunotoxin lesion of hypothalamically projecting norepinephrine and epinephrine neurons differentially affects circadian and stressor-stimulated corticosterone secretion. Endocrinology 144, 1357–1367.

Rivest, S., 2001. How circulating cytokines trigger the neural circuits that control the hypothalamic–pituitary–adrenal axis. Psychoneuroendocrinology 26, 761–788.

Rivet, J.M., Stinus, L., LeMoal, M., Mormede, P., 1989. Behavioral sensitization to amphetamine is dependent on corticosteroid receptor activation. Brain Res. 498, 149–153.

Rivier, C., Rivier, J., Mormede, P., Vale, W., 1984. Studies on the nature of the interaction between vasopressin and corticotropin-releasing factor on adrenocorticotropin release in the rat. Endocrinology 115, 882–886.

Robbins, T.W., Everitt, B.J., 1996. Neurobehavioural mechanisms of reward and motivation. Curr. Opin. Neurobiol. 6, 228–236.

Robbins, T.W., Koob, G.F., 1980. Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. Nature 285, 409–412.

Robbins, T.W., Roberts, D.C., Koob, G.F., 1983. Effects of d-amphetamine and apomorphine upon operant behavior and schedule-induced licking in rats with 6-hydroxydopamine-induced lesions of the nucleus accumbens. J. Pharmacol. Exp. Ther. 224, 662–673.

Roberts, J.L., Lundblad, J.R., Eberwine, J.H., Fremeau, R.T., Salton, S.R., Blum, M., 1987. Hormonal regulation of POMC gene expression in pituitary. Ann. N.Y. Acad. Sci. 512, 275–285.

Robinson, S., Winnik, H.Z., 1973. Severe psychotic disturbances following crash diet weight loss. Arch. Gen. Psychiatry 29, 559–562.

Robinson, T.E., Becker, J.B., 1986. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res. 396, 157–198.

Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Brain Res. Rev. 18, 247–291.

Robinson, T.E., Berridge, K.C., 2000. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 95, 91–117.

Robinson, T.E., Gorny, G., Mitton, E., Kolb, B., 2001. Cocaine self-administration alters the morphology of dendrites and dendritic spines in the nucleus accumbens and neocortex. Synapse 39, 257–266.

Robinson, T.E., Kolb, B., 1997. Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. J. Neurosci. 17, 8491–8497.

Robinson, T.E., Kolb, B., 1999a. Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. Eur. J. Neurosci. 11, 1598–1604.

Robinson, T.E., Kolb, B., 1999b. Morphine alters the structure of neurons in the nucleus accumbens and neocortex of rats. Synapse 33, 160–162.

Rocher, C., Spedding, M., Munoz, C., Jay, T.M., 2004. Acute stress-induced changes in hippocampal/prefrontal circuits in rats: effects of antidepressants. Cereb. Cortex 14, 224–229.

Rodd, Z.A., Bell, R.L., Kuc, K.A., Murphy, J.M., Lumeng, L., Li, T.K., McBride, W.J., 2003. Effects of repeated alcohol deprivations on operant ethanol self-administration by alcohol-preferring (P) rats. Neuropsychopharmacology 28, 1614–1621.

Roderick, M.L., Farquhar, G.D., 2002. The cause of decreased pan evaporation over the past 50 years. Science 298, 1410–1411.

Rodgers, R.J., Haller, J., Holmes, A., Halasz, J., Walton, T.J., Brain, P.F., 1999. Corticosterone response to the plus-maze: high correlation with risk assessment in rats and mice. Physiol. Behav. 68, 47–53.

Rodriguez Manzanares, P.A., Isoardi, N.A., Carrer, H.F., Molina, V.A., 2005. Previous stress facilitates fear memory, attenuates GABAergic inhibition, and increases synaptic plasticity in the rat basolateral amygdala. J. Neurosci. 25, 8725–8734.

Rogan, M.T., Staubli, U.V., LeDoux, J.E., 1997. Fear conditioning induces associative long-term potentiation in the amygdala. Nature 390, 604–607.

Roitman, M.F., Patterson, T.A., Sakai, R.R., Bernstein, I.L., Figlewicz, D.P., 1999. Sodium depletion and aldosterone decrease dopamine transporter activity in nucleus accumbens but not striatum. Am. J. Physiol. 276, R1339–R1345.

Romanski, L.M., LeDoux, J.E., 1992. Equipotentiality of thalamo-amygdala and thalamo-cortico-amygdala circuits in auditory fear conditioning. J. Neurosci. 12, 4501–4509.

Roozendaal, B., 2002. Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval. Neurobiol. Learn. Mem. 78, 578–595.

Roozendaal, B., 2003. Systems mediating acute glucocorticoid effects on memory consolidation and retrieval. Prog. Neuropsychopharmacol. Biol. Psychiatry 27, 1213–1223.

Roozendaal, B., Bohus, B., McGaugh, J.L., 1996a. Dose-dependent suppression of adrenocortical activity with metyrapone: effects on emotion and memory. Psychoneuroendocrinology 21, 681–693.

Roozendaal, B., Carmi, O., McGaugh, J.L., 1996b. Adrenocortical suppression blocks the memory-enhancing effects of amphetamine and epinephrine. Proc. Natl. Acad. Sci. 93, 1429–1433.

Roozendaal, B., Brunson, K.L., Holloway, B.L., McGaugh, J.L., Baram, T.Z., 2002. Involvement of stress-released corticotropin-releasing hormone in the basolateral amygdala in regulating memory consolidation. PNAS 99, 13908–13913.

Roozendaal, B., Griffith, Q.K., Buranday, J., de Quervain, D.J.-F., McGaugh, J.L., 2003. The hippocampus mediates glucocorticoid-induced impairment of spatial memory retrieval: dependence on the basolateral amygdala. Proc. Natl. Acad. Sci. U.S.A. 100, 1328–1333.

Roozendaal, B., Hui, G.K., Hui, I.R., Berlau, D.J., McGaugh, J.L., Weinberger, N.M., 2006. Basolateral amygdala noradrenergic activity mediates corticosterone-induced enhancement of auditory fear conditioning. Neurobiol. Learn. Mem. [Epub ahead of print].

Roozendaal, B., McGaugh, J.L., 1996a. Amygdaloid nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. Neurobiol. Learn. Mem. 65, 1–8.

Roozendaal, B., McGaugh, J.L., 1996b. The memory-modulatory effects of glucocortcoids depend on an intact stria terminalis. Brain Res. 709, 243–250.

Roozendaal, B., Portillo-Marquez, G., McGaugh, J.L., 1996c. Basolateral amygdala lesions block glucocorticoid-induced modulation of memory for spacial learning. Behav. Neurosci. 110, 1074–1083.

Roozendaal, B., McGaugh, J.L., 1997. Glucocorticoid receptor agonist and antagonist administration into the basolateral but not central amygdala modulates memory storage. Neurobiol. Learn. Mem. 67, 176–179.

Roozendaal, B., Nguyen, B.T., Power, A.E., McGaugh, J.L., 1999a. Basolateral amygdala noradrenergic influence enables enhancement of memory consolidation induced by hippocampal glucocorticoid receptor activation. Proc. Natl. Acad. Sci. U.S.A. 96, 11642–11647.

Roozendaal, B., Williams, C.L., McGaugh, J.L., 1999b. glucocorticoid receptor activation in the rat nucleus of the solitary tract facilitates memory consolidation: involvement of the basolateral amygdala. Eur. J. Neurosci. 11, 1317–1323.

Roozendaal, B., Okuda, S., Van der Zee, E.A., McGaugh, J.L., 2006b. Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. PNAS 103, 6741–6746.

Roozendaal, B., Phillips, R.G., Power, A.E., Brooke, S.M., Sapolsky, R.M., McGaugh, J.L., 2001. Memory retrieval impairment induced by hippocampal CA3 lesions is blocked by adrenocortical suppression. Nat. Neurosci. 4, 1169–1171.

Roper, T.J., Nieto, J., 1979. Schedule-induced drinking and other behavior in the rat, as a function of body weight deficit. Physiol. Behav. 23, 673–678.

Rose, S.P., 1995. Cell-adhesion molecules, glucocorticoids and long-term-memory formation. Trends Neurosci. 18, 502–506.

Rosen, E.D., Spiegelman, B.M., 2000. Molecular regulation of adipogenesis. Annu. Rev. Cell Dev. Biol. 16, 145–171.

Rosen, J.B., Hitchcock, J.M., Sananes, C.B., Miserendino, M.J., Davis, M., 1991. A direct projection from the central nucleus of the amygdala to the acoustic startle pathway: anterograde and retrograde tracing studies. Behav. Neurosci. 105, 817–825.

