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Potentiation of opioid-induced conditioned place preference by the selective serotonin reuptake inhibitor fluoxetine

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Abstract

The ability of the selective serotonin reuptake inhibitor, fluoxetine, to modify the effects of morphine, *N*-((*S*)-2-benzyl-3[(*S*) 2-amino-4-methylthio)butyldithio-]-1-oxopropyl)-L-alanine benzylester (RB 120; mixed inhibitor of enkephalin metabolism), and 4-{[2-[[3-(1*H*-indol-3-yl))-2-methyl-1-oxo-2-[[(tricyclo[3,3,1,1] dec-2-yloxy) carbonyl] amino} propyl] amino]-1-phenylethyl] amino}-4-oxo-[*R*-(*R**,*R**)]-butanoate *N*-methyl-D-glucamine (CI 988; cholecystokinin receptor subtype [CCK_2] antagonist), was assessed using conditioned place preference. RB 120 and morphine both induced significant, dose-dependent conditioned place preference, whilst CI 988 failed to elicit conditioned place preference. A subthreshold dose of fluoxetine (2.5 mg/kg) potentiated the morphine submaximal response. Notably, the combination of a subthreshold dose of fluoxetine (2.5 mg/kg) with RB 120 (5 mg/kg) or CI 988 (3 mg/kg) was devoid of any significant conditioned place preference properties. Fluoxetine may act via enhanced serotonergic activity to modulate enkephalinergic tone. Agents that increase enkephalinergic tone more directly such as RB 120 and CI 988, at submaximal doses, did not induce conditioned place preference when co-administered with fluoxetine. These data suggest that fluoxetine, in combination with CI 988 or RB 120, might prove to be a beneficial treatment strategy for opioid drug addiction, though further studies are necessary.

Keywords: Fluoxetine; Conditioned place preference; Morphine; RB 120; CI 988; CCK_2 receptor antagonist

1. Introduction

Developing a suitable management strategy for the symptoms of drug withdrawal is becoming increasingly recognised as an important route for successful weaning of drug abusers from their source of addiction. Akaoka and Aston-Jones (1993) proposed that the use of serotonin reuptake inhibitors, such as fluoxetine, might prove to be one such strategy based on their findings that enhanced serotonergic neurotransmission attenuated opioid withdrawal-induced hyperactivity in the locus coeruleus. It was subsequently demonstrated by Rafieian-Kopeai et al. (1995) that chronic treatment with the serotonin reuptake inhibitor paroxetine attenuated negative motivational components of naloxone-induced morphine withdrawal in the place aversion paradigm.

Costall et al. (1991) suggested that the cholecystokinin receptor subtype (CCK_2) antagonist, 4-{[2-[[3-(1*H*-indol-3-yl))-2-methyl-1-oxo-2-[[(tricyclo[3,3,1,1] dec-2-yloxy) carbonyl] amino} propyl] amino]-1-phenylethyl] amino}-4-oxo-[*R*-(*R**,*R**)]-butanoate *N*-methyl-D-glucamine (formerly known as PD 134308, but now referred to as CI 988), might also be of therapeutic benefit against withdrawal symptoms (especially anxiety) generated from drugs of abuse. Interestingly, localization of CCK peptide and its receptors in the brain closely matches that of endogenous opioids and their receptors (Gall et al., 1987) and moreover, CCK_2 receptor antagonists potentiate the antinociceptive (Valverde et al., 1994) and rewarding (Valverde et al., 1996) properties of endogenous enkephalins protected by RB 101, a structural analogue of *N*-((*S*)-2-benzyl-3[(*S*) 2-amino-4-methylthio)butyldithio-]-1-oxopropyl)-L-alanine benzylester (RB 120), both of which are mixed inhibitors of enkephalin catabolism. The ability of RB 101 to elicit antidepressant-like effects and alleviate symptoms of morphine withdrawal is also potentiated by CI 988, possibly via a weak increase in enkephalin activity induced by CI

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988 (Maldonado et al., 1995). Consequently, Maldonado et al. (1995) have proposed that the combination of CCK_2 receptor antagonism (e.g., using CI 988) with enkephalinase inhibition (e.g., using RB 101) may be a potential therapy for morphine withdrawal states. Thus, it may be important to determine whether such a combined pharmacotherapy possesses inherent reinforcing properties. We have therefore employed the well-established and sensitive technique of conditioned place preference to determine whether the selective serotonin reuptake inhibitor, fluoxetine, generates positive motivational effects either alone, or in combination with CI 988, morphine or RB 120 (the orally active analogue of RB 101). This has acquired greater significance due to accumulating anecdotal clinical evidence that certain antidepressants, such as fluoxetine, can be abused by some patients (Pollack and Rosenbaum, 1991; Pagliaro and Pagliaro, 1993; Tinsley et al., 1994; Gross, 1996; Menecier et al., 1997).

