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Relationship between the effects of dexamphetamine on locomotion and on striatal [^{3}H]GBR 12783 binding in vivo

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In mice, low doses (1-2-4 mg/kg s.c.) of dexamphetamine stimulated locomotor activity in a dose-dependent manner. Over the same range of doses the drug dose dependently inhibited the in vivo striatal binding of the dopamine uptake inhibitor, [^{3}H]GBR 12783. At 3 mg/kg dexamphetamine, the stimulant effect and the inhibition of the striatal binding of [^{3}H]GBR 12783 displayed a similar time course. Pretreatments that either increased (L-DOPA 200 mg/kg, benserazide 50 mg/kg i.p.) or decreased (reserpine 5 mg/kg s.c., α-methyl-p-tyrosine 200 mg/kg) striatal dopamine levels did not modify the inhibition by dexamphetamine of [^{3}H]GBR 12783 binding in vivo. This suggests that the inhibition is due to a direct effect of dexamphetamine, not mediated by endogenous dopamine, and further that a unique site is responsible for the neuronal uptake of dexamphetamine and for the binding of pure dopamine uptake inhibitors.

Dexamphetamine; [^{3}H]GBR 12783 binding in vivo; Dopamine uptake complex; Locomotor activity

1. Introduction

Dexamphetamine is a potent indirect dopamine (DA) agonist, virtually devoid of direct DA agonist activity, which increases locomotor activity and/or induces stereotyped behaviours (Scheel-Krüger, 1972; Sharp et al., 1987; Thornburg and Moore, 1972). This drug releases newly synthesized cytosolic DA both in vivo and in vitro, apparently as a consequence of its uptake into dopaminergic nerve endings by diffusion or active transport through the DA uptake system (Fischer and Cho, 1979; Langer and Arbilla, 1984). This transport is competitive with that of DA, and this might explain, either totally or partially, the inhibition of DA uptake which is associated with the DA releasing effect (Heikkila et al., 1975; Bonnet et al., 1984). In addition, dexamphetamine binds with apparent low affinity (in the 10 μM range) to a site on the DA uptake complex, as do DA uptake inhibitors devoid of DA releasing effect such as mazindol, nomifensine, cocaine (Richelson and Pfenning, 1984) and several aryl dialk(en)yl piperazines (Bonnet and Costentin, 1986; Pileblad and Engberg, 1986; Andersen, 1989). This site is labelled by various specific ligands (review by Langer and Schoemaker, 1988) including [^{3}H]GBR 12783 (Bonnet et al., 1986). From these data it can be speculated that, before its transport, dexamphetamine binds to the same site as the pure DA uptake inhibitor GBR 12783. For this purpose, we compared the doses of dexamphetamine that trigger behavioural responses in mice with the doses

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that prevent the in vivo binding of [^{3}H]GBR 12783 to the DA uptake complex.

2. Materials and methods

2.1. Animals

Male Swiss albino mice CD1, weighing 21-23 g, were purchased from Charles River (Saint Aubin lès Elbeuf, France). They were housed in groups (30 per cage) with laboratory chow and water ad libitum and were exposed to an artificial light-dark cycle (7 : 00-19 : 00 h light). The experiments were carried out between 10 : 00-15 : 00 h.

2.2. In vivo binding of [^{3}H]GBR 12783

Studies of the in vivo binding of [^{3}H]GBR 12783 were performed as described by Chagraoui et al. (1987). Briefly, [^{3}H]GBR 12783 (5 μCi in 200 μl saline–5% ethanol) was injected via a tail vein and 1 h later the mice were decapitated. The brain was rapidly removed and the striatum and cerebellum were dissected at 4°C. These regions were sonicated in 0.9% saline (5 ml for cerebellum, 1 ml for striatum). A 750 μl sample of each homogenate was counted in a minivial containing 5 ml Aqualyte® (J.T. Baker chemicals, Deventer, Holland) by liquid scintillation spectrometry (SL2000, Kontron Intertechnique, Trappes, France). Protein concentrations were determined with a 20 μl sample of each homogenate according to the method of Lowry et al. (1951). The results are expressed in d.p.m./mg protein. The cerebellum was chosen as 'blank' since it has no dopaminergic innervation.