Rosen, J.B., Pishevar, S.K., Weiss, S.R., Smith, M.A., Kling, M.A., Gold, P.W., Schulkin, J., 1994. Glucocorticoid treatment increases the ability of CRH to induce seizures. Neurosci. Lett. 174, 113–116.

Rosenkranz, J.A., Grace, A.A., 1999. Modulation of basolateral amygdala neuronal firing and afferent drive by dopamine receptor activation in vivo. J. Neurosci. 19, 11027–11039.

Rosenkranz, J.A., Grace, A.A., 2001. Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. J. Neurosci. 21, 4090–4103.

Rosenkranz, J.A., Moore, H., Grace, A.A., 2003. The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. J. Neurosci. 23, 11054–11064.

Rosenthal, M.J., Morley, J.E., 1989. Corticotropin releasing factor (CRF) and age-related differences in behavior of mice. Neurobiol. Aging 10, 167–171.

Rosmond, R., 2005. Role of stress in the pathogenesis of the metabolic syndrome. Psychoneuroendocrinol 30, 1–10.

Rouge-Pont, F., Deroche, V., Le Moal, M., Piazza, P.V., 1998. Individual differences in stress-induced dopamine release in the nucleus accumbens are influenced by corticosterone. Eur. J. Neurosci. 10, 3903–3907.

Routh, V.H., 2002. Glucose-sensing neurons: are they physiologically relevant? Physiol. Behav. 76, 403–1403.

Routh, V.H., 2003. Glucosensing neurons in the ventromedial hypothalamic nucleus (VMN) and hypoglycemia-associated autonomic failure (HAAF). Diabetes Metab. Res. Rev. 19, 348–356.

Rowland, C.V., 1968. Psychotherapy of six hyper-obese adults during total starvation. Arch. Gen. Psychiatry 18, 541–548.

Russell, J.W., Singer, G., Bowman, G., 1983. Effects of interactions between amphetamine and food deprivation on covariation of muricide, consummatory behaviour and activity. Pharmacol. Biochem. Behav. 18, 917–926.

Rylander, G., 1939. Personality Changes after Operations on the Frontal Lobes. Oxford University Press, Oxford, UK.

Saal, D., Dong, Y., Bonci, A., Malenka, R.C., 2003. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron 37, 577–582.

Saeb-Parsy, K., Lombardelli, S., Khan, F.Z., McDowall, K., Au-Yong, I.T., Dyball, R.E., 2000. Neural connections of hypothalamic neuroendocrine nuclei in the rat. J. Neuroendocrinol. 12, 635–648.

Sage, D., Maurel, D., Bosler, O., 2002. Corticosterone-dependent driving influence of the suprachiasmatic nucleus on adrenal sensitivity to ACTH. Am. J. Physiol. 282, E458–E465.

Sainsbury, A., Cusin, I., Rohner-Jeanrenaud, F., Jeanrenaud, B., 1997. Adrenalectomy prevents the obesity syndrome produced by chronic central neuropeptide Y infusion in normal rats. Diabetes 46, 209–214.

Saito, M., Murakami, E., Nishida, T., Fujisawa, Y., Suda, M., 1975. Circadian rhythms in digestive enzymes in the small intestine of rats. I. Patterns of the rhythms in various regions of the small intestine. J. Biochem. (Tokyo) 78, 475–480.

Saito, M., Murakami, E., Nishida, T., Fujisawa, Y., Suda, M., 1976. Circadian rhythms of digestive enzymes in the small intestine of the rat. II. Effects of fasting and refeeding. J. Biochem. (Tokyo) 80, 563–568.

Sakellaris, P.C., Vernikos-Danellis, J., 1975. Increased rate of response of the pituitary–adrenal system in rats adapted to chronic stress. Endocrinology 97, 597–602.

Samarghandian, S., Ohata, N., Yamauchi, N., Shibasaki, T., 2003. Corticotropin-releasing factor as well as opioid and dopamine are involved in tail-pinch-induced food intake of rats. Neuroscience 116, 519–524.

Samuels, M.H., Kramer, P., 1996. Differential effects of short-term fasting on pulsatile thyrotropin, gonadotropin and a-subunit secretion in healthy men—a clinical research center study. J. Clin. Endocrinol. Metab. 81, 32–36.

Samuels, M.H., McDaniel, P.A., 1997. Thyrotropin levels during hydrocortisone infusion that mimic fasting-induced cortisol elevations: a clinical research center study. J. Clin. Endocrinol. Metab. 82, 3700–3704.

Sandi, C., Loscertales, M., 1999. Opposite effects on NCAM expression in the rat frontal cortex induced by acute vs. chronic corticosterone treatments. Brain Res. 828, 127–134.

Sandi, C., Loscertales, M., Guaza, C., 1997. Experience-dependent facilitating effect of corticosterone on spatial memory formation in the water maze. Eur. J. Neurosci. 9, 637–642.

Sandi, C., Merino, J.J., Cordero, M.I., Touyarot, K., Venero, C., 2001. Effects of chronic stress on contextual fear conditioning and the hippocampal expression of the neural cell adhesion molecule, its polysialylation, and L1. Neuroscience 102, 329–339.

Sandi, C., Rose, S.P., 1994a. Corticosteroid receptor antagonists are amnestic for passive avoidance learning in day-old chicks. Eur. J. Neurosci. 6, 1292–1297.

Sandi, C., Rose, S.P., 1994b. Corticosterone enhances long-term retention in one-day-old chicks trained in a weak passive avoidance learning paradigm. Brain Res. 647, 106–112.

Sandi, C., Rose, S.P., 1997. Training-dependent biphasic effects of corticosterone in memory formation for a passive avoidance task in chicks. Psychopharmacology (Berl.) 133, 152–160.

Saper, C.B., 2000. Hypothalamic connections with the cerebral cortex. Prog. Brain Res. 126, 39–48.

Saper, C.B., Chou, T.C., Elmquist, J.K., 2002. The need to feed: homeostatic and hedonic control of eating. Neuron 36, 199–211.

Sapolsky, R.M., 1987a. Glucocorticoids and hippocampal damage. Trends Neurosci. 10, 346–349.

Sapolsky, R.M., 1987b. Stress, Social Status and Reproductive Physiology in Free-Living Baboons. Prentice-Hall Inc., New Jersey.

Sapolsky, R.M., 1992. Stress, the Aging Brain, and the Mechanisms of Neuron Death. MIT Press, Cambridge, MA.

Sapolsky, R.M., 2004. The frontal cortex and the criminal justice system. Philos. Trans. R. Soc. Lond. B Biol. Sci. 359, 1787–1796.

Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1986. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr. Rev. 7, 284–301.

Sarkar, S., Wittmann, G., Fekete, C., Lechan, R.M., 2004. Central administration of cocaine- and amphetamine-regulated transcript increases phosphorylation of cAMP response element binding protein in corticotropin-releasing hormone-producing neurons but not in prothyrotropin-releasing hormone-producing neurons in the hypothalamic paraventricular nucleus. Brain Res. 999, 181–192.

Sarnyai, B., Shaham, Y., Heinrichs, S.C., 2001. The role of corticotropin-releasing factor in drug addiction. Pharmacol. Rev. 53, 209–243.

Sarnyai, Z., Veldhuis, J.D., Mello, N.K., Mendelson, J.H., Eros-Sarnyai, M., Mercer, G., Gelles, H., Kelly, M., 1995. The concordance of pulsatile ultradian release of adrenocorticotropin and cortisol in male rhesus monkeys. J. Clin. Endocrinol. Metab. 80, 54–59.

Sauvage, M., Steckler, T., 2001. Detection of corticotropin-releasing hormone receptor 1 immunoreactivity in cholinergic, dopaminergic and noradrenergic neurons of the murine basal forebrain and brainstem nuclei–potential implication for arousal and attention. Neuroscience 104, 643–652.

Savontaus, E., Conwell, I.M., Wardlaw, S.L., 2002. Effects of adrenalectomy on AGRP, POMC, NPY and CART gene expression in the basal hypothalamus of fed and fasted rats. Brain Res. 958, 130–138.

Sawchenko, P.E., 1987. Adrenalectomy-induced enhancement of CRF and vasopressin immunoreactivity in parvocellular neurosecretory neurons: anatomic, peptide and steroid specificity. J. Neurosci. 7, 1093–1106.

Sawchenko, P.E., Bohn, M.C., 1989. Glucocorticoid receptor-immunoreactivity in C1, C2, and C3 adrenergic neurons that project to the hypothalamus or to the spinal cord in the rat. J. Comp. Neurol. 285, 107–116.

Sawchenko, P.E., Li, H.-Y., Ericsson, A., 2000. Circuits and mechanisms governing hypothalamic responses to stress: a tale of two paradigms. Prog. Brain Res. 122, 61–78.