2. Materials and methods

2.1. Subjects

Drug-naive, male Wistar rats (UWC stock), weighing 160–180 g (35–40 days old) at the start of the place conditioning schedule, were used in the study. Animals, housed four per cage with free access to food (standard laboratory chow) and water, were maintained at 22.0 ± 1.0°C on a 12/12 h light/dark cycle (lights on at 0800 h). All animals were allowed to habituate to laboratory conditions for at least 1 week and handled daily during this period before the study began. Experiments were performed between 10.00 and 16.00 h in a quiet room under dim red lighting conditions (< 10 lux). Experiments were performed in accordance with project licences issued under the authority of the UK Home Office Animals (Scientific Procedures) Act 1986.

2.2. Drugs

Fluoxetine hydrochloride (Eli Lily, USA) morphine hydrochloride (Martindale Pharmaceuticals, UK) and the CCK_2 antagonist, CI 988 (generously provided by Prof. J. Hughes, Parke-Davis, UK) were dissolved in saline; whereas RB 120 was dissolved in water for injection. All drugs were injected intraperitoneally (i.p.) using a dose volume of 1 ml/kg and they were administered 30 min before the animals were placed into the conditioning apparatus.

2.3. Conditioned place preference apparatus

A three-compartment conditioning chamber measuring $88 \times 36 \times 34$ cm^3 (length × width × height) was used, consisting of two compartments measuring $39 \times 36 \times 34$ cm^3 (length × width × height), one having grey sides and stippled floor, the other having black and white stripes (2 cm wide) and a smooth floor. The third compartment consisted of a white central platform 10 cm in length, 36 cm wide and raised by 2 cm, which separated the two main compartments. During the conditioning phase, compartments were isolated using guillotine doors.

2.4. Conditioned place preference procedure

The conditioned place preference procedure consisted of three phases: Habituation and Pre-test (phase 1), Conditioning (phase 2) and Test (phase 3). During phase 1, animals were allowed to explore the three compartments for 20 min each day for three consecutive days. On the third day, they were assessed for place preference (Pre-test) occupancy times (s). The compartment (grey/stippled or black/white/smooth) occupied for the least time was designated as the least preferred side. In phase 2, animals were given drug or saline on alternate days, counterbalanced over a total period of 8 days, and paired with one compartment for 30 min. Animals given saline were paired to their most preferred side, whilst those given drug were paired with their least preferred side. Following a drug-free interval of 1 day, the guillotine doors were removed and the animals were allowed free access to all compartments, the time spent in each compartment being recorded for 20 min as before (phase 3). The difference in occupancy time between the least preferred side during the pre-test stage and the test stage was taken as a measure of their place preference and, by inference, the rewarding properties of the drug.

2.5. Data analysis and statistics

Results were expressed as the mean (± S.E.M.) difference in occupancy time (s) between the post- and pre-conditioning trials such that a positive difference reflected reward. The data were analysed by one-way analysis of variance (ANOVA) coupled with either Dunnett's post hoc test to assess dose–response relationships or Student–Newman–Keuls test for drug comparison analysis.

3. Results

Analysis of the pre-test preference times across all groups of animals revealed a 40.3%:59.7% mean bias of the procedure in favour of the grey compartment of the box. This degree of bias is probably due to the highly controlled environmental conditions such as lighting and acclimatisation applied to the experiments (Mucha and Iversen, 1984).

3.1. Dose–response relationships to morphine, RB 120, fluoxetine and CI 988

Morphine induced significant conditioned place preference at the two highest doses used, 1.5 and 3.0 mg/kg

($F(3,27) = 4.068$, $P < 0.01$), saline vehicle versus morphine 1.5 mg/kg and $P < 0.05$, saline vehicle versus morphine 3 mg/kg; see Fig. 1a). The submaximal statistically inactive morphine dose of 0.75 mg/kg was used for all other subsequent drug combination experiments.