2.3. Assay of dopamine and metabolites

For the determination of the striatal content of DA and its metabolites, the striatum was sonicated in 1 ml of 1 N perchloric acid containing 0.1% cysteine. The homogenate was centrifuged (10 000 × g, 20 min) and the supernatant was filtered and injected onto a Merck RP18 Lichrosorb column coupled to an electrochemical detector set at 0.8 V potential. The mobile phase was 0.1 M phosphate buffer (KH_2PO_4), pH 3.85, containing 7.5% methanol, 0.05% EDTA and 6 mM heptane sulfonic acid.

2.4. Locomotor activity

Locomotor activity was measured with a Digiscan actometer (Omnitech Electronics Inc., Columbus, OH, U.S.A.), which monitors horizontal activity. The individual compartments (L = 20; W = 20; H = 30 cm) were put in a dimly lit room. The response to the drug is expressed either as the number of beams crossed between the 50th and the 70th min after the treatment (dose-response study) or as the difference between the number of beams crossed by controls and by dexamphetamine-treated mice during consecutive 10-min periods for 4 h after the administration of dexamphetamine (kinetic study).

2.5. Drugs

[^{3}H]GBR 12783 (25 Ci/mmol, > 97% purity, 1-[2-(diphenylmethoxy)ethyl]4-(3-phenyl-1[^{3}H]2-propenyl)-piperazine) was prepared by the reduction of the amide precursor (kindly synthesized by Professor Robba, Caen, France) with [^{3}H]diborane, by Amershan, Les Ulis, France. Dexamphetamine sulfate (La Cooper, Melun, France) was dissolved in saline; reserpine (Sigma) was dissolved in distilled water containing 5% dimethyl sulfoxide and 5% cremophor EL; α-methyl-p-tyrosine methylester (Sigma) was dissolved in distilled water; L-DOPA associated with benserazide (Modopar® Roche) were suspended in 1% (w/v) sodium carboxymethylcellulose water solution. All doses are expressed as the base and were injected in a volume of 0.2 ml/20 g.

2.6. Statistics

The ED_{50} and their confidence limits were calculated according to the method of Lichtfield and Wilcoxon (1949). The significance of differences between means was checked with Student's t-test preceded, if necessary, by a two-way ANOVA.

3. Results

In mice injected with increasing doses of dexamphetamine (1-8 mg/kg s.c.) and a tracer dose of [^{3}H]GBR 12783 (5 μCi i.v.) 1 h before they were killed, a dose-dependent decrease in the difference between the radioactivity retained in the striatum vs. cerebellum was observed (fig. 1, upper panel). The ED_{50} for dexamphetamine (the dose which reduced the difference between the radioactivity measured in the striatum and in cerebellum by 50%) was 2.8 (1.4-5.6) mg/kg. Dexamphetamine exerted a biphasic effect on locomotion over the range of the tested doses (fig. 1, lower panel). At the dose of 1 mg/kg, dexamphetamine did not significantly decrease striatal [^{3}H]GBR 12783 binding or significantly increase locomotion; however, these two effects were observed with 2 and 4 mg/kg dexamphetamine. The behavioural effects of dexamphetamine were more pronounced than those induced by pure uptake inhibitors (Duterte-Boucher et al., in press). At 8 mg/kg dexamphetamine, the radioactivity in the striatum was almost similar to that measured in cerebellum. This high dose of dexamphetamine (8 mg/kg) induced marked stereotyped behaviour (not

