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The intrinsic antinociceptive effects of oxycodone appear to be κ-opioid receptor mediated

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Abstract

Our previous studies in the Sprague–Dawley rat showed that the intrinsic antinociceptive effects of oxycodone are naloxone reversible in a manner analogous to morphine but that in contrast to morphine, oxycodone's antinociceptive effects have a rapid onset of maximum effect (≈5–7 min compared to 30–45 min for morphine), comprise one antinociceptive phase (compared to two phases) and are of relatively short duration (≈90 min compared to ≈180 min). In the present study, administration of a range of selective opioid receptor antagonists has shown that the intrinsic antinociceptive effects of oxycodone (171 nmol) are not attenuated by i.c.v. administration of (i) naloxonazine, a μ_1-selective opioid receptor antagonist, or (ii) naltrindole, a δ-selective opioid receptor antagonist, in doses that completely attenuated the intrinsic antinociceptive effects of equipotent doses of the respective μ- and δ-opioid agonists, morphine and enkephalin-[D-Pen^{2,5}] (DPDPE). Although β-funaltrexamine (β-FNA) attenuated the antinociceptive effects of oxycodone (171 nmol i.c.v.), it also attenuated the antinociceptive effects of morphine and bremazocine (κ-opioid agonist) indicative of non-selective antagonism. Importantly, the antinociceptive effects of oxycodone (171 nmol i.c.v.) were markedly attenuated by the prior i.c.v. administration of the selective κ-opioid receptor antagonist, norbinaltorphimine (nor-BNI), in a dose (0.3 nmol) that did not attenuate the antinociceptive effects of an equipotent dose of i.c.v. morphine (78 nmol). Taken together, these data strongly suggest that the intrinsic antinociceptive effects of oxycodone are mediated by κ-opioid receptors, in contrast to morphine which interacts primarily with μ-opioid receptors.

Keywords: Oxycodone; κ-Opioid receptors; Antinociception; Norbinaltorphimine; Intracerebroventricular dosing; Morphine

1. Introduction

Oxycodone is a semi-synthetic opioid analgesic derived from the naturally occurring alkaloid, thebaine. In humans, oxycodone has been shown to have an analgesic potency 0.7 times that of morphine after systemic administration (Beaver et al., 1978; Kalso et al., 1990). Although oxycodone has been used clinically for over 75 years, little is known about the intrinsic pharmacology of this drug. Oxycodone has been thought to induce analgesia by a similar mechanism to morphine, or it has been proposed to be a prodrug for an analgesically active metabolite such as oxymorphone (Beaver et al., 1978), its *O*-demethylated derivative. Oxymorphone is a potent μ-opioid receptor agonist with an analgesic potency approximately 10 times that of morphine (Beaver et al., 1977).

Recently however the putative role of oxymorphone as an analgesically active metabolite of oxycodone has been questioned. In human plasma and urine, levels of unconjugated oxymorphone have been reported to be very low (<1 ng/ml) after administration of oxycodone (Poyhia et al., 1992; Ross et al., 1993; Kaiko et al., 1996; Lacouture et al., 1996). In addition, Dark Agouti rats that are deficient in the enzyme (CYP2D1) required to *O*-demethylate benzomorphan opioids, achieved maximum antinociception following subcutaneous administration of oxycodone (Cleary et al., 1994). Furthermore, when oxycodone was administered by the i.c.v. route to rats, preventing any form of hepatic metabolism, maximum antinociception was observed within 7 min of dosing (ED_{50} = 78 nmol, c.f.

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ED_{50} = 34 nmol for morphine), indicating that oxycodone itself has intrinsic antinociceptive properties (Leow and Smith, 1994). This antinociception was completely reversed by naloxone (54 nmol i.c.v.), indicating that the intrinsic antinociceptive effects of oxycodone are mediated by CNS opioid receptors (Leow and Smith, 1994).