RB 120 was tested at dose levels of 5, 10 and 20 mg/kg (Fig. 1b) and only the highest dose (20 mg/kg) was found to induce conditioned place preference ($F(3,27) = 3.10$, $P < 0.05$). The subthreshold dose of 5 mg/kg was chosen for subsequent combination studies.

CI 988 failed to produce place preference at any of the doses employed over the range of 1–5 mg/kg ($F(3,26) = 1.21$, $P = 0.20$). A dose of 3 mg/kg was used for subsequent drug combination studies since this was in the mid-range of doses lacking place preference activity (Fig. 1c).

Fluoxetine produced a significant conditioned place preference by itself and this was of comparable magnitude at both 5 and 10 mg/kg ($F(3,27) = 5.56$, $P < 0.05$). The 2.5 mg/kg dose of fluoxetine did not induce significant

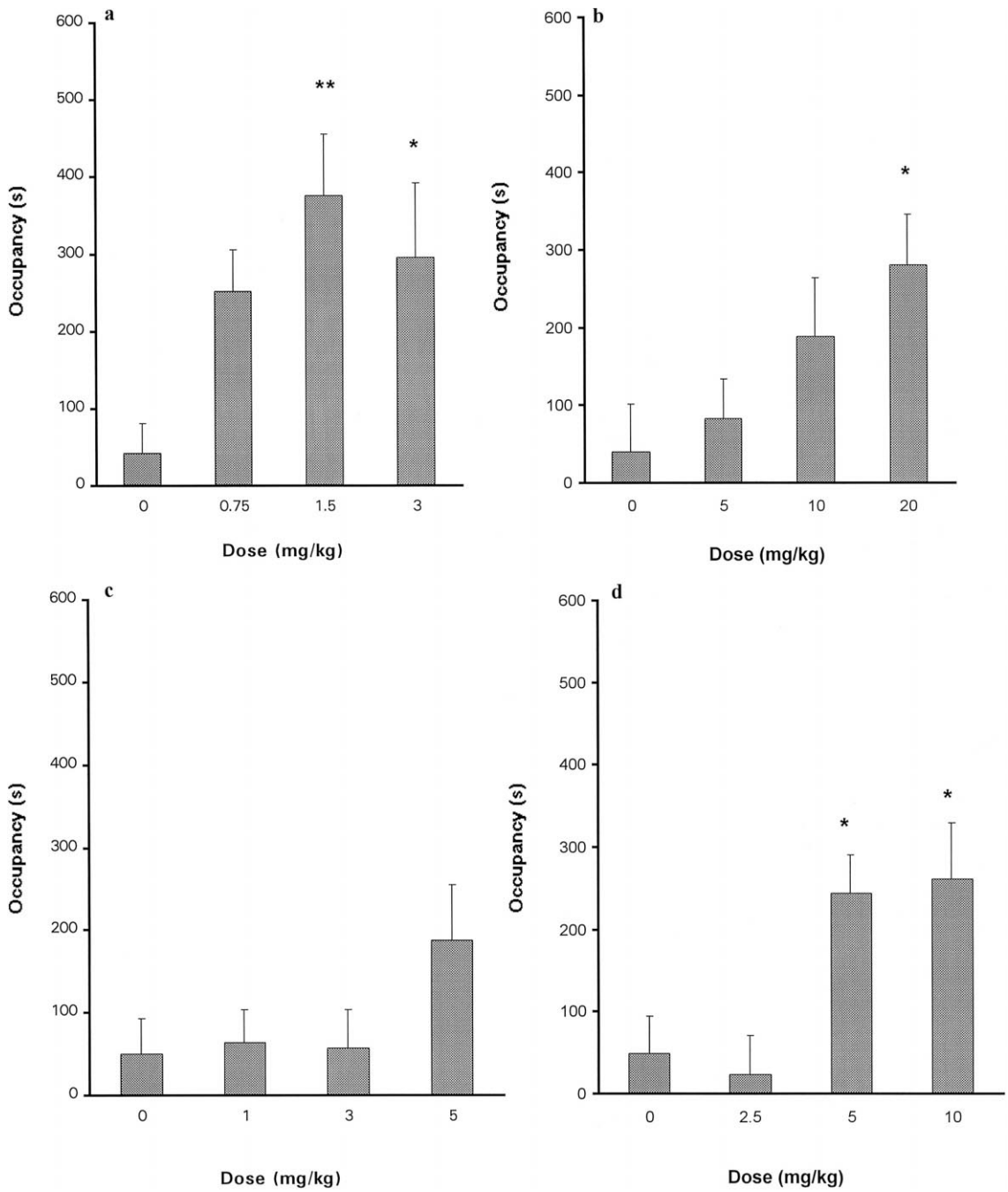

Fig. 1. The effect of saline or (a) morphine, (b) RB 120, (c) CI 988 or (d) fluoxetine on conditioned place preference. The compartment occupancy represents the mean time (±S.E.M.; $n = 7–8$) difference between the post-conditioning and pre-conditioning trials ($^{*}P < 0.05$, $^{**}P < 0.01$, ANOVA with Dunnett's post hoc test).

conditioned place preference and was therefore used as a subthreshold dose for later combination experiments (Fig. 1d).

3.2. Potentiation of morphine place preference with fluoxetine or CI 988

The combination of a subthreshold dose of either CI 988 (3 mg/kg) or fluoxetine (2.5 mg/kg) with a submaximal dose of morphine (0.75 mg/kg) produced significant place preference. Subsequent post hoc analysis using Student–Newman–Keuls test indicated that both combinations produced a highly significant increase in conditioned place preference compared to the saline control group (morphine plus fluoxetine: $F(3,27) = 20.47$, $P < 0.001$ and morphine plus CI 988: $F(3,26) = 7.78$, $P < 0.01$; Fig. 2a and d). Comparison between morphine plus fluoxetine and