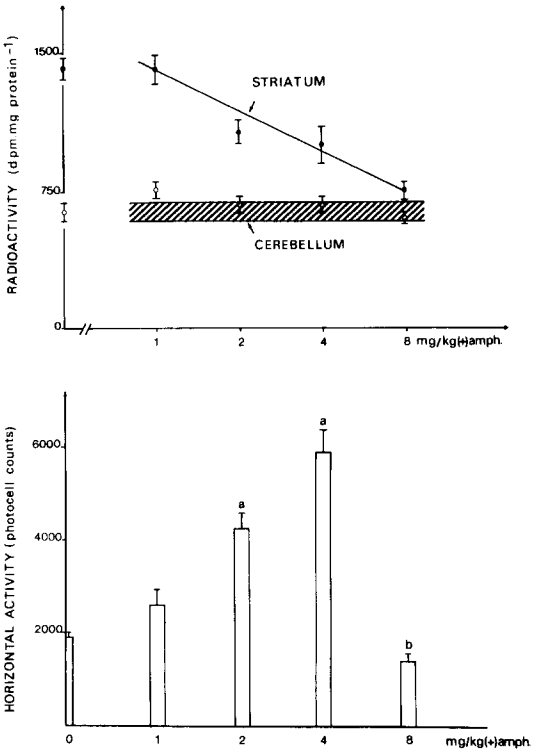

Fig. 1. Effects of increasing doses of dexamphetamine on the binding of [^{3}H]GBR 12783 in the striatum in vivo and on the locomotor activity of mice. Upper panel: mice were injected s.c. with increasing doses of dexamphetamine and i.v. with a tracer dose of [^{3}H]GBR 12783. The animals were killed 1 h later. Means ± S.E.M. of six mice for each dose. Lower panel: mice were injected s.c. with increasing doses of dexamphetamine immediately before their introduction into the actometers. The number of beams crossed between the 50th and the 70th min after the introduction into the actometer was registered. Means ± S.E.M. of 11 mice per group. [a] $P < 0.001$; [b] $P < 0.05$ as compared to saline controls.

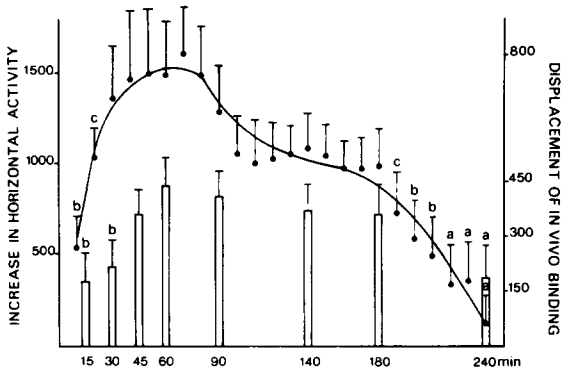

Fig. 2. Time course of the effects of a 3 mg/kg dose of dexamphetamine on the striatal binding of [^{3}H]GBR 12783 and on the locomotor activity of mice. The curve corresponds to the increase in locomotor activity of mice injected s.c. with dexamphetamine immediately before their introduction into the actometers. Each point corresponds to the difference between the number of beams crossed by the dexamphetamine-treated mice and by the saline-treated controls during consecutive 10-min periods. Means ± S.E.M. of differences for two groups of 12 mice. The columns correspond to the displacement of the striatal binding of [^{3}H]GBR 12783 by dexamphetamine at the times indicated on the abscissa. Displacement is given by the difference between the radioactivity (d.p.m./mg protein) in the striatum minus that in the cerebellum in saline-treated controls and dexamphetamine-treated mice = $[R^*str_{saline} - R^*cereb_{saline}] - [R^*str_{dexamphetamine} - R^*cereb_{dexamphetamine}]$. The tracer dose of [^{3}H]GBR 12783 was always injected 1 h before the animals were killed. Means ± S.E.M. of differences for groups of 6-12 mice. [a] $P > 0.05$ (not significant); [b] $P < 0.05$; [c] $P < 0.01$ and for other values $P < 0.001$ as compared to the respective saline controls. The mean difference between the radioactivity in the striatum and cerebellum of control mice was 800 d.p.m./mg protein.