Given that naloxone is a universal opioid receptor antagonist that does not effectively discriminate between the three major classes of opioid receptors, μ, δ, and κ, with binding affinities of 0.93, 17 and 2.3 n*M* for each of these receptor classes respectively (Raynor et al., 1994), it is not possible to determine the specific class of opioid receptor mediating the antinociceptive effects of oxycodone unless more selective antagonists are utilized. Although β-funaltrexamine (β-FNA) has been reported previously to be an irreversible μ-selective opioid receptor antagonist (Takahashi et al., 1988), recent radioligand binding data obtained using cloned opioid receptor preparations have prompted reclassification of this ligand as a non-selective opioid antagonist (Raynor et al., 1994). Naloxonazine has been reported to be an irreversible μ_1-selective opioid receptor antagonist provided it is administered 24 h prior to administration of the corresponding opioid receptor agonist. Additionally, naloxonazine has been shown to antagonize the antinociceptive effects of both morphine and the μ-selective opioid peptide enkephalin-[D-Ala^2,*N*-Phe^4,Gly-ol^5] (DAMGO) (Pasternak and Wood, 1986). In contrast, naloxonazine did not reduce the antinociceptive effects of the δ-selective opioid peptide agonist, enkephalin-[D-Pen^{2,5}] (DPDPE) (Hahn et al., 1982; Johnson and Pasternak, 1984; Nishimura et al., 1984).

Naltrindole has been reported to be a non-peptide δ-opioid receptor antagonist with a 100-fold selectivity for δ-opioid receptors relative to μ-opioid receptors, and a 10 000-fold selectivity for δ- relative to κ-opioid receptors (Portoghese et al., 1988a; Portoghese et al., 1988b). Similarly nor-binaltorphimine (nor-BNI) has been reported to be an irreversible κ-opioid receptor antagonist that antagonizes the antinociceptive effects of both benzacetamide (U69,593 and U50,488H) and benzomorphan (bremazocine) κ-opioid receptor agonists (Takemori et al., 1988; Horan et al., 1991).

Therefore the aim of this study was to determine using i.c.v. administration of selective opioid receptor antagonists, the major class of opioid receptors mediating the intrinsic antinociceptive effects of oxycodone following i.c.v. administration to rats.

This research was presented in preliminary form at the 8th World Congress on Pain (Ross and Smith, 1996).

2. Materials and methods

Ethical approval for this study was obtained from the Animal Experimentation Ethics Committee of The University of Queensland.

2.1. Drugs

Oxycodone hydrochloride was a generous gift from The Boots Company (Australia) Pty Ltd (Sydney, Australia). Morphine hydrochloride was purchased from the Pharmacy Department, Royal Brisbane Hospital (Brisbane, Australia). Naloxonazine, naltrindole, nor-binaltorphimine, β-funaltrexamine, (5α,7α,8β)-(+)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide (U69,593), trans-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide methanesulfonate (U50, 488H), bremazocine and DPDPE were purchased from Research Biochemicals Inc. (Sydney, Australia). Xylazine and ketamine were purchased from Bayer (Sydney, Australia) and Marlab (Brisbane, Australia), respectively.

2.2. Animals

Adult male Sprague–Dawley rats (200 ± 20 g, mean ± SD) were purchased from the Faculty of Medicine Animal Breeding Facility, The University of Queensland. Rats were housed in a temperature controlled environment (21 ± 2°C) with a 12:12 h light/dark cycle and free access to both food and water.

2.3. Surgery

The technique for stereotaxic insertion of an indwelling stainless steel guide cannula into the left lateral ventricle of the rat brain has been described previously (Smith et al., 1990; Leow and Smith, 1994). Rats were deeply anesthetized with a mixture of ketamine (100 mg/kg) and xylazine (16 mg/kg) administered by intraperitoneal (i.p.) injection. The skull was exposed and a hole drilled 1.5 mm L and 0.8 mm P with respect to bregma. The stainless steel guide cannula (21 G with a 45° bevel) was inserted stereotaxically to 1 mm above the left lateral ventricle (3.2 mm V) and fixed in position with dental cement. The wound was sutured and a stainless steel plug extending 1 mm below the guide cannula was inserted and kept in place except during drug injections. Rats received vancomyocin (50 000 IU i.p.) to prevent infection and were kept warm during recovery from anesthesia. Following cannula insertion, rats were housed singly for a recovery period of 5–7 days prior to i.c.v. drug administration.