Sawchenko, P.E., Swanson, L.W., 1981. Central noradrenergic pathways for the integration of hypothalamic neuroendocrine and autonomic responses. Science 214, 685–687.

Sawchenko, P.E., Swanson, L.W., 1982. The organization of noradrenergic pathways from the brainstem to the paraventricular and supraoptic nuclei in the rat. Brain Res. Rev. 4, 275–325.

Sawchenko, P.E., Swanson, L.W., 1983. The organization of forebrain afferents to the paraventricular and supraoptic nuclei of the rat. J. Comp. Neurol. 218, 121–144.

Sawchenko, P.E., Swanson, L.W., 1989. Organization of CRF immunoreactive cells and fibers in the rat brain: immunohistochemical studies. In: CRC Critical Reviews in Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide. CRC Press, Boca Raton, pp. 29–51.

Schacke, H., Docke, W.D., Asadullah, K., 2002. Mechanisms involved in the side effects of glucocorticoids. Pharmacol. Ther. 96, 23–43.

Schenk, S., Lacelle, G., Gorman, K., Amit, Z., 1987. Cocaine self-administration in rats influenced by environmental conditions: implications for the etiology of drug abuse. Neurosci. Lett. 81, 227–231.

Scheuer, D.A., Bechtold, A.G., Shank, S.S., Akana, S.F., 2003. Glucocorticoids act in the dorsal hindbrain to increase arterial pressure. Am. J. Physiol. 286, H458–H467.

Scheuer, D.A., Mifflin, S.W., 1997. Chronic corticosterone treatment increases myocardial infarct size in rats with ischemia-perfusion injury. Am. J. Physiol. 272, R2017–R2024.

Scheuer, D.A., Mifflin, S.W., 1998. Repeated intermittent stress exacerbates myocardial ischemia-reperfusion injury. Am. J. Physiol. 274, 470–475.

Scheuer, D.A., Mifflin, S.W., 2001. Glucocorticoids modulate baroreflex control of renal sympathetic nerve activity. Am. J. Physiol. 280, R1440–R1449.

Schlotz, W., Hellhammer, J., Schulz, P., Stone, A.A., 2004. Perceived work overload and chronic worrying predict weekend–weekday differences in the cortisol awakening response. Psychosom. Med. 66, 207–214.

Schoenbaum, G., Chiba, A.A., Gallagher, M., 1998. Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nat. Neurosci. 1, 155–159.

Schoenbaum, G., Setlow, B., Ramus, S.J., 2003. A systems approach to orbitofrontal cortex function: recordings in rat orbitofrontal cortex reveal interactions with different learning systems. Behav. Brain Res. 146, 19–29.

Schulkin, J., Gold, P.W., McEwen, B.S., 1998. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. Psychoneuroendocrinology 23, 219–243.

Schulkin, J., Morgan, M.A., Rosen, J.B., 2005. A neuroendocrine mechanism for sustaining fear. Trends Neurosci. 28 (12), 629–635.

Schwartz, M.W., Seeley, R.J., Woods, S.C., Weigle, D.S., Campfield, L.A., Burn, P., Baskin, D.G., 1997. Leptin increases hypothalamic pro-opiomelanocortin mRNA expression in the rostral arcuate nucleus. Diabetes 46, 2119–2123.

Scribner, K., Walker, C.-D., Cascio, C.S., Dallman, M.F., 1991. Chronic streptozotocin diabetes in rats facilitates the acute stress response without altering pituitary or adrenal responsiveness to secretagogues. Endocrinology 129, 99–108.

Segall, L.A., Perrin, J.S., Robinson, B., Rodaros, D., Amir, S., 2005. Exogenous corticosterone restores rhythmic expression of the clock gene, per2, in the central extended amygdala in adrenalectomized rats. Society for Neuroscience, vol. Abstract, Washington, DC.

Self, D.W., Nestler, E.J., 1998. Relapse to drug-seeking: neural and molecular mechanisms. Drug Alcohol Depend. 51, 49–60.

Selye, H., 1936. A syndrome produced by diverse nocuous agents. Nature 138, 32–35.

Selye, H., 1956. The Stress of Life. McGraw-Hill, New York.

Sgoifo, A., Koolhaas, J.M., de Boer, A.G., Musso, E., Stilli, D., Buwalda, B., Meerlo, P., 1999. Social stress, autonomic neural activation, and cardiac activity in rats. Neurosci. Biobehav. Rev. 23, 915–923.

Shaham, Y., Erb, S., Leung, S., Buczek, Y., Stewart, J., 1998. CP-154,526, a selective, non-peptide antagonist of the corticotropin-releasing factor1 receptor attenuates stress-induced relapse to drug seeking in cocaine- and heroin-trained rats. Psychopharmacology (Berl.) 137, 184–190.

Shaham, Y., Funk, D., Erb, S., Brown, T.J., Walker, C.-D., Stewart, J., 1997. Corticotropin-releasing factor, but not corticosterone, is involved in stress-induced relapse to heroin seeking in rats. J. Neurosci. 17, 2605–2614.

Shaham, Y., Shalev, U., Lu, L., de Wit, H., Stewart, J., 2002. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology (Online 26 October).

Shakesby, A.C., Anwyl, R., Rowan, M.J., 2002. Overcoming the effects of stress on synaptic plasticity in the intact hippocampus: rapid actions of serotonergic and antidepressant agents. J. Neurosci. 22, 3638–3644.

Shalev, U., Highfield, D., Yap, J., Shaham, Y., 2000. Stress and relapse to drug seeking in rats: studies on the generality of the effect. Psychopharmacology 150, 337–346.

Shalev, U., Marinelli, M., Baumann, M.H., Piazza, P.V., Shaham, Y., 2003. The role of corticosterone in food deprivation-induced reinstatement of cocaine seeking in the rat. Psychopharmacology (Berl.) 168, 170–176.

Shallice, T., 1982. Specific impairments of planning. Philos. Trans. R. Soc. Lond. B Biol. Sci. 298, 199–209.

Shepard, J.D., Barron, K.W., Myers, D.A., 2000. Corticosterone delivery to the amygdala increases corticotropin-releasing factor mRNA in the central amygdaloid nucleus and anxiety-like behavior. Brain Res. 861, 288–295.

Shepard, J.D., Barron, K.W., Myers, D.A., 2003. Stereotaxic localization of corticosterone to the amygdala enhances hypothalamo–pituitary–adrenal responses to behavioral stress. Brain Res. 963, 203–213.

Sherman, J.E., Kalin, N.H., 1987. The effects of ICV-CRH on novelty-induced behavior. Pharmacol. Biochem. Behav. 26, 699–703.

Shi, C.J., Cassell, M.D., 1998. Cortical, thalamic, and amygdaloid connection of the anterior and posterior insular cortices. J. Comp. Neurol. 399, 440–468.

Shibasaki, T., Imaki, T., Hotta, M., Ling, N., Demura, H., 1994. Restraint changes pentobarbital-induced sleeping time in rats: evidence that arousal is modulated by brain corticotropin-releasing hormone and opioid in stress. Regul. Pept. 51, 141–149.

Shiekhattar, R., Aston-Jones, G., 1993. Modulation of opiate responses in brain noradrenergic neurons by the cyclic AMP cascade: changes with chronic morphine. Neuroscience 57, 879–885.

Shilling, P.D., Kelsoe, J.R., Segal, D.S., 1996. Hippocampal glucocorticoid receptor mRNA is up-regulated by acute and down-regulated by chronic amphetamine treatment. Brain Res. Mol. Brain. Res. 38, 156–160.

Shimomura, Y., Bray, G.A., Lee, M., 1987. Adrenalectomy and steroid treatment in obese (ob/ob) and diabetic (db/db) mice. Horm. Metab. Res. 19, 295–299.

Shippenberg, T.S., Herz, A., Spanagel, R., Bals-Kubik, R., Stein, C., 1992. Conditioning of opioid reinforcement: neuroanatomical and neurochemical substrates. Ann. N.Y. Acad. Sci. 654, 347–356.

Shiraishi, I., Honma, K., Honma, S., Hiroshige, T., 1984. Ethosecretogram: relation of behavior to plasma corticosterone in freely moving rats. Am. J. Physiol. 247, R40–R45.

Shirasaka, T., Takasaki, M., Kannan, H., 2003. Cardiovascular effects of leptin and orexins. Am. J. Physiol. Regul. Integr. Comp. Physiol. 284, R639–R651.

Shively, C.A., Laber-Laird, K., Anton, R.F., 1997. Behavior and physiology of social stess and depression in female Cynomolgus monkeys. Biol. Psychiatry 41, 871–882.

Shizgal, P., Fulton, S., Woodside, B., 2001. Brain reward circuitry and the regulation of energy balance. Int. J. Obes. 25, S17–S21.

