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European Journal of Pharmacology 451 (2002) 287–293

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The effects of dopamine receptor agents on naloxone-induced jumping behaviour in morphine-dependent mice

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Received 21 May 2002; received in revised form 12 July 2002; accepted 18 July 2002

Abstract

In the present study, the effects of dopamine receptor agonists and antagonists on naloxone-induced jumping in morphine-dependent mice were examined. Mice were rendered dependent as described in the methods section. Naloxone was injected to elicit jumping (as withdrawal sign). The first group received dopamine receptor drugs before naloxone injection to test the effects of the drugs on the expression of jumping. Administration of the dopamine D1/D2 receptor agonist, apomorphine (0.25, 0.5 and 1 mg/kg), decreased jumping, but not diarrhoea, induced by naloxone. The effect of apomorphine on jumping was reduced by the dopamine D2 receptor antagonist, sulpiride. The dopamine D2 receptor agonist, quinpirole (0.1, 0.3 and 0.5 mg/kg), increased jumping, while it decreased diarrhoea in mice. Different doses of sulpiride did not alter jumping, but one dose of the drug (12.5 mg/kg) decreased jumping. Neither the dopamine D1 receptor agonist, SKF38393 (1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride; 8 and 16 mg/kg), nor the dopamine D1 receptor antagonist, SCH23390 (R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-benzazepine-7-ol maleate; 5, 10 and 25 mg/kg), altered jumping, but they decreased diarrhoea. The second group of animals received the drugs during the development of dependence. Administration of quinpirole (0.1, 0.3 and 0.5 mg/kg), but not bromocriptine (4, 8 and 16 mg/kg), apomorphine (0.25, 0.5, 1 and 2 mg/kg) or sulpiride (12.5, 25 and 50 mg/kg) decreased naloxone-induced jumping and diarrhoea. A dose of SKF38393 (8 mg/kg) decreased jumping, while both SKF38393 (4 and 16 mg/kg) and SCH23390 (5 and 10 μg/kg) increased diarrhoea. It is concluded that activation of both dopamine D1 and D2 receptors may suppress naloxone-induced jumping in morphine-dependent mice, and that stimulation of dopamine D1 receptors during development of morphine dependence may increase diarrhoea through peripheral mechanism.

Keywords: Jumping; Dopamine receptor agent; Morphine; Naloxone; (Mouse)

1. Introduction

A major factor restricting the clinical use of opioids is the fear of drug dependence (Weis et al., 1983) and their ability to induce behavioural reinforcing effects (Bilsky et al., 1992). Changes in catecholaminergic, serotonergic, cholinergic, γ-aminobutyric acid (GABAergic) or peptidergic transmission have been reported during chronic opiate administration. Central catecholamines seem to have an important role in the expression of the somatic signs of withdrawal or abstinence syndrome of opioids (see Maldonado, 1997). Several effects of morphine, such as locomotion (Zarrindast and Zarghi, 1992) and change in temperature (Zarrindast et al., 1994b), may be mediated through the dopaminergic system. Furthermore, morphine inhibits yawning (Zarrindast and Jamshidzadeh, 1992) or penile erection (Zarrindast et al., 1994a) induced by dopamine D2 receptor stimulation. The dopaminergic system also has been implicated in the expression of signs of morphine withdrawal. It has been shown that a low dose of apomorphine potentiates, while a higher dose decreases withdrawal in rodents. The effects of dopamine receptor agonists and antagonists depend, at least partly, on intact catecholaminergic neurons (El-Kadi and Sharif, 1998). It has been shown that the behavioural signs induced during morphine withdrawal are similar to those elicited by activa-

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0014-2999/02/$ - see front matter © 2002 Published by Elsevier Science B.V.
PII: S0014-2999(02)02149-0

tion by dopamine D2 receptors (Druhan et al., 2000). It has been proposed that during morphine dependence, dopamine and morphine exert opposite effects on striatal neurons, and also withdrawal is associated with a down-regulation of postsynaptic dopamine D1 and D2 receptors (Georges et al., 1999). One of the important anatomical areas that is thought to represent a site of origin of the opioid withdrawal syndrome is the locus coeruleus and nucleus accumbens (Maldonado et al., 1992; Redmond and Krystal, 1984; Self and Nestler, 1995). Mesolimbic dopaminergic neurons are thought to serve as a final common neural pathway for mediating reinforcement processes. Furthermore, long-lasting neuroadaptive changes in mesolimbic dopamine-mediated transmission that develop during chronic drug use might contribute to compulsive drug-seeking behaviour and relapse (Spanagel and Weiss, 1999). The fundamental role of the different dopamine receptor subtypes in the morphine withdrawal syndrome is not quite clear.

In the present study, the effects of dopamine receptor subtypes on the expression of jumping as a withdrawal sign, and development of morphine dependence in mice were investigated.

2. Materials and methods

2.1. Animals

Male NMRI mice (20–30 g) were housed in plastic cages in an animal room maintained at 22–25 °C on a 12-h dark cycle. Food and water were available at all times except during the experiments. Each animal was used once only and was killed immediately after the experiment.

2.2. Induction of dependence

The mice were rendered dependent on morphine, based on the method we used previously (Zarrindast and Farzin, 1996). Morphine sulfate was injected subcutaneously (s.c.) three times daily at 8, 12 and 16 h on the following dosage schedule. The three doses were 50, 50 and 75 mg/kg, respectively. The highest dose of the third daily injection was used to minimize any overnight withdrawal. Morphine administration was carried out over a maximum of 3 days for any group of mice. A dose of 50 mg/kg of morphine sulphate was also injected on the 4th day (2 h before naloxone injection). Loss of weight (8–9%) and death (1%) were observed with chronic administration of morphine sulphate.

2.3. Naloxone-induced jumping and diarrhoea

Groups of 10 mice were tested for the occurrence of jumping after their tenth injection of morphine on day 4. Two hours after the last dose of morphine (50 mg/kg), abstinence was precipitated by a subcutaneous (s.c.) injection of naloxone (2 mg/kg). Then the animals were placed individually in a Perspex observation cylinder (15-cm diameter, 50-cm height) lined with preweighed paper toweling to allow collection of wet and dry faecal material. The number of jumps was recorded immediately after naloxone injection over a 30-min period. The diarrhoea induced after naloxone administration was expressed as the weight in grams of faecal material/100 g body weight in 