2.4. Dosing regimens

Intracerebroventricular injections were made using a 5-μl Hamilton syringe with a 25-gauge needle under light anesthesia (50% O_2/50% CO_2) and all drugs were dissolved in isotonic saline. All rats were tested for correct cannula placement 5–7 days after surgery by a single injection of oxycodone in a dose that would elicit a brief period of maximum antinociception (171 nmol i.c.v.) and measuring

the tail flick latency for the first 10 min post-injection. Rats that displayed no antinociception were omitted from the study as previous experience had shown that a lack of antinociception at this dose was due to incorrect cannula placement. One group of rats ($n = 4$) dosed with i.c.v. oxycodone, underwent antinociceptive testing for a 3-h experimental period as described in the next section. Additional groups of rats for each selective opioid antagonist included in the study were give a further 2–3-day recovery period, after which they received i.c.v. injections of the appropriate selective opioid antagonist followed by either oxycodone (171 nmol i.c.v.) or the complementary selective opioid agonist.

Additional groups of rats received i.c.v. administration of a selective opioid antagonist followed by saline (1 μl) or the corresponding selective opioid agonist (positive controls), in a dose previously determined to be approximately equipotent with 171 nmol of oxycodone (data not shown). Naloxonazine (1.0 nmol, $n = 4$) (Hahn et al., 1982; Johnson and Pasternak, 1984; Nishimura et al., 1984) and nor-BNI (0.3 nmol, $n = 8$ and 1.2 nmol, $n = 4$) were injected 24 h prior to i.c.v. administration of the respective opioid agonist to ensure that only the irreversible effects of each opioid antagonist were being studied (Clark et al., 1988). In contrast, the competitive δ-selective opioid receptor antagonist naltrindole (1 nmol, $n = 4$) (Portoghese et al., 1988a; Portoghese et al., 1988b), was administered only 15 min prior to i.c.v. administration of an opioid agonist or saline. The irreversible opioid antagonist, β-FNA (4 nmol, $n = 4$) (Takahashi et al., 1988), was injected 24 h prior to i.c.v. administration of an opioid agonist or saline.

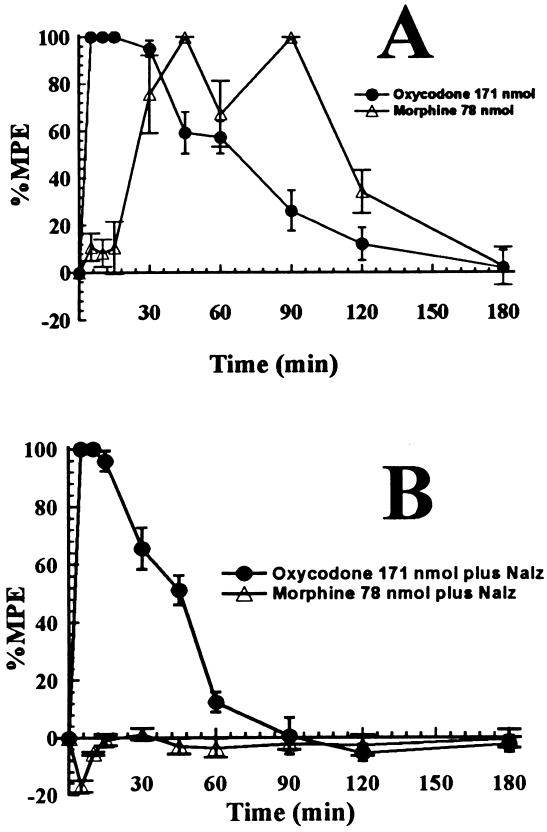

Fig. 1. (A) Mean (±SEM) degree of antinociception versus time curves observed following i.c.v. administration of oxycodone (171 nmol, ●) and morphine (78 nmol, △). (B) Mean (±SEM) degree of antinociception versus time curves observed following i.c.v. administration of the μ_1-selective opioid receptor antagonist, naloxonazine (1 nmol) 24 h prior to i.c.v. administration of oxycodone (171 nmol, ●) and morphine (78 nmol, △).

2.5. Antinociceptive assessment

The tail flick latency test (D'Amour and Smith, 1941) was used to quantify the degree of antinociception achieved in rats following i.c.v. administration of opioid agonists or saline. A cut-off time of 9 s was electronically maintained to minimize tissue damage to the rat's tail. Pre-injection reaction times were typically 3–4.5 s and were the average of two readings taken approximately 5 min apart. Tail flick latency times were determined following i.c.v. administration of opioid agonist or saline at the following times: 5, 10, 15, 30, 45, 60, 90, 120 and 180 min. After completion of the experiment, correct cannula placement was visually checked following an injection of malachite green dye (1 μl), decapitation and gross dissection of the brain.