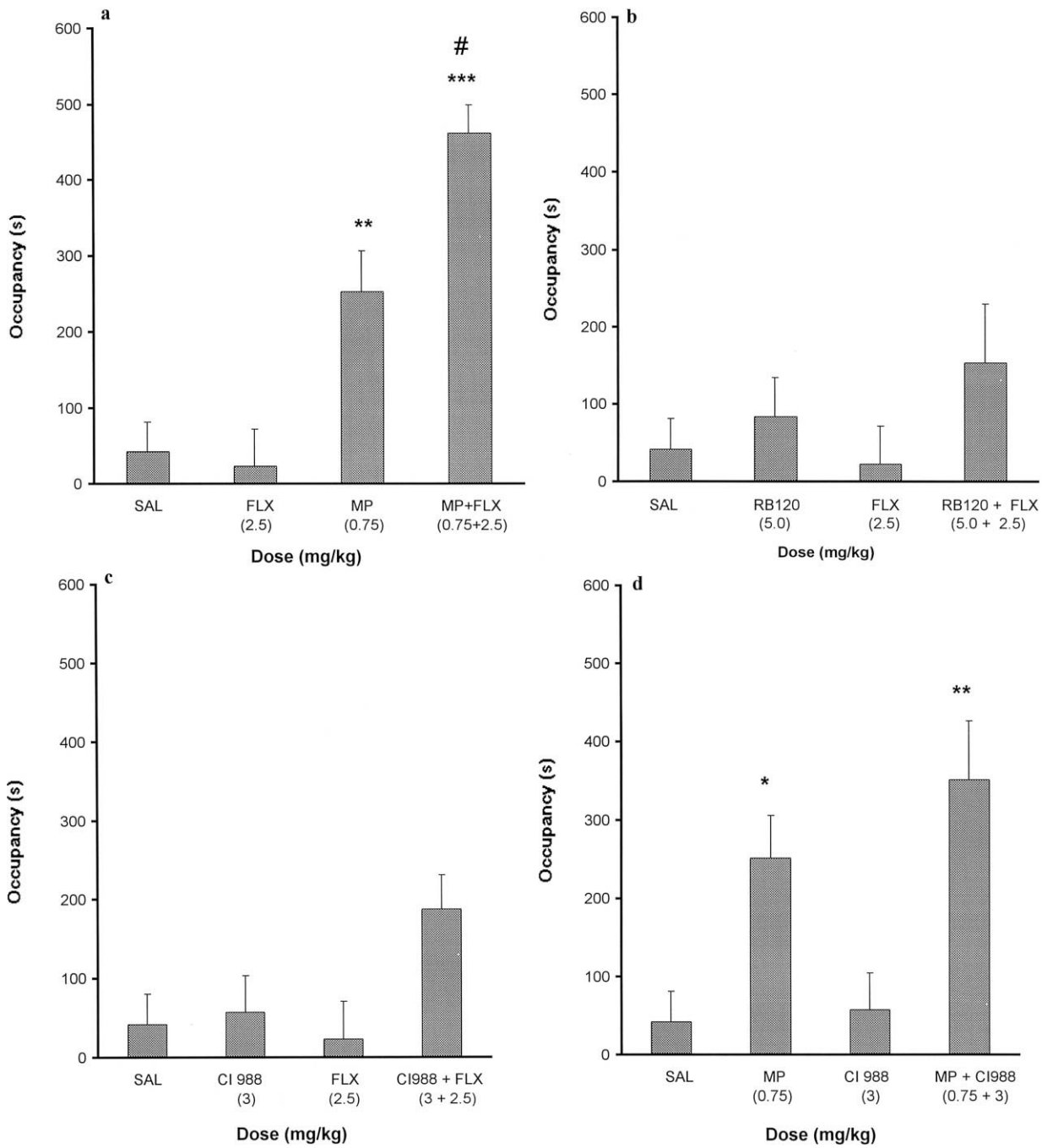

Fig. 2. The effect of combined treatment on conditioned place preference: (a) morphine (MP) and fluoxetine (FLX); (b) RB 120 and fluoxetine; (c) CI 988 and fluoxetine; and (d) morphine and CI 988. The compartment occupancy represents the mean time (±S.E.M.; $n = 7–8$) difference between the post-conditioning and pre-conditioning trials ($^{*}P < 0.01$, saline versus morphine; $^{**}P < 0.01$, morphine versus saline and morphine plus CI 988 versus saline; $^{***}P < 0.001$, morphine plus fluoxetine versus saline; $^{\#}P < 0.01$, morphine plus fluoxetine versus morphine. ANOVA followed by Student–Newman–Keuls multiple comparison test).

morphine alone also revealed a significant difference ($P < 0.01$) between the two treatment groups (Fig. 2a).

3.3. Effect of combining RB 120 or CI 988 with fluoxetine

The combination of CI 988 (3 mg/kg) or RB 120 (5 mg/kg) with fluoxetine (2.5 mg/kg) failed to produce significant conditioned place preference when compared with the saline control group (Student–Newman–Keuls multiple comparison test; $F(3,28) = 1.07$, $P = 0.38$, RB 120 plus fluoxetine and $F(3,28) = 2.87$, $P = 0.054$, CI 988 plus fluoxetine; Fig. 2b and c).

4. Discussion

It is well-established that morphine exerts positive motivational effects that can be readily demonstrated using the conditioned place preference paradigm (e.g., Phillips and Lepaine, 1980; Mucha and Iversen, 1984; Mucha and Herz, 1985, 1986; Barr et al., 1985; Bozarth, 1987). Preliminary experiments conducted with standard doses of morphine consistently produced conditioned place preference, thereby validating the conditioned place preference procedure employed in this study (see Fig. 1a). In agreement with anecdotal reports (e.g., Pollack and Rosenbaum, 1991; Pagliaro and Pagliaro, 1993; Tinsley et al., 1994; Gross, 1996; Menecier et al., 1997), we found that fluoxetine could produce conditioned place preference, that is, fluoxetine has some intrinsic positive motivational properties (Fig. 1d). We also found that a subthreshold dose of fluoxetine (2.5 mg/kg) would potentiate conditioned place preference when administered in conjunction with a submaximal dose of morphine (0.75 mg/kg). Evidence suggests that fluoxetine might act via enkephalinergic and dopaminergic mechanisms in order to elicit such effects.