TABLE 1

Influence of the treatments with reserpine plus α-methyl-p-tyrosine or L-DOPA plus benserazide on the striatal content of dopamine and metabolites. The treatments with reserpine (5 mg/kg s.c.) and α-methyl-p-tyrosine (100 mg/kg s.c. + 100 mg/kg i.p.) were given 5 h and 4.5 h, respectively, before the animals were killed (four mice per group). The treatment with L-DOPA (200 mg/kg i.p.) and benserazide (50 mg/kg i.p.) was given 3 h before the animals were killed (8 mice per group). [a] $P < 0.001$ as compared to the respective controls (Student's t-test). n.d. = not detectable. DA: dopamine; DOPAC: dihydroxyphenylacetic acid; HVA = homovanillic acid; 3MT = 3-methoxytyramine.

Treatment	Striatal levels (ng/mg protein ± S.E.M.)			
	DA	DOPAC	HVA	3MT
Solvent	123 ± 2	7.5 ± 0.3	15.9 ± 0.3	2.7 ± 0.1
Reserpine 5 mg/kg s.c. (5 h) + α-methyl-p-tyrosine 100 mg/kg i.p. + 100 mg/kg s.c. (4.5 h)	0.7 ± 0.1 [a]	1.1 ± 0.4 [a]	2.8 ± 0.4 [a]	n.d.
Solvent	116 ± 4	6.6 ± 0.4	13.7 ± 0.7	3.4 ± 0.3
L-DOPA 200 mg/kg i.p. + benserazide 50 mg/kg i.p. (3 h)	222 ± 10 [a]	138 ± 4 [a]	82 ± 3 [a]	2.1 ± 0.1 [a]

TABLE 2

Influence of treatments that modify the striatal content of dopamine on the displacement by dexamphetamine of the striatal binding of [^{3}H]GBR 12783. The pretreatment with reserpine (5 mg/kg s.c.) was given 5 h before the animals were killed. The pretreatment with α-methyl-p-tyrosine (100 mg/kg s.c. + 100 mg/kg i.p.) was given 4.5 h before the animals were killed. The pretreatment with L-DOPA and benserazide (respectively 200 and 50 mg/kg, i.p.) was given 3 h before the animals were killed. The administration of dexamphetamine (3 mg/kg s.c.) and the i.v. injection of the tracer dose of [^{3}H]GBR 12783 were given simultaneously 1 h before the animals were killed. Statistics: analysis of variance was performed after the data were converted to their common logarithms because the sample variances were heterogeneous. [a] Indicates that the reserpine + α-methyl-p-tyrosine treatment induces a significant ($P < 0.01$) increase in the content of cerebellar radioactivity (ANOVA two way). [b] Indicates that the L-DOPA + benserazide treatment induces a significant ($P < 0.001$) increase in the content of cerebellar radioactivity (ANOVA two way). The pretreatment with either reserpine + α-methyl-p-tyrosine or L-DOPA + benserazide did not significantly modify the differences between the radioactivity in the striatum and cerebellum in saline-treated controls. [c] $P < 0.001$ and [d] $P < 0.01$ for the comparison between dexamphetamine-treated mice and their respective saline controls (Student's t-test, preceded by a two-way ANOVA which was significant at $P < 0.001$). Means ± S.E.M. of seven mice per group.