2.6. Data analysis

Tail flick latency times were converted to the percentage of maximum possible effect (%MPE) according to the following formula (Brady and Holtzmann, 1982):

$$\%\text{MPE} = \frac{(\text{Post-drug latency}) - (\text{Pre-drug latency})}{(\text{Maximum latency}) - (\text{Pre-drug latency})} \times \frac{100}{1}$$

2.7. Statistical analysis

Data were analyzed for significant differences using the paired Wilcoxon test or the unpaired Wilcoxon Rank-Sum test, where appropriate. The statistical significance criterion was $P < 0.05$.

3. Results

The mean degree of antinociception observed following i.c.v. oxycodone (171 nmol, $n = 4$) administration reached peak values of 100% MPE at 5 min post-dosing, thereafter decreasing in a monoexponential manner reaching baseline values by approximately 90 min post-dosing (Fig. 1A). In contrast, the antinociceptive effects observed in control rats that received i.c.v. saline (1 μl) were not significantly different from baseline values ($P > 0.05$) throughout the 3-h study period (data not shown).

Administration of the irreversible μ_1-opioid receptor antagonist, naloxonazine (1 nmol i.c.v.) 24 h prior to administration of oxycodone (171 nmol i.c.v., $n = 4$) had a rela-

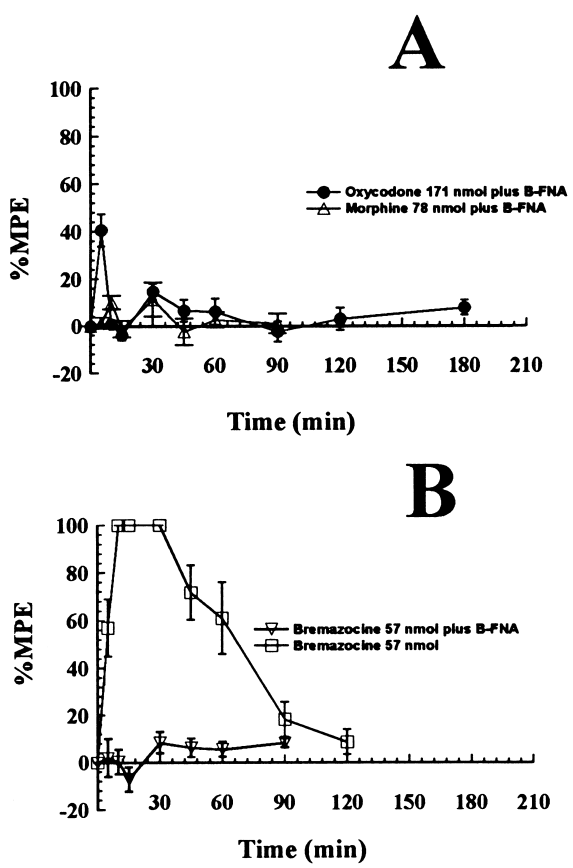

Fig. 2. Mean (±SEM) degree of antinociception versus time curves observed following i.c.v. administration of β-FNA (irreversible opioid receptor antagonist) 6 h prior to the i.c.v. administration of (A) oxycodone (171 nmol, ●) and morphine (78 nmol, △), and (B) bremazocine (57 nmol, ▽) (control data for bremazocine (57 nmol i.c.v., □) administered to untreated rats is also shown). Control data for i.c.v. administration of both oxycodone and morphine alone are shown in Fig. 1A.

tively minor effect on the levels of antinociception achieved. The mean duration of action of oxycodone was shortened from approximately 90 min to 60 min but the magnitude of antinociception did not appear to be significantly reduced during the first 15 min post-dosing (Fig. 1B), when compared with rats receiving oxycodone (171 nmol i.c.v.) alone (Fig. 1A). However, naloxonazine completely attenuated the antinociceptive effects of morphine (78 nmol i.c.v., $n = 4$) administered to the same rats 24 h later (Fig. 1B). In contrast, this same dose of morphine ($n = 4$) administered alone to rats by the i.c.v. route produced maximum antinociception which decreased in a biphasic manner over the 3-h study period (Fig. 1A).