In this context, antidepressants have been shown to increase both enkephalin levels (De Felipe et al., 1985) and preproenkephalin mRNA (Dziedzicka-Wasylewska and Rogoz, 1995) levels in the limbic region. Indeed, fluoxetine itself has more recently been shown to increase preproenkephalin mRNA levels by up to 200% via a serotonin-dependent mechanism (Rossby et al., 1996). Since enkephalins, and agents that elevate enkephalin levels, can give rise to conditioned place preference (Agmo and Gomez, 1991; Valverde et al., 1996), it can be argued that the weak rewarding properties of fluoxetine might reflect facilitation of enkephalinergic tone in reward-associated brain areas. It should be noted, however, that no conditioned place preference has been observed previously with CI 988, a compound known to enhance enkephalin levels (Maldonado et al., 1995), either in our laboratory or that of others (Valverde et al., 1996). In the present study, we have not observed any statistically significant conditioned place preference effect with CI 988, but it did display activity in the context of enhancing a submaximal response elicited by low-dose morphine. This is probably the result of a facilitatory effect of CI 988 on enkephalinergic tone (Valverde et al., 1996). Interestingly, combinations of fluoxetine with CI 988 or RB 120 failed to produce conditioned place preference, although in the latter instance, the subthreshold dose might have been inappropriate since higher doses of either RB 120 or fluoxetine alone appeared to possess some rewarding properties as evidenced by conditioned place preference activity.

It is possible, therefore, that mechanisms might be operative, and function synergistically, to produce the positive motivational effects associated with fluoxetine. Several studies have implicated mesolimbic dopaminergic pathways in the action of antidepressants (Papp, 1988). The role of this system in the mechanisms of reward is well documented (e.g., see Koob, 1992). Fluoxetine increases the extracellular levels of 5-hydroxytryptamine (5-HT) in the raphe nuclei, and activates somatodendritic 5-HT_{1A} and terminal autoreceptors (5-HT_{1B} 5-HT_{1D}). This effect could ultimately result in presynaptic inhibition and reduced firing of 5-HT neurones. Consequently, 5-HT biosynthesis and turnover are reduced after acute administration of fluoxetine (for review, see Stanford, 1996). This sequence of events could lead to an enhanced level of dopamine in a reward-related area such as the nucleus accumbens. Fluoxetine, may also influence the dopaminergic system indirectly via the serotonergic system. Thus, the ability of fluoxetine to induce conditioned place preference or to potentiate morphine conditioned place preference could be related to its effect on mesolimbic dopamine. In support of this concept, it has been hypothesised that conditioned place preference induced by fluoxetine arises from stimulation of raphe 5-HT_{1A} somatodendritic autoreceptors resulting in the facilitation of mesolimbic dopaminergic transmission (Collu et al., 1997). 5-HT-bearing neurones project from the dorsal raphe nucleus to A10 dopamine cell bodies in the ventral tegmentum, and A9 neurones in the substantia nigra, and also to the respective terminal fields of these dopamine neurones such as the nucleus accumbens and striatum (Van der Kooy and Hattori, 1980; Herve et al., 1987). Fluoxetine may act by increasing synaptic serotonin availability throughout the central nervous system including the striatum (Perry and Fuller, 1992) and limbic areas such as the nucleus accumbens (Guan and McBridge, 1989). This change in serotonin levels may be at least partly involved in the rewarding properties of morphine (Rockman et al., 1980). The finding that fluoxetine potentiates the rewarding properties of morphine closely accords with that of Spyraki et al. (1988) who demonstrated that serotonin-containing neurones of the nucleus accumbens are a component of the neural circuitry mediating the rewarding properties of morphine.

The present study has important implications for the use of fluoxetine and other selective serotonin reuptake inhibitors in a clinical setting. Patients may benefit from the

use of fluoxetine alone or as an adjunct in the management of pain and withdrawal from opioids and other drugs of abuse. However, care must be taken in the long-term use of selective serotonin reuptake inhibitors particularly in addicts, to prevent possible addiction to these drugs. The finding that fluoxetine has the ability to elicit conditioned place preference (Collu et al., 1997) and to potentiate morphine conditioned place preference (present findings) suggests that fluoxetine has a positive motivational component and if this is a general property of selective serotonin reuptake inhibitors, it may explain the ability of paroxetine and fluvoxamine to decrease morphine withdrawal aversion in rats (Rafieian-Kopeai et al., 1995). Furthermore, fluoxetine decreases cocaine and amphetamine self-administration in rats (Carrol et al., 1990) and improves cocaine abstinence outcome and craving in humans (Batki et al., 1995; Washburn et al., 1995), which also suggests that fluoxetine may be used as a substitute therapeutic agent in treating drug addicts. However, further studies with a range of selective serotonin reuptake inhibitors are needed to further clarify the mechanism of action and the value of these agents in the management of drug abuse, particularly with respect to possible side effect profiles of any such combinations.

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