Sholter, D.E., Armstrong, P.W., 2000. Adverse effects of corticosteroids on the cardiovascular system. Can. J. Cardiol. 16, 505–511.

Silva, M.T., 1977. Saccharin aversion in the rat following adrenalectomy. Physiol. Behav. 19, 239–244.

Silver, R., Moore, R.Y., 1998. The suprachiasmatic nucleus and circadian function: an introduction. Chronobiol. Int. 15, vii–x.

Silverman, M.B., Hermes, S.M., Zadina, J.E., Aicher, S.A., 2005. Mu-opioid receptor is present in dendritic targets of Endomorphin-2 axon terminals in the nuclei of the solitary tract. Neuroscience 135, 887–896.

Simmons, M.R., 2005. Twilight in the Desert: The Coming Saudi Oil Shock and the World Economy. John Wiley & Sons, Hoboken, NJ.

Sinclair, J.D., Senter, R.J., 1968. Development of an alcohol-deprivation effect in rats. Q. J. Stud. Alcohol 29, 863–867.

Sirinathsinghji, D.J., 1986. Regulation of lordosis behaviour in the female rat by corticotropin-releasing factor, beta-endorphin/corticotropin and luteinizing hormone-releasing hormone neuronal systems in the medial preoptic area. Brain Res. 375, 49–56.

Sirinathsinghji, D.J., 1987. Inhibitory influence of corticotropin releasing factor on components of sexual behaviour in the male rat. Brain Res. 407, 185–190.

Sirinathsinghji, D.J., Rees, L.H., Rivier, J., Vale, W., 1983. Corticotropin-releasing factor is a potent inhibitor of sexual receptivity in the female rat. Nature 305, 232–235.

Skinner, B.F., 1992. 'Superstition' in the pigeon. 1948. J. Exp. Psychol. Gen. 121, 273–274.

Smagin, G.N., Howell, L.A., Redmann Jr., S., Ryan, D.H., Harris, R.B., 1999. Prevention of stress-induced weight loss by third ventricle CRF receptor antagonist. Am. J. Physiol. 276, R1461–R1468.

Smith, D.W., Buller, K.M., Day, T.A., 1995. Role of ventrolateral medulla catecholamine cells in hypothalamic neuroendocrine cell responses to systemic hypoxia. J. Neurosci. 15, 7979–7988.

Smith, S.M., Vaughan, J.M., Donaldson, C.J., Rivier, J., Li, C., Chen, A., Vale, W.W., 2004. Cocaine- and amphetamine-regulated transcript activates the hypothalamic–pituitary–adrenal axis through a corticotropin-releasing factor receptor-dependent mechanism. Endocrinology 145, 5202–5209.

Sokolov, E.N., 1963. Perception and the Conditioned Reflex. Pergamon Press, Oxford, UK.

Solomon, R.L., Corbit, J.D., 1973. An opponent-process theory of motivation. II. Cigarette addiction. J. Abnorm. Psychol. 81, 158–171.

Solomon, R.L., Corbit, J.D., 1974. An opponent-process theory of motivation. I. Temporal dynamics of affect. Psychol. Rev. 81, 119–145.

Soltis, R.P., DiMicco, J.A., 1991a. GABAA and excitatory amino acid receptors in dorsomedial hypothalamus and heart rate in rats. Am. J. Physiol. 260, R13–R20.

Soltis, R.P., DiMicco, J.A., 1991b. Interaction of hypothalamic GABAA and excitatory amino acid receptors controlling heart rate in rats. Am. J. Physiol. 261, R427–R433.

Soufer, R., 2004. Neurocardiac interaction during stress-induced myocardial ischemia. How does the brain cope? Circulation 110, 1710–1713.

Soufer, R., Arrighi, J.A., Burg, M.M., 2002. Brain, behavior, mental stress, and the neurocardiac interaction. J. Nucl. Cardiol. 9, 650–662.

Soufer, R., Bremner, J.D., Arrighi, J.A., Cohen, I., Zaret, B.L., Burg, M.M., Goldman-Rikic, P., 1998. Cerebral cortical hyperactivation in response to mental stress in patients with coronary artery disease. Proc. Natl. Acad. Sci. U.S.A. 95, 6454–6459.

Spanagel, R., Herz, A., Shippenberg, T.S., 1992. Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. Proc. Natl. Acad. Sci. U.S.A. 89, 2046–2050.

Specker, S.M., Lac, S.T., Carroll, M.E., 1994. Food deprivation history and cocaine self-administration: an animal model of binge eating. Pharmacol. Biochem. Behav. 48, 1025–1029.

Spencer, R.L., McEwen, B.S., 1990. Adaptation of the hypothalamic–pituitary–adrenal axis to chronic ethanol stress. Neuroendocrinology 52, 481–489.

Spencer, R.L., Miller, A.H., Moday, H., Stein, M., McEwen, B.S., 1993. Diurnal differences in basal and acute stress levels of type I and type II adrenal steroid activation in neural and immune tissues. Endocrinology 133, 1941–1950.

Spencer, R.L., Miller, A.H., Stein, M., McEwen, B.S., 1991. Corticosterone regulation of type I and type II adrenal steroid receptors in brain, pituitary, and immune tissue. Brain Res. 549, 236–246.

Spencer, R.L., Paul, J.K., Kalman, B.A., Cole, M.A., 1998. Evidence for mineralocorticoid receptor facilitation of glucocorticoid receptor-dependent regulation of hypothalamic–pituitary–adrenal axis activity. Endocrinology 2718–2726.

Spiaggia, A., Bodnar, R.J., Kelly, D.D., Glusman, M., 1979. Opiate and non-opiate mechanisms of stress-induced analgesia: cross-tolerance between stressors. Pharmacol. Biochem. Behav. 10, 761–765.

Spyraki, C., Fibiger, H.C., Phillips, A.G., 1983. Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology (Berl.) 79, 278–283.

Staddon, J.E., Simmelhag, V.L., 1970. The "superstition" experiment: a reexamination of its implications for the principles of adaptive behavior. Psychol. Rev. 78, 3–43.

Stanhill, G., Cohen, S., 2001. Global dimming. Agric. Forest Meteorol. 107, 255–278.

Stanley, B.G., Daniel, D.R., Chin, A.S., Leibowitz, S.F., 1985. Paraventricular nucleus injections of peptide YY and neuropeptide Y preferentially enhance carbohydrate ingestion. Peptides 6, 1205–1211.

Stanley, B.G., Kyrkouli, S.E., Lampert, S., Leibowitz, S.F., 1986. Neuropeptide Y chronically injected into the hypohtalamus: a powerful neurochemical inducer of hyperphagia and obesity. Peptides 7, 1189–1192.

Stanley, B.G., Lanthier, D., Chin, A.S., Leibowitz, S.F., 1989. Suppression of neuropeptide Y-elicited eating by adrenalectomy or hypophysectomy: reversal with corticosterone. Brain Res. 501, 32–36.

Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., Leibowitz, S.F., 1992. Evidence for neuopeptide Y mediation of eating produced by food deprivation and for a varient of the Y1 receptor mediating this peptide's effect. Peptides 11, 581–587.

Stanley, S.A., Murphy, K.G., Bewick, G.A., Kong, W.M., Opacka-Juffry, J., Gardiner, J.V., Ghatei, M., Small, C.J., Bloom, S.R., 2004. Regulation of rat pituitary cocaine- and amphetamine-regulated transcript (CART) by CRH and glucocorticoids. Am. J. Physiol. Endocrinol. Metab. 287, E583–E590.

Stanley, S.A., Small, C.J., Murphy, K.G., Rayes, E., Abbott, C.R., Seal, L.J., Morgan, D.G.A., Sunter, D., Dakin, C.L., Kim, M.-S., Hunter, R., Kuhar, M., Ghatei, M.A., Bloom, S.R., 2001. Actions of cocaine- and amphetamine-regulated transcript (CART) peptide on regulation of appetite and hypothalamo–pituitary axes in vitro and in vivo in male rats. Brain Res. 893, 186–194.

Starkman, M.N., Gebarski, S.S., Berent, S., Schteingart, D.E., 1992. Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. Biol. Psychiatry 32, 756–765.

Steinmetz, J.E., 2000. Brain substrates of classical eyeblink conditioning: a highly localized but also distributed system. Behav. Brain Res. 110, 13–24.

Stephan, F.K., 1997. Calories affect zeitgeber properties of the feeding entrained circadian oscillator. Physiol. Behav. 62, 995–1002.

Stephan, F.K., 2001. Food-entrainable oscillators in mammals. In: Takahashi, J., Turek, F., Moore, R. (Eds.), Circadian Clocks, vol. 12. Kluwer Academic/Plenum, New York, pp. 223–246.