It was also noted that the %MPE values observed in control rats that received naloxonazine (1 nmol i.c.v.) followed 24 h later by saline (1 μl, $n = 4$) were 5–10% lower than those of untreated rats indicating that naloxonazine may have prevented the normal functioning of the endogenous opioidergic system. Rats treated with naloxonazine displayed minor excitatory behaviours (mild tremors and teeth chattering) after dosing.

Administration of the irreversible opioid receptor antagonist, β-FNA (4 nmol i.c.v.) (Takahashi et al., 1988), 24 h prior to oxycodone (171 nmol i.c.v., $n = 4$) dosing, completely attenuated the intrinsic antinociceptive effects of oxycodone (Fig. 2A). Similarly, β-FNA (4 nmol i.c.v.) also completely attenuated the antinociceptive effects of the κ-opioid agonist bremazocine (57 nmol i.c.v., $n = 4$, Fig. 2B) and the μ-opioid receptor agonist, morphine (78 nmol i.c.v., $n = 4$, Fig. 2A). Thus it is evident that at a dose of 4 nmol (i.c.v.) β-FNA was unable to differentially antagonize morphine induced antinociception from that of the κ-opioid receptor agonist bremazocine in rats, consistent with the data from recent radioligand binding studies in cloned opioid receptor preparations that have led to the reclassification of β-FNA as a non-selective opioid antagonist. Rats that received β-FNA (4 nmol i.c.v.) followed by saline (1 μl, $n = 4$) exhibited %MPE values that were not significantly different ($P > 0.05$) from pre-dosing baseline values for the duration of the 3-h observation period (data not shown).

The competitive δ-opioid receptor antagonist, naltrindole (2.2 nmol i.c.v.), administered 15 min prior to oxycodone (171 nmol i.c.v., $n = 4$), did not significantly alter ($P > 0.05$) the antinociceptive effects of oxycodone (Fig. 3) but completely reversed antinociception induced by DPDPE (55 nmol i.c.v., $n = 4$) the δ-selective opioid receptor agonist in a dose equipotent with 171 nmol i.c.v. oxycodone (Fig. 3). Rats that received naltrindole (2.2 nmol i.c.v.) followed 15 min later by saline (1 μl, $n = 4$) did not achieve significant antinociception as the %MPE values achieved over the 3-h observation period were not significantly different ($P > 0.05$) from pre-dosing baseline values (data not shown).

In contrast, i.c.v. administration of the κ-selective opioid receptor antagonist nor-BNI (0.3 nmol), 24 h prior to the i.c.v. administration of oxycodone (171 nmol, $n = 8$), U69,593 (133 nmol, $n = 4$) or bremazocine (57 nmol, $n = 4$), resulted in complete attenuation of the antinociceptive effects of each of these compounds (Fig. 4). Importantly the antinociceptive effects of morphine (78 nmol i.c.v.,

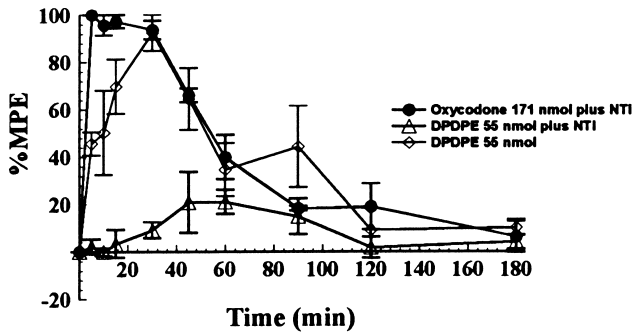

Fig. 3. Mean (±SEM) degree of antinociception versus time curve observed following i.c.v. administration of the δ-selective opioid antagonist, naltrindole (2.2 nmol) administered 15 min prior to i.c.v. oxycodone (171 nmol, ●) and an equipotent dose of i.c.v. DPDPE (55 nmol, △), plus control data for DPDPE (55 nmol i.c.v. alone, ◇). Control data for i.c.v. administration of oxycodone alone are shown in Fig. 1A.