Pretreatment	Treatment	Radioactivity (d.p.m./mg protein)			Variation (%)
		Striatum	Cerebellum	Difference str. − cereb.	
Solvent	Saline	1728 ± 110	796 ± 49	932 ± 71 [c]	
	(+) Amph 3 mg/kg s.c.	1183 ± 101	786 ± 65 [a]	398 ± 39 [c]	−57%
Reserpine 5 mg/kg s.c. (5 h) + α methyl-p-tyrosine 100 mg/kg i.p. 100 mg/kg s.c. (4.5 h)	Saline	1994 ± 173	1179 ± 133 [a]	815 ± 52 [d]	
	(+) Amph 3 mg/kg s.c.	1694 ± 197	1192 ± 164 [a]	516 ± 54 [d]	−37%
Solvent	Saline	1636 ± 106	765 ± 51 [b]	871 ± 62 [c]	
	(+) Amph 3 mg/kg s.c.	1135 ± 84	764 ± 40 [b]	371 ± 49 [c]	−57%
L-DOPA 200 mg/kg i.p. + benserazide 50 mg/kg i.p. (3 h)	Saline	1803 ± 154	1037 ± 104 [b]	766 ± 80 [c]	
	(+) Amph 3 mg/kg s.c.	1413 ± 91	1060 ± 58 [b]	352 ± 49 [c]	−54%

shown), which probably accounted for the decrease in locomotion.

The decrease in the striatal binding of [^{3}H]GBR 12783 and the increase in locomotor activity were apparently related over the 240 min period following the administration of dexamphetamine (3 mg/kg s.c.). The maximal increase in locomotion and the maximal reduction in striatal [^{3}H]GBR 12783 binding were both observed 60 min after the administration of dexamphetamine. The duration of the significant increase in locomotion (about 3 h-4 h) was similar to that of the significant reduction in radioactivity in the striatum (fig. 2).

In mice injected with reserpine (5 mg/kg s.c.) and α-methyl-p-tyrosine (100 mg/kg s.c. + 100 mg/kg i.p.) 5 h and 4.5 h, respectively, before the animals were killed, there was an almost complete disappearance of DA in the striatum (−99%) and a marked decrease in its metabolites (table 1). On the contrary, the treatment with L-DOPA (200 mg/kg i.p.) and benserazide (50 mg/kg i.p.) 3 h before the animals were killed induced an about 100% increase in the striatal DA content and a marked rise in dihydroxyphenylacetic acid and homovanillic acid levels; 3-methoxytyramine levels were significantly decreased.

The pretreatment with reserpine and α-methyl-p-tyrosine did not modify the decrease in striatal [^{3}H]GBR 12783 binding produced by dexamphetamine relative to that observed in the controls (table 2, upper part). Similarly, the pretreatment with L-DOPA and benserazide did not modify the decrease in striatal [^{3}H]GBR 12783 produced by dexamphetamine, since the effect had the same amplitude in the controls and the pretreated animals (table 2, lower part).

Both pretreatments induced a significant increase in cerebellar radioactivity but did not significantly modify the difference between the radioactivity in the striatum and cerebellum of the saline-treated controls.

4. Discussion

A carrier-mediated exchange of amphetamine with DA has been suggested to be responsible for the ability of amphetamine to induce neurotransmitter release (Fischer and Cho, 1979; Raiteri et al., 1979). Several studies have reported that pure uptake inhibitors, including nomifensine, benztropine or GBR 12783, block amphetamine-induced [^{3}H]DA release from striatal synaptosomes or slices (Raiteri et al., 1979; Liang and Rutledge, 1982; Bonnet and Costentin, 1986). In the same way, uptake blockers such as methylphenidate, mazindol, GBR 12783 and GK 13 antagonize amphetamine-induced behaviours (Ross, 1978; Heikkila et al., 1981; Duterte-Boucher et al., in press).

The stimulant effects of dexamphetamine on locomotion are known to depend on an increase in DA transmission in the nucleus accumbens (Costall et al., 1979; Sharp et al., 1987). It would have been more satisfactory to consider the interaction of the drug with the [^{3}H]GBR 12783 binding in this structure rather than in the striatum. However, since it is easier to work with the striatum we used this tissue, assuming that presynaptic events (i.e. DA release and DA reuptake) are similar in both structures.