Stephan, F.K., 2002. The ''other'' circadian system: food as a Zeitgeber. J. Biol. Rhythms 17, 284–292.

Stephan, F.K., Swann, J.M., Sisk, C.L., 1979. Anticipation of 24-hr feeding schedules in rats with lesions of the suprachiasmatic nucleus. Behav. Neural. Biol. 25, 346–363.

Stewart, J., 2004. Pathways to relapse: factors controlling the reinitiation of drug seeking after abstinence. Nebr. Symp. Motiv. 50, 197–234.

Stewart, J., de Wit, H., Eikelboom, R., 1984. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. Psychol. Rev. 91, 251–268.

Stewart, P.M., Boulton, A., Kumar, S., Clark, P.M., Shackleton, C.H., 1999. Cortisol metabolism in human obesity: impaired cortisone—cortisol conversion in subjects with central adiposity. J. Clin. Endocrinol. Metab. 84, 1022–1027.

Stiglitz, J., 2000. What I learned at the world economic crisis. In: The New Republic, .

Stimmel, B., Kreek, M.J., 2000. Neurobiology of addictive behaviors and its relationship to methadone maintenance. Mt. Sinai J. Med. 67, 375–380.

Stinus, L., Nadaud, D., Deminiere, J.M., Jauregui, J., Hand, T.T., Le Moal, M., 1989. Chronic flupentixol treatment potentiates the reinforcing properties of systemic heroin administration. Biol. Psychiatry 26, 363–371.

Stohr, T., Almeida, O.F., Landgraf, R., Shippenberg, T.S., Holsboer, F., Spanagel, R., 1999. Stress- and corticosteroid-induced modulation of the locomotor response to morphine in rats. Behav. Brain Res. 103, 85–93.

Stotz-Potter, E.H., Willis, L.R., DiMicco, J.A., 1996. Muscimol acts in dorsomedial but not paraventricular hypothalamic nucleus to suppress cardiovascular effects of stress. J. Neurosci. 16, 1173–1179.

Strack, A.M., Bradbury, M.J., Dallman, M.F., 1995a. Corticosterone decreases nonshivering thermogenesis and increases lipid storage in brown adipose tissue. Am. J. Physiol. 268, R183–R191.

Strack, A.M., Horsley, C.J., Sebastian, R.J., Akana, S.F., Dallman, M.F., 1995b. Glucocorticoids and insulin: complex interaction on brown adipose tissue. Am. J. Physiol. 268, R1209–R1216.

Strack, A.M., Sebastian, R.J., Schwartz, M.W., Dallman, M.F., 1995c. Glucocorticoids and insulin: reciprocal signals for energy balance. Am. J. Physiol. 268, R142–R149.

Stretch, R., Gerber, G.J., Wood, S.M., 1971. Factors affecting behavior maintained by response-contingent intravenous infusions of amphetamine in squirrel monkeys. Can. J. Physiol. Pharmacol. 49, 581–589.

Stricker, E.M., Friedman, M.I., Zigmond, M.J., 1975. Glucoregulatory feeding by rats after intraventricular 6-hydroxydopamine or lateral hypothalamic lesions. Science 189, 895–897.

Strik, J.J.M.H., Lousberg, R., Cheriex, E.C., Honig, A., 2004. One year cumulative incidence of depression following myocardial infarction and impact on cardiac outcome. J. Psychosom. Res. 56, 59–66.

Strike, P.C., Steptoe, A., 2004. Psychosocial factors in the development of coronary artery disease. Prog. Cardiovasc. Dis. 46, 337–347.

Stubbs, P.J., Laycock, J., Alaghband-Zadeh, J., Carter, G., Noble, M.I., 1999. Circulating stress hormone and insulin concentrations in acute coronary syndromes: identification of insulin resistance on admission. Clin. Sci. (Lond.) 96, 589–595.

Suda, T., Nakano, Y., Tozawa, F., Sumitomo, T., Sato, Y., Yamada, M., Demura, H., 1992. The role of corticotropin-releasing factor and vasopressin in hypoglycemia-induced proopiomelanocortin gene expression in the rat anterior pituitary gland. Brain Res. 579, 303–308.

Suemaru, S., Dallman, M.F., Darlington, D.N., Cascio, C.S., Shinsako, J., 1989. Role of alpha-adrenergic mechanism in effects of morphine on the hypothalamo–pituitary–adrenaocortical and cardiovascular systsems in the rat. Neuroendocrinology 49, 181–190.

Sullivan, G.M., Apergis, J., Bush, D.E., Johnson, L.R., Hou, M., Ledoux, J.E., 2004. Lesions in the bed nucleus of the stria terminalis disrupt corticosterone and freezing responses elicited by a contextual but not by a specific cue-conditioned fear stimulus. Neuroscience 128, 7–14.

Sullivan, R.M., Gratton, A., 1999. Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. J. Neurosci. 19, 2834–2840.

Sullivan, R.M., Gratton, A., 2002a. Behavioral effects of excitotoxic lesions of ventral medial prefrontal cortex in the rat are hemisphere-dependent. Brain Res. 927, 69–79.

Sullivan, R.M., Gratton, A., 2002b. Prefrontal cortical regulation of hypothalamic–pituitary–adrenal function in the rat and implications for psychopathology: side matters. Psychoneuroendocrinology 27, 99–114.

Swanson, L.W., 1982. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res. Bull. 9, 321–353.

Swanson, L.W., 2000. Cerebral hemisphere regulation of motivated behavior. Brain Res. 886, 113–164.

Swanson, L.W., Sawchenko, P.E., 1983. Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. Annu. Rev. Neurosci. 6, 269–324.

Swanson, L.W., Sawchenko, P.E., Rivier, J., Vale, W.W., 1983. Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. Neuroendocrinology 36, 165–186.

Swanson, L.W., Simmons, D.M., 1989. Differential steroid hormone and neural influences on peptide mRNA levels in CRH cells of the paraventricular nucleus: a hybridization histochemical study in the rat. J. Comp. Neurol. 285, 413–435.

Swerdlow, N.R., Britton, K.T., Koob, G.F., 1989. Potentiation of acoustic startle by corticotropin-releasing factor (CRF) and by fear are both reversed by a-helical CRF (9–41). Neuropsychopharmacology 2, 285–292.

Swerdlow, N.R., Geyer, M.A., Vale, W.W., Koob, G.F., 1986. Corticotropin-releasing factor potentiates acoustic startle in rats: blockade by chlordiazepoxide. Psychopharmacology (Berl.) 88, 147–152.

Swinburn, C.R., Wakefield, J.M., Newman, S.P., Jones, P.W., 1988. Evidence of prednisolone induced mood change ('steroid euphoria') in patients with chronic obstructive airways disease. Br. J. Clin. Pharmacol. 26, 709–713.

Szafarczyk, A., Alonso, G., Ixart, G., Malaval, F., Assenmacher, I., 1985. Diurnal-stimulated and stress-induced ACTH release in rats is mediated by ventral noradrenergic bundle. Am. J. Physiol. 249, E219–E226.

Szafarczyk, A., Malaval, F., Laurent, A., Gibaud, R., Assenmacher, I., 1987. Further evidence for a central stimulatory action of catecholamines on adrenocorticotropin release in the rat. Endocrinology 121, 883–892.

Szechtman, H., Lambrou, P.J., Caggiula, A.R., Redgate, E.S., 1974. Plasma corticosterone levels during sexual behavior in male rats. Horm. Behav. 5, 191–200.

Takahashi, L.K., Kalin, N.H., Vanden Burgt, J.A., Sherman, J.E., 1989. Corticotropin-releasing factor modulates defensive-withdrawal and exploratory behavior in rats. Behav. Neurosci. 103, 648–654.

Tamura, Y., Okinaga, H., Takami, H., 2004. Glucocorticoid-induced osteoporosis. Biomed. Pharmacother. 58, 500–504.

Tanimura, S.M., Sanchez-Watts, G., Watts, A.G., 1998. Peptide gene activation, secretion, and steroid feedback during stimulation of rat neuroendocrine corticotropin-releasing hormone neurons. Endocrinology 139.

Tanimura, S.M., Watts, A.G., 2001. Corticosterone modulation of ACTH secretogogue gene expression in the paraventricular nucleus. Peptides 22, 775–783.

Tannenbaum, B.M., Brindley, D.N., Tannenbaum, G.S., Dallman, M.F., McArthur, M.D., Meaney, M.J., 1997. High-fat feeding alters both basal and stress-induced hypothalamic–pituitary–adrenal activity in the rat. Am. J. Physiol. 273, E1168–E1177.

Tardiff, K., 1992. The current state of psychiatry in the treatment of violent patients. Arch. Gen. Psychiatry 49, 439–499.

Taylor, H.L., Keys, A., 1950. Adaptation to caloric restriction. Science 112, 215–218.