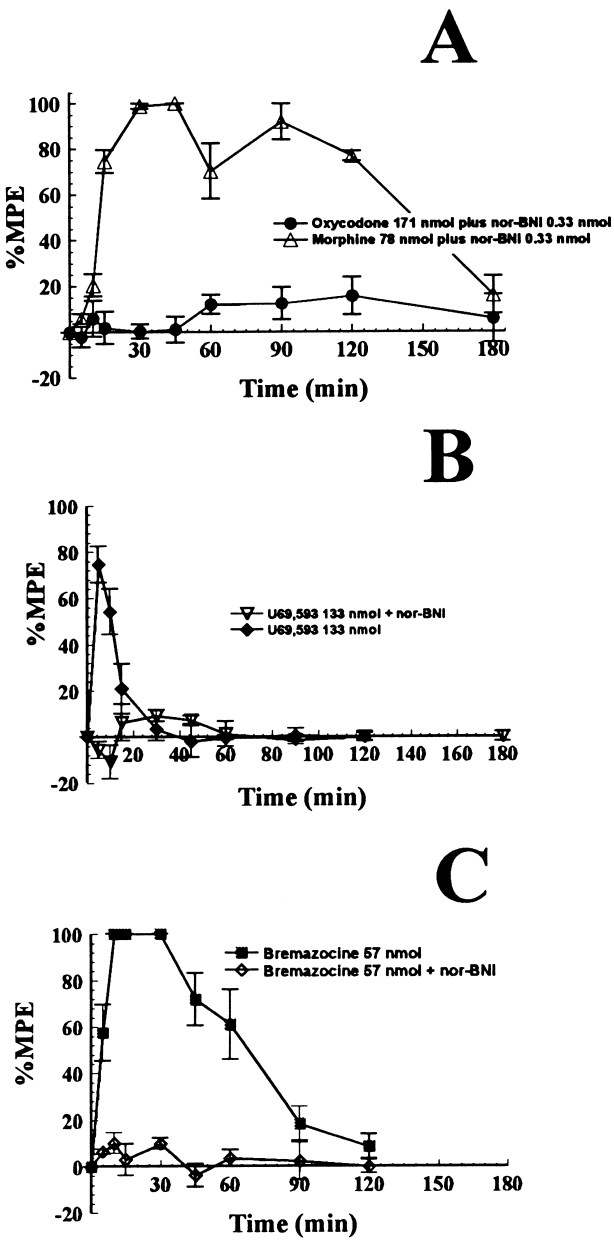

Fig. 4. Mean (± SEM) degree of antinociception versus time curve observed following i.c.v. administration of the κ-selective opioid receptor antagonist, nor-BNI (0.3 nmol) 24 h prior to i.c.v. administration of (A) oxycodone (171 nmol, ●) and morphine (78 nmol, △), (B) U69,593 (133 nmol, ▽), (control data for U69,593 (133 nmol i.c.v., ♦) in untreated rats are also shown), (C) bremazocine (57 nmol, ◇) (control data for bremazocine (57 nmol, ■) are also shown). Control data for i.c.v. administration of both oxycodone and morphine alone are shown in Fig. 1A.

$n = 4$) were not attenuated (Fig. 4A). However, a fourfold increase in the dose of nor-BNI (1.2 nmol i.c.v.) administered not only attenuated the antinociceptive effects of oxycodone (171 nmol i.c.v., $n = 4$) but also attenuated the antinociceptive effects of morphine (78 nmol i.c.v., $n = 4$) (Fig. 5A), suggesting that at this dose (1.2 nmol i.c.v.) nor-BNI did not differentiate between κ- and μ-opioid receptors. Additionally, the antinociceptive effects of the κ-opioid agonists U50,488H (120 nmol i.c.v., $n = 4$, Fig. 5B) and bremazocine (57 nmol i.c.v., $n = 4$, Fig. 5C) were reduced to baseline levels by the larger dose of nor-BNI.

Behaviorally, rats that received oxycodone (171 nmol i.c.v.) did not exhibit any signs of spontaneous bladder emptying or incontinence in contrast to rats that received i.c.v. morphine (78 nmol), nor did they exhibit the catatonic behaviour previously reported in rats which had received oxycodone by a systemic route (Poyhia and Kalso, 1992; Cleary et al., 1994).