The dose-response study of the effect of dexamphetamine on locomotion revealed a biphasic effect since only low doses stimulated locomotion whereas the highest dose tested (8 mg/kg) was ineffective. This was probably caused by the appearance of stereotyped behaviours which disturbed locomotion. Such a competition between locomotor activity and stereotypies has been reported already (Scheel-Krüger, 1972; Tyler and Tessel, 1979; Sharp et al., 1987).

Dexamphetamine reduced the striatal accumulation of the [^{3}H]GBR 12783 in a dose-dependent manner, from 1 mg/kg to 8 mg/kg. The efficacy of such low doses was rather surprising because, in vitro, micromolar concentrations of dexamphetamine are required to prevent the specific binding of [^{3}H]GBR 12783 to a membrane fraction prepared from the striatum (Bonnet et al., 1986). Other DA uptake inhibitors (GBR 12783, mazindol, nomifensine) with a 200-10000 fold higher affinity than dexamphetamine for the site labelled in vitro by [^{3}H]GBR 12783 were also quite effective in vivo (Bonnet et al., 1986; Chagraoui et al., 1987). This apparent discrepancy might have several explanations. The high lipophilicity of dex-

amphetamine might lead to its high cerebral concentration, which could compensate for its low apparent affinity for the DA uptake complex (Axelrod, 1970). Another explanation could be that dexamphetamine, at doses inducing behavioural effects, releases endogenous DA at a level sufficient to be an effective competitor for the binding of [^{3}H]GBR 12783. Although high DA concentrations are required in vitro for such a competition (in the μM range) (Bonnet et al., 1986), these concentrations could be reached in the synaptic cleft. Against this hypothesis, we observed that neither DA depletion (induced by reserpine plus α-methyl-p-tyrosine), nor an increase in the DA content (induced by L-DOPA plus benserazide) significantly modified the effect of dexamphetamine on the striatal binding of [^{3}H]GBR 12783. However, these treatments are known to inhibit and potentiate, respectively, the DA-mediated behavioural effects of dexamphetamine (Protais et al., 1976).

The increase in cerebellar radioactivity observed after [^{3}H]GBR 12783 injection in mice pretreated with either L-DOPA and benserazide or reserpine and α-methyl-p-tyrosine might be due to modifications in the permeability of the blood-brain barrier to [^{3}H]GBR 12783 and/or to modifications in cerebral blood flow. Although this increase means that one must be cautious in drawing conclusions, the experimental data suggest that synaptic DA released by dexamphetamine does not compete for the [^{3}H]GBR 12783 binding site. Furthermore, it is noteworthy that neither pretreatment significantly modified the difference between the radioactivity in the striatum and cerebellum in the saline-treated controls.

Previous assessments of the effects of a systemic administration of dexamphetamine on dopamine uptake ex vivo have provided conflicting results, including a ED_{50} as high as 65 mg/kg (Hadfield, 1985) or a lack of dose-response inhibition (Carruba et al., 1977; Keller et al., 1982). The present results are at variance with the results mentioned above but are consistent with those reported by Ross and Rényi (1975).

The distinction between the substrate binding site and the [^{3}H]GBR 12783 binding site, which has been sometimes suggested in the literature (Kennedy and Hanbauer, 1983; Dubocovich and Zahniser, 1985; Bonnet et al., 1986), could be caused by the experimental conditions used for in vitro studies. The dexamphetamine-induced increase in the locomotor activity of mice is well correlated with a release of cytosolic DA (Moore, 1978). In the same way, this functional link has been demonstrated in rats for the locomotor activation and stereotyped behaviours elicited by doses of dexamphetamine that induce a non-exocytotic release of DA (Carboni et al., 1989; Sharp et al., 1987). It is noteworthy that two results obtained in the present study suggest that the 'substrate effect' of dexamphetamine (which is linked to a DA release) and the occupancy of the [^{3}H]GBR 12783 binding site occur at similar brain concentrations of dexamphetamine: (i) dexamphetamine doses that induce a stimulation of locomotion result in a decrease in striatal radioactivity and (ii) the time course of these two parameters seem to be related. These experimental data suggest that dexamphetamine acts, at the same dosage, as a substrate of the DA uptake complex and as an effective competitor for the [^{3}H]GBR 12783 binding site. This could indicate that a unique binding site exists which is responsible for both the uptake of substrates and the blockade of uptake by pure inhibitors.