Tempel, D.L., Leibowitz, S.F., 1994. Adrenal steroid receptors: interactions with brain neuropeptide systems in relation to nutrient intake and metabolism. J. Neuroendocrinol. 6, 479–501.

ter Horst, G.J., Luiten, P.G., 1986. The projections of the dorsomedial hypothalamic nucleus in the rat. Brain Res. Bull. 16, 231–248.

Terry, L.C., Martin, J.B., 1978. Hypothalamic–pituitary responses to intracranial self-stimulation in the rat. Brain Res. 157, 89–104.

Thierry, A.M., Tassin, J.P., Blanc, G., Glowinski, J., 1976. Selective activation of mesocortical DA system by stress. Nature 263, 242–244.

Thomas, B.L., Papini, M.R., 2001. Adrenalectomy eliminates the extinction spike in autoshaping with rats. Physiol. Behav. 72, 543–547.

Thompson, B.L., Erickson, K., Schulkin, J., Rosen, J.B., 2004. Corticosterone facilitates retention of contextually conditioned fear and increases CRH mRNA expression in hte amygdala. Behav. Brain Res. 149, 209–215.

Thompson, K.M., Wonderlich, S.A., Crosby, R.D., Mitchell, J.E., 1999. The neglected link between eating disturbances and aggressive behavior in girls. J. Am. Acad. Child Adolesc. Psychiatry 38, 1277–1284.

Thompson, R.H., Canteras, N.S., Swanson, L.W., 1996. Organization of projections from the dorsomedial nucleus of the hypothalamus: a PHA-L study in the rat. J. Comp. Neurol. 376, 143–173.

Thompson, R.H., Swanson, L.W., 2003. Structural characterization of a hypothalamic visceromotor pattern generator network. Brain Res. Brain Res. Rev. 41, 153–202.

Tidey, J.W., Miczek, K.A., 1997. Acquisition of cocaine self-administration after social stress: role of accumbens dopamine. Psychopharmacology (Berl.) 130, 203–212.

Timberlake, W., 1980. An equilibrium theory of learned performance. In: Bower, G.H. (Ed.), Psychology of Learning and Motivation (Vol. 14). Academic Press, New York.

Timberlake, W., 1993. Behavior systems and reinforcement: an integrative approach. J. Exp. Anal. Behav. 60, 105–128.

Timberlake, W., Wahl, G., King, D., 1982. Stimulus and response contingencies in the misbehavior of rats. J. Exp. Psychol. Anim. Behav. Process 8, 62–85.

Timberlake, W.D., White, W.O., 1990. Winning isn't everything: rats need only food deprivation not food reward to traverse a radial arm maze efficiently. Learn. Motiv. 21, 122–130.

Timofeeva, E., Deshaies, Y., Picard, F., Richard, D., 1999. Corticotropin-releasing hormone-binding protein in brain and pituitary of food-deprived obese (fa/fa) Zucker rats. Am. J. Physiol. 277, R1749–R1759.

Timofeeva, E., Picard, F., Duclos, M., Deshaies, Y., Richard, D., 2002. Neuronal activation and corticotropin-releasing hormone expression in the brain of obese (fa/fa) and lean (fa/?) Zucker rats in response to refeeding. Eur. J. Neurosci. 15, 1013–1029.

Tinbergen, N., 1951. The Study of Instinct. Oxford University Press.

Tomie, A., Silberman, Y., Williams, K., Pohorecky, L.A., 2002. Pavlovian autoshaping procedures increase plasma corticosterone levels in rats. Pharmacol. Biochem. Behav. 72, 507–513.

Treichler, F.R., Hall, J.F., 1962. The relationship between deprivation weight loss and several measures of activity. J. Comp. Physiol. Psychol. 55, 346–349.

Treichler, F.R., Hamilton, D.M., 1967. Relationships between deprivation and air-drinking behavior. J. Comp. Physiol. Psychol. 63, 541–544.

Treit, D., Pinel, J.P., Fibiger, H.C., 1981. Conditioned defensive burying: a new paradigm for the study of anxiolytic agents. Pharmacol. Biochem. Behav. 15, 619–626.

Trowill, J.A., Panksepp, J., Gandelman, R., 1969. An incentive model of rewarding brain stimulation. Psychol. Rev. 76, 264–281.

Turner, B.H., Herkenham, M., 1991. Thalamoamygdaloid projections in the rat: a test of the amygdala's role in sensory processing. J. Comp. Neurol. 313, 295–325.

Ulrich-Lai, Y.M., Arnhold, M.M., Engeland, W.C., 2005. Adrenal splanchnic innervation contributes to the diurnal rhythm of plasma corticosterone in rats by modulating adrenal sensitivity to ACTH. Am. J. Physiol. 290, R1128–R1135.

Ungless, M.A., Singh, V., Crowder, T.L., Yaka, R., Ron, D., Bonci, A., 2003. Corticotropin-releasing factor requires CRF binding protein to potentiate NMDA receptors via CRF receptor 2 in dopamine neurons. Neuron 39, 401–407.

Uryu, K., Okumura, T., Shibasaki, T., Sakanaka, M., 1992. Fine structure and possible origins of nerve fibers with corticotropin-releasing factor-like immunoreactivity in the rat central amygdaloid nucleus. Brain Res. 577, 175–179.

Valadez, A., Schenk, S., 1994. Persistence of the ability of amphetamine preexposure to facilitate acquisition of cocaine self-administration. Pharmacol. Biochem. Behav. 47, 203–205.

Vale, W., Spiess, J., Rivier, C., Rivier, J., 1981. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 213, 1394–1397.

Valentino, R.J., Chen, S., Zhu, Y., Aston-Jones, G., 1996. Evidence for divergent projections to the brain noradrenergic system and the spinal parasympathetic system from Barrington's nucleus. Brain Res. 732, 1–15.

Valentino, R.J., Foote, S.L., Aston-Jones, G., 1983. Corticotropin-releasing factor activates noradrenergic neurons of the locus coeruleus. Brain Res. 270, 363–367.

Valentino, R.J., Van Bockstaele, E.J., 2001. Opposing regulation of the locus coeruleus by corticotropin-releasing factor and opioids. Psychopharmacology 158, 331–342.

Valentino, R.J., Wehby, R.G., 1989. Locus ceruleus discharge characteristics of morphine-dependent rats: effects of naltrexone. Brain Res. 488, 126–134.

Van Bockstaele, E.J., 1998. Morphological substrates underlying opioid, epinephrine and gamma-aminobultyric acid inhibitory actions in the rat locus coeruleus. Brain Res. Bull. 47, 1–15.

Van Bockstaele, E.J., Bajic, D., Proudfit, H., Valentino, R.J., 2001. Topographic architecture of stress-related pathways targeting the noradrenergic locus coeruleus. Physiol. Behav. 73, 273–283.

Van Bockstaele, E.J., Branchereau, P., Pickel, V.M., 1995. Morphologically heterogeneous met-enkephalin terminals form synapses with tyrosine hydroxylase-containing dendrites in the rat nucleus locus coeruleus. J. Comp. Neurol. 363, 423–438.

Van Bockstaele, E.J., Colago, E.E., Valentino, R.J., 1998. Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites: substrate for the co-ordination of emotional and cognitive limbs of the stress response. J. Neuroendocrinol. 10, 743–757.

Van Bockstaele, E.J., Peoples, J., Valentino, R.J., 1999. A. E. Bennett Research Award. Anatomic basis for differential regulation of the rostrolateral peri-locus coeruleus region by limbic afferents. Biol. Psychiatry 46, 1352–1363.

Van der Werf, Y.D., Witter, M.P., Groenewegen, H.J., 2002. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res. Rev. 39 (23), 107–140.

Van Eden, C.G., Buijs, R.M., 2000a. Functional neuroanatomy of the prefrontal cortex: autonomic interactions. Prog. Brain Res. 126, 49–62.

Van Eden, C.G., Buijs, R.M., 2000b. Functional neuroanatomy of the prefrontal cortex: autonomic interactions. In: Uylings, H.B.M., Van Eden, C.G., De Bruin, J.P.C., Feenstra, M.G.P., Pennartz, C.M.A. (Eds.), Prog. Brain Res., vol. 126. Elsevier Science, BV.

Van Haarst, A., Oitzl, M., de Kloet, E., 1997. Facilitation of feedback inhibition through blockade of glucocorticoid receptors in the hippocampus. Neurochem. Res. 22, 1323–1328.

Van Pett, K., Viau, V., Bittencourt, J.C., Chan, R.K., Li, H.Y., Arias, C., Prins, G.S., Perrin, M., Vale, W., Sawchenko, P.E., 2000. Distribution of mRNAs encoding CRF receptors in brain and pituitary of rat and mouse. J. Comp. Neurol. 428, 191–212.