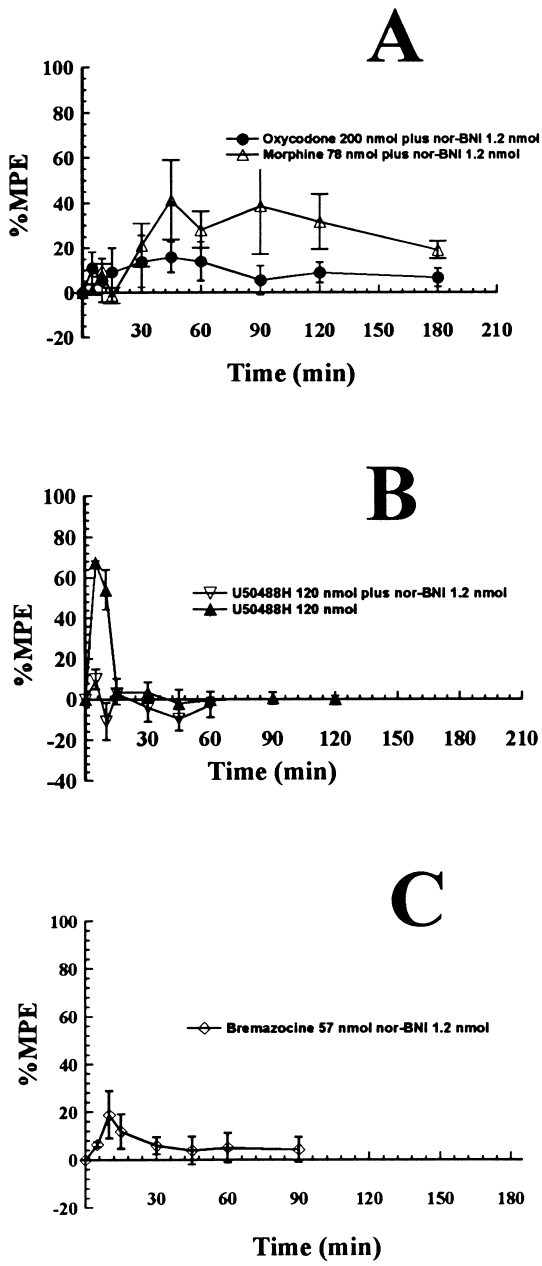

Fig. 5. Mean (±SEM) degree of antinociception versus time curves observed following i.c.v. administration of a fourfold higher dose of nor-BNI (1.2 nmol), 24 h prior to the i.c.v. administration of (A) oxycodone (171 nmol, ●) and morphine (78 nmol, △), (B) U50,488H (120 nmol, ▽), (control data for U50,488H (120 nmol, ▲, in untreated rats is also shown), (C) bremazocine (57 nmol, ◇). Control data for i.c.v. administration of oxycodone and morphine alone are shown in Fig. 1A.

4. Discussion

Our findings strongly indicate that in contrast to morphine, oxycodone's intrinsic antinociceptive effects are mediated by κ-opioid receptors as these effects were markedly attenuated by nor-BNI (κ-selective antagonist) in a dose that did not attenuate morphine's intrinsic antinociceptive effects (Fig. 4A). This is further supported by the observation that oxycodone's antinociceptive effects were not attenuated by naloxonazine (μ_1-selective antagonist) or naltrindole (δ-selective antagonist) in doses that completely attenuated the intrinsic antinociceptive effects of equipotent doses of the respective μ- and δ-agonists, morphine (Fig. 1B) and DPDPE (Fig. 3).