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References

Andersen, P.H., 1989, The dopamine uptake inhibitor GBR 12909: selectivity and molecular mechanism of action, European J. Pharmacol. 166, 493.

Axelrod, J., 1970, Amphetamine: metabolism, physiological disposition and its effects on catecholamine storage, in: Amphetamines and Related Compounds, eds. E. Costa and S. Garattini (Raven Press, New York) p. 207.

Bonnet, J.-J. and J. Costentin, 1986, GBR 12783, a potent and selective inhibitor of dopamine uptake: Biochemical studies in vivo and ex vivo, European J. Pharmacol. 121, 199.

Bonnet, J.-J., M.-H. Lemasson and J. Costentin, 1984, Simultaneous evaluation by a double labelling method of drug-induced uptake inhibition and release of dopamine in syn-

aptosomal preparation of rat striatum, Biochem. Pharmacol. 33, 2129.

Bonnet, J.-J., P. Protais, A. Chagraoui and J. Costentin, 1986, High-affinity [^{3}H]GBR 12783 binding to a specific site associated with the neuronal dopamine uptake complex in the central nervous system, European J. Pharmacol. 126, 211.

Carboni, E., A. Imperato, L. Perezzani and G. Di Chiara, 1989, Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats, Neuroscience 28, 653.

Carruba, M.O., G.B. Picotti, F. Zambotti and P. Mantegazza, 1977, Mazindol and amphetamine as inhibitors of the uptake and releasers of ^{3}H-dopamine by rat striatal synaptosomes, Naunyn-Schmiedeb. Arch. Pharmacol. 298, 1.

Chagraoui, A., J.-J. Bonnet, P. Protais and J. Costentin, 1987, In vivo binding of [^{3}H]GBR 12783, a selective dopamine uptake inhibitor, in mouse striatum, Neurosci. Lett. 78, 175.

Costall, B., R.J. Naylor and V. Nohria, 1979, Hyperactivity response to apomorphine and amphetamine in the mouse: the importance of the nucleus accumbens and caudate-putamen, J. Pharm. Pharmacol. 31, 259.

Dubocovich, M.L. and N.R. Zahniser, 1985, Binding characteristics of the dopamine uptake inhibitor [^{3}H]nomifensine to striatal membranes, Biochem. Pharmacol. 34, 1137.

Duterte-Boucher, D., J.M. Kamenka and J. Costentin, Comparison of the effects of 3 indirect dopamine agonists, GK 13, GBR 12783 and dexamphetamine on behavioral tests involving central catecholaminergic transmissions, Psychopharmacology (in press).

Fischer, J.F. and A.K. Cho, 1979, Chemical release of dopamine from striatal homogenates: evidence for an exchange diffusion model, J. Pharmacol. Exp. Ther. 208, 203.

Hadfield, M.G., 1985, A comparison of in vivo and in vitro amphetamine on the synaptosomal uptake of dopamine in mouse striatum, Res. Commun. Chem. Pathol. Pharmacol. 48, 183.

Heikkila, R.E., R.G. Babington and W.J. Houlihan, 1981, Pharmacological studies with several analogs of mazindol: correlation between effects on dopamine uptake and various in vivo responses, European J. Pharmacol. 71, 277.

Heikkila, R.E., H. Orlansky and G. Cohen, 1975, Studies on the distinction between uptake inhibition and release of ^{3}H-dopamine in rat brain tissue slices, Biochem. Pharmacol. 24, 847.