Van Ree, J.M., Gerrits, M.A., Vanderschuren, L.J., 1999. Opioids, reward and addiction: an encounter of biology, psychology, and medicine. Pharmacol. Rev. 51, 341–396.

Van Ree, J.M., Niesink, R.J., 1978. Pituitary–adrenal axis and oral morphine consumption in rats. Pharmacol. Biochem. Behav. 9, 493–498.

Van Staa, T.P., Leufkens, H.G., Abenhaim, L., Zhang, B., Cooper, C., 2000. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxf.) 39, 1383–1389.

Van Stegeren, A.H., Everaerd, W., Cahill, L., McGaugh, J.L., Gooren, L.J., 1998. Memory for emotional events: differential effects of centrally versus peripherally acting beta-blocking agents. Psychopharmacology (Berl.) 138, 305–310.

Van Veen, V., Carter, C.S., 2002. The anterior cingulate as a conflict monitor: fMRI and ERP studies. Physiol. Behav. 77, 477–482.

Vandereycken, W., Van Houdenhove, V.D., 1996. Stealing behavior in eating disorders: characteristics and associated psychopathology. Compr. Psychiatry 37, 316–321.

Veldhuis, H.D., De Wied, D., 1984. Differential behavioral actions of corticotropin-releasing factor (CRF). Pharmacol. Biochem. Behav. 21, 707–713.

Veldhuis, J.D., Iranmanesh, A., Naftolowitz, D., Tatham, N., Cassidy, F., Carroll, B.J., 2001. Corticotropin secretory dynamics in humans under low glucocorticoid feedback. J. Clin. Endocrinol. Metab. 86, 5554–5563.

Vernikos, D., Dallman, M.F., Bonner, C., Katzen, A., Shinsako, J., 1982. Pituitary–adrenal function in rats chronically exposed to cold. Endocrinology 110, 413–420.

Viau, V., Sawchenko, P.E., 1995. The pattern of cellular activation seen in response to acute restraint suggests commonalities among neurogenic stress models. Society for Neuroscience Abstract.

Vicentic, A., Dominguez, G., Hunter, R.G., Philpot, K., Wilson, M., Kuhar, M.J., 2004. Cocaine- and amphetamine-regulated transcript peptide levels in blood exhibit a diurnal rhythm: regulation by glucocorticoids. Endocrinology 145, 4119–4124.

Vicentic, A., Hunter, R.G., Kuhar, M.J., 2005a. Effect of corticosterone on CART peptide levels in rat blood. Peptides 26, 531–533.

Vicentic, A., Lakatos, A., Hunter, R., Philpot, K., Dominguez, G., Kuhar, M.J., 2005b. CART peptide diurnal rhythm in brain and effect of fasting. Brain Res. 1032, 111–115.

Volkow, N.D., Li, T.K., 2005. Drugs and alcohol: treating and preventing abuse, addiction and their medical consequences. Pharmacol. Ther. 108, 3–17.

Vouimba, R.M., Yaniv, D., Diamond, D., Richter-Levin, G., 2004. Effects of inescapable stress on LTP in the amygdala versus the dentate gyrus of freely behaving rats. Eur. J. Neurosci. 19, 1887–1894.

Vrang, N., Larsen, P.J., Tang-Christensen, M., Larsen, L.K., Kristensen, P., 2003. Hypothalamic cocaine-amphetamine regulated transcript (CART) is regulated by glucocorticoids. Brain Res. 965 (1–2), 45–50.

Vrang, N., Mikkelsen, J.D., Larsen, P.J., 1997. Direct link from the suprachiasmatic nucleus to hypothalamic neurons projecting to the spinal cord: a combined tracing study using cholera toxin subunit B and Phaseolus vulgaris-leucoagglutinin. Brain Res. Bull. 44, 671–680.

Vrang, N., Tang-Christensen, M., Larsen, P.J., Kristensen, P., 1999. Recombinant CART peptide induces *c*-Fos expression in central areas involved in control of feeding behaviour. Brain Res. 818, 499–509.

Vyas, A., Bernal, S., Chattarji, S., 2003. Effects of chronic stress on dendritic arborization in the central and extended amygdala. Brain Res. 965, 290–294.

Vyas, A., Mitra, R., Shankaranarayana Rao, B.S., Chattarji, S., 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J. Neurosci. 22, 6810–6818.

Vyas, A., Pillai, A.G., Chattarji, S., 2004. Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. Neuroscience 128, 667–673.

Wajchenberg, B.L., 2000. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr. Rev. 21, 697–738.

Wald, G., jackson, B., 1944. Activity and nutritional deprivation. Proc. Natl. Acad. Sci. U.S.A. 30, 255–263.

Walsh, P.D., Abernethy, K.A., Bermejo, M., Beyers, R., De Wachter, P., Akou, M.E., Huijbregts, B., Mambounga, D.I., Toham, A.K., Kilbourn, A.M., Lahm, S.A., Latour, S., Maisels, F., Mbina, C., Mihindou, Y., Obiang, S.N., Effa, E.N., Starkey, M.P., Telfer, P., Thibault, M., Tutin, C.E., White, L.J., Wilkie, D.S., 2003. Catastrophic ape decline in western equatorial Africa. Nature 422, 611–614.

Wang, B., Shaham, Y., Zitzman, D., Azari, S., Wise, R.A., You, Z.-B., 2005. Cocaine experience establishes control of midbrain glutamate and dopamine by corticotropin-releasing factor: a role in stress-induced relapse to drug seeking. J. Neurosci. 25, 5389–5396.

Wang, M., 2005. The role of glucocorticoid action in the pathophysiology of the Metabolic Syndrome. Nutr. Metab. (Lond.) 2, 3.

Wang, Y.Y., Aghajanian, G.K., 1987. Intracellular GTP gamma S restores the ability of morphine to hyperpolarize rat locus coeruleus neurons after blockade by pertussis toxin. Brain Res. 436, 396–401.

Warden, C.J., 1932. The relative strength of primary drives in the white rat. J. Genetic Psychol. 41, 16–35.

Wassertheil-Smoller, S., Shumaker, S., Ockene, J., Talavera, G.A., Greenland, P., Cochrane, B., Robbins, J., Aragaki, A., Dunbar-Jacob, J., 2004. Depression and cardiovascular sequelae in postmenopausal women. Arch. Intern. Med. 164, 289–298.

Watanabe, Y., Gould, E., McEwen, B.S., 1992. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res. 588, 341–345.

Watts, A.G., 1992a. Disturbance of fluid homeostasis leads to temporally and anatomically distinct responses in neuropeptide and tyrosine hydroxylase mRNA levels in the paraventricular and supraoptic nuclei of the rat. Neuroscience 46, 859–879.

Watts, A.G., 1992b. Osmotic stimulation differentially affects cellular levels of corticotropin-releasing hormone and neurotensin/neuromedin N mRNAs in the lateral hypothalamic area and central nucleus of the amygdala. Brain Res. 581, 208–216.

Watts, A.G., Sanchez-Watts, G., 1995. Region-specific regulation of neuropeptide mRNAs in rat limbic forebrain neurones by aldosterone and corticosterone. J. Physiol. 484, 721–736.

Watts, A.G., Tanimura, S.M., Sanchez-Watts, G., 2004. Corticotropin-releasing hormone and arginine vasopressin gene transcription in the hypothalamic paraventricular nucleus of unstressed rats: daily rhythms and their interactions with corticosterone. Endocrinology 145, 529–540.

Wayner, M.J., Rondeau, D.B., 1976. Schedule dependent and schedule induced behavior at reduced and recovered body weight. Physiol. Behav. 17, 325–336.

Wedzony, K., Czyrak, A., Mackowiak, M., Fijal, K., 1996. The impact of a competitive and a non-competitive NMDA receptor antagonist on dopaminergic neurotransmission in the rat ventral tegmental area and substantia nigra. Naunyn. Schmiedebergs Arch. Pharmacol. 353, 517–527.

Wei, L., MacDonald, T.M., Walker, B.D., 2004. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann. Intern. Med. 141, 764–770.

Weinstein, R.S., Jilka, R.L., Parfitt, A.M., Manolagas, S.C., 1998. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. J. Clin. Invest. 102, 274–282.

Welch, C.C., Grace, M.K., Billington, C.J., Levine, A.S., 1994. Preference and diet type affect macronutrient selection after morphine, NPY, norepinephrine, and deprivation. Am. J. Physiol. 266, R426–R433.

Wellman, C.L., 2001. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. J. Neurobiol. 49, 245–253.

White, W., Schwartz, G.J., Moran, T.H., 1999. Meal-synchronized CEA in rats: effects of meal size, intragastric feeding, and subdiaphragmatic vagotomy. Am. J. Physiol. Regul. Integr. Comp. Physiol. 45, R1276–R1288.