Furthermore the characteristics of the degree of antinociception versus time profiles for oxycodone (Fig. 1A) were similar to those observed following i.c.v. administration of known κ-opioid agonists of both the benzacetamide (U69,593 and U50,488H; Leighton et al., 1988) and the benzomorphan classes (bremazocine and ethylketazocine; Horan et al., 1991) but were completely different from those observed following i.c.v. morphine dosing (Fig. 1A), consistent with previous findings from our laboratory (Leow and Smith, 1994). Specifically, oxycodone, U50,488H, U69,593 and bremazocine had a rapid onset of maximum antinociception (5–7 min) (Fig. 1A, Fig. 5B, Fig. 4B and Fig. 2B, respectively) compared with the 30–45 min required for morphine (Fig. 1A) and only a single antinociceptive phase was observed compared with the two antinociceptive phases evoked by i.c.v. morphine. The initial antinociceptive phase of morphine is due primarily to activation of supraspinal μ-opioid receptors whereas the second phase (onset $\approx$ 90 min post dosing) probably results from caudal redistribution of morphine, activating spinal μ-opioid receptors (Leow and Smith, 1994). The single phase of antinociception observed following i.c.v. administration of oxycodone was essentially complete by 90 min post-dosing (Leow and Smith, 1994). This is not surprising as the potency of oxycodone administered by the intrathecal (i.t.) route has been reported to be only 0.09 times that of i.t. morphine (Yaksh and Harty, 1987; Poyhia and Kalso, 1992), indicating that oxycodone has poor affinity for spinal opioid receptors. Thus redistribution of oxycodone from supraspinal sites at the time of the i.c.v. injection to the spinal region by 90 min post-injection would be expected to result in a reduction of antinociception to baseline values at this time. Additionally, radioligand binding studies using [^{3}H]DAMGO have shown that oxycodone's affinity for the μ-opioid receptor is relatively low compared with that of morphine (Chen et al., 1991).

Our present findings also illustrate that the in vivo selectivity of so-called selective opioid receptor antagonists is very much dose-related. For example, a fourfold increase in the i.c.v. dose of the κ-opioid antagonist, nor-BNI, from 0.3 to 1.2 nmol (compare Fig. 4A and Fig. 5A) introduced μ-antagonist effects indicated by the attenuation of the antinociceptive effects of the μ-opioid agonist, morphine, in addition to the antagonism of the antinociceptive effects of oxycodone and the κ-agonists, U69,593 and bremazocine. This is supported by the findings of Raynor et al. (1994) which demonstrated that the binding affinity of nor-BNI for cloned κ_1-opioid receptors was approximately 100 times greater than that for μ_1-opioid receptors (0.027 and 2.2 nM, respectively). This two orders of magnitude difference in binding affinity was sufficient to allow in vivo pharmacological differentiation between κ- and μ-opioid receptors with nor-BNI at an i.c.v. dose of 0.3 nmol but not 1.2 nmol in Sprague–Dawley rats. Therefore great care is needed in selecting the appropriate dose of selective opioid receptor antagonists (such as nor-BNI) to achieve the desired in vivo selectivity.

The apparent lack of in vivo selectivity of β-FNA to distinguish between μ- and κ-opioid receptors following i.c.v. administration to Sprague–Dawley rats is also consistent with the findings of Raynor et al. (1994) who reported that the relative binding affinities of β-FNA for cloned μ_1- and κ_1-opioid receptors were 0.33 and 2.8 nM respectively, i.e., a separation of less than one order of magnitude, a finding which has contributed to the reclassification of β-FNA as a non-selective opioid receptor antagonist. In addition β-FNA acts as a long lasting κ-opioid agonist, which may further confound the interpretation of experiments where it is used (Jiang et al., 1988).

Although oxycodone has an intrinsic antinociceptive potency approximately equal to 0.44 that of morphine in rats (Leow and Smith, 1994), oxycodone has been reported to have an analgesic potency 0.7 times that of morphine in surgical patients (Poyhia and Kalso, 1992). Whether the greater potency observed after systemic oxycodone administration to humans is due to the greater density of κ-opioid receptors in primate brain compared with rodent brain (Emmerson et al., 1994), or due to metabolism of oxycodone in the patient's liver to an as yet unidentified analgesically active metabolite (which may also contribute to oxycodone's side-effect profile), as has been suggested by Beaver et al. (1978), remains to be determined.

In summary, the studies reported in this paper strongly suggest that the intrinsic antinociceptive effects of oxycodone are mediated by CNS κ-opioid receptors, in contrast to morphine which interacts primarily with μ-opioid receptors. However, given that at least three κ-opioid receptor subtypes, κ_1, κ_2 and κ_3, have been pharmacologically defined (Von Voightlander et al., 1983; Nock et al., 1988; Clark et al., 1989), further studies are required to determine which of these subtypes mediate the intrinsic antinociceptive effects of oxycodone.

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