Keller, H.H., R. Schaffner, M.O. Carruba, W.P. Burkard, M. Pieri, E.P. Bonetti, R. Scherschlicht, M. Da Prada and W.E. Haefely, 1982, Diclofensine (Ro 8-4650) – a potent inhibitor of monoamine uptake: Biochemical and behavioural effects in comparison with nomifensine, in: Typical and Atypical Antidepressants: Molecular Mechanisms, eds. E. Costa and G. Racagni (Raven Press, New York) p. 249.

Kennedy, L.T. and I. Hanbauer, 1983, Sodium-sensitive cocaine binding to striatal membranes: possible relationship to dopamine uptake sites, J. Neurochem. 41, 172.

Langer, S.Z. and S. Arbilla, 1984, The amphetamine paradox in dopaminergic neurotransmission, Trends Pharmacol. Sci. 5, 387.

Langer, S.Z. and H. Schoemaker, 1988, Effects of antidepressants on monoamine transporters, Prog. Neuropsychopharmacol. Biol. Psychiat. 12, 193.

Liang, N.Y. and C.O. Rutledge, 1982, Comparison of the release of ^{3}H dopamine from isolated corpus striatum by amphetamine, fenfluramine and unlabelled dopamine, Biochem. Pharmacol. 31, 983.

Litchfield, J.T. and F. Wilcoxon, 1949, A simplified method of evaluating dose effect experiments, J. Pharmacol. Exp. Ther. 96, 99.

Lowry, O.H., N.J. Rosebrough, A.L. Farr and R.J. Randall, 1951, Protein measurement with the Folin phenol reagent, J. Biol. Chem. 193, 265.

Moore, K.E., 1978, Amphetamines: biochemical and behavioral actions in animals, in: Stimulants, Handbook of Psychopharmacology, Vol. 11, eds. L.L. Iversen, S.D. Iversen and S.H. Snyder (Plenum Press, New York) p. 41.

Pileblad, E. and G. Engberg, 1986, GBR 13098, a selective dopamine uptake inhibitor; behavioural, biochemical and electrophysiological studies, Naunyn-Schmiedeb. Arch. Pharmacol. 334, 383.

Protais, P., J. Costentin and J.C. Schwartz, 1976, Climbing behavior induced by apomorphine in mice: a simple test for the study of dopamine receptors in striatum, Psychopharmacology 50, 1.

Raiteri, M., F. Cerrito, A.M. Cervoni and G. Levi, 1979, Dopamine can be released by two mechanisms differentially affected by the dopamine transport inhibitor nomifensine, J. Pharmacol. Exp. Ther. 208, 195.

Richelson, E. and M. Pfenning, 1984, Blockade by antidepressants and related compounds of biogenic amine uptake into rat brain synaptosomes: most antidepressants selectively block norepinephrine uptake, European J. Pharmacol. 104, 277.

Ross, S.B., 1978, Antagonism by methylphenidate of the stereotyped behavior produced by (+)amphetamine in reserpinized rats, J. Pharm. Pharmacol. 30, 253.

Ross, S.B. and A.L. Rényi, 1975, Inhibition of the uptake of ^{3}H-dopamine and ^{14}C-5-hydroxytryptamine in mouse striatum slices, Acta Pharmacol. Toxicol. 36, 56.

Scheel-Krüger, J., 1972, Behavioural and biochemical comparison of amphetamine derivatives, cocaine, benztropine and tricyclic anti-depressant drugs, European J. Pharmacol. 18, 63.

Sharp, T., T. Zetterström, T. Ljungberg and U. Ungerstedt, 1987, A direct comparison of amphetamine-induced behaviours and regional brain dopamine release in the rat using intracerebral dialysis, Brain Res. 401, 322.

Thornburg, J.E. and K.E. Moore, 1972, A comparison of the locomotor stimulant properties of amantadine and l- and d-amphetamine in mice, Neuropharmacology 11, 675.

Tyler, T.D. and R.E. Tessel, 1979, A new device for the simultaneous measurement of locomotor and stereotypic frequency in mice, Psychopharmacology 64, 285.