White, W., Timberlake, W., 1999. Meal-engendered circadian-ensuing activity in rats. Physiol. Behav. 65, 625–642.

Wible Jr., J.H., DiMicco, J.A., Luft, F.C., 1989. Hypothalamic GABA and sympathetic regulation in spontaneously hypertensive rats. Hypertension 14, 623–628.

Wible Jr., J.H., Luft, F.C., DiMicco, J.A., 1988. Hypothalamic GABA suppresses sympathetic outflow to the cardiovascular system. Am. J. Physiol. 254, R680–R687.

Widmaier, E.P., 1992. Metabolic feedback in mammalian endocrine systems. Horm. Metab. Res. 24, 147–153.

Widmaier, E.P., Dallman, M.F., 1984. The effects of corticotropin-releasing factor on adrenocorticotropin secretion from perifused pituitaries in vitro: rapid inhibition by glucocorticoids. Endocrinology 115, 2368–2374.

Widmaier, E.P., Rosen, K., Abbott, B., 1992. Free fatty acids activate the hypothalamic–pituitary–adrenocortical axis in rats. Endocrinology 131, 2313–2318.

Wikler, A., 1973a. Conditioning of successive adaptive responses to the initial effects of drugs. Cond. Reflex 8, 193–210.

Wikler, A., 1973b. Dynamics of drug dependence. Implications of a conditioning theory for research and treatment. Arch. Gen. Psychiatry 28, 611–616.

Wild, M., Gilgen, H., Roesch, A., Ohmura, A., Long, C.N., Dutton, E.G., Forgan, B., Kallis, A., Russak, V., Tsvetkov, A., 2005. From dimming to brightening: decadal changes in solar radiation at Earth's surface. Science 308, 847–850.

Wilkinson, C.W., Shinsako, J., Dallman, M.F., 1979. Daily rhythms in adrenal responsiveness to adrenocorticortopin are determined primarily by the time of feeding in the rat. Endocrinology 104, 350–359.

Will, M.J., Franzblau, E.B., Kelley, A.E., 2003. Nucleus accumbens μ-opioids regulate intake of a high-fat diet via activation of a distributed brain network. J. Neurosci. 23, 2882–2888.

Will, M.J., Franzblau, E.B., Kelley, A.E., 2004. The amygdala is critical for opioid-mediated binge eating of fat. Neuroreport 15, 1857–1860.

Williams, D.R., Williams, H., 1969. Auto-maintenance in the pigeon: sustained pecking despite contingent non-reinforcement. J. Exp. Anal. Behav. 12, 511–520.

Williams, J.T., Egan, T.M., North, R.A., 1982. Enkephalin opens potassium channels on mammalian central neurones. Nature 299, 74–77.

Williams, J.T., North, R.A., 1984. Opiate-receptor interactions on single locus coeruleus neurones. Mol. Pharmacol. 26, 489–497.

Williams, L.S., Ghose, S.S., Swindle, R.W., 2004. Depression and other mental health diagnoses increase mortality risk after ischemic stroke. Am. J. Psychiatry 161, 1090–1095.

Willinger, U., Lenzinger, E., Hornik, K., Fischer, G., Schonbeck, G., Aschauer, H.N., Meszaros, K., 2002. Anxiety as a predictor of relapse in detoxified alcohol-dependent patients. Alcohol Alcohol. 37, 609–612.

Wise, R.A., 1987. The role of reward pathways in the development of drug dependence. Pharmacol. Ther. 35, 227–263.

Wise, R.A., Bozarth, M.A., 1987. A psychomotor stimulant theory of addiction. Psychol. Rev. 94, 469–492.

Wise, R.A., Rompre, P.-P., 1989. Brain dopamine and reward. Ann. Rev. Psychol. 40, 191–225.

Wittmann, G., Liposits, Z., Lechan, R.M., Fekete, C., 2005. Origin of cocaine- and amphetamine-regulated transcript-containing axons innervating hypophysiotropic corticotropin-releasing hormone-synthesizing neurons in the rat. Endocrinology 146, 2985–2991.

Wolkowitz, O.M., 1994. Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. Psychoneuroendocrinology 19, 233–255.

Woolverton, W.L., Cervo, L., Johanson, C.E., 1984. Effects of repeated methamphetamine administration on methamphetamine self-administration in rhesus monkeys. Pharmacol. Biochem. Behav. 21, 737–741.

Wright, C.I., Beijer, A.V., Groenewegen, H.J., 1996. Basal amygdaloid complex afferents to the rat nucleus accumbens are compartmentally organized. J. Neurosci. 16, 1877–1893.

Xu, G.-P., Van Bockstaele, E.J., Reyes, B.A.S., Bethea, T., Valentino, R.J., 2004. Chronic morphine sensitizes the brain norepinephrine system to corticotropin-releasing factor and stress. J. Neurosci. 24, 8193–8197.

Yamada, T., Katagiri, H., Ishigaki, Y., Ogihara, T., Imai, J., Uno, K., Hasegawa, Y., Gao, J., Ishihara, H., Niijima, A., Mano, H., Aburatani, H., Asano, T., Oka, Y., 2006. Signals from intra-abdominal fat modulate insulin and leptin sensitivity through different mechanisms: neuronal involvement in food-intake regulation. Cell Metab. 3, 223–229.

Yamauchi, N., Shibasaki, T., Wakabayashi, I., Demura, H., 1997. Brain B-endorphin and other opioids are involved in restraint stress-induced stimulation of the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system, and the adrenal medulla in the rat. Brain Res. 777, 140–146.

Yaryura-Tobias, J.A., Neziroglu, F.A., Kaplan, S., 1995. Self-mutilation, anorexia, and dysmenorrhea in obsessive compulsive disorder. Int. J. Eat. Disord. 17, 33–38.

Yoshihara, T., Honma, S., Honma, K., 1996a. Effects of restricted daily feeding on neuropeptide Y release in the rat paraventricular nucleus. Am. J. Physiol. 270, E589–E595.

Yoshihara, T., Honma, S., Honma, K., 1996b. Prefeeding release of paraventricular neuropeptide Y is mediated by ascending noradrenergic neurons in rats. Am. J. Physiol. 270, E596–E600.

Yoshihara, T., Honma, S., Katsuno, Y., Honma, K., 1996c. Dissociation of paraventricular NPY release and plasma corticosterone levels in rats under food deprivation. Am. J. Physiol. 271, E239–E245.

Yoshioka, M., Matsumoto, M., Togashi, H., Saito, H., 1995. Effects of conditioned fear stress on 5-HT release in the rat prefrontal cortex. Pharmacol. Biochem. Behav. 51, 515–519.

Young, E.A., Akana, S.F., Dallman, M.F., 1990. Decreased sensitivity to glucocorticoid fast feedback in chronically stressed rats. Neuroendocrinology 51, 536–542.

Young 3rd, W.S., Lightman, S.L., 1992. Chronic stress elevates enkephalin expression in the rat paraventricular and supraoptic nuclei. Brain Res. Mol. Brain Res. 13, 111–117.

Zahm, D.S., 2000. An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. Neurosci. Biobehav. Rev. 24, 85–105.

Zahm, D.S., Jensen, S.L., Williams, E.S., Martin III, J.R., 1999. Direct comparison of projections from the central amygdaloid region and the nucleus accumbens shell. Eur. J. Neurosci. 11, 1119–1126.

Zahm, D.S., Williams, E.A., Latimer, M.P., Winn, P., 2001. Ventral mesopontine projections of the caudomedial shelll of the nucleus accumbens and extended amygdala in the rat: double dissociation by organization and development. J. Comp. Neurol. 436, 111–125.

Zener, K., McCurdy, H.G., 1939. Analysis of motivational factors in conditioned behaviors. I. The differential effect ofchanges in hunger upon conditioned, unconditioned, and spontaneous salivary secretion. J. Psychol. Interdisc. App. 8, 321–350.

Zhang, H.H., Kumar, S., Barnett, A.H., Eggo, M.C., 2001. Dexamethasone inhibits tumor necrosis factor-alpha-induced apoptosis and interleukin-1 beta release in human subcutaneous adipocytes and preadipocytes. J. Clin. Endocrinol. Metab. 86, 2817–2825.

Zhang, M., Gosnell, B.A., Kelley, A.E., 1998. Intake of high-fat food is selectively enhanced by mu opioid receptor stimulation within the nucleus accumbens. J. Pharmacol. Exp. Ther. 285, 908–914.

Ziegler, D.R., Cass, W.A., Herman, J.P., 1999. Excitatory influence of the locus coeruleus in hypothalamic–pituitary–adrenocortical axis responses to stress. J. Neuroendocrinol. 11, 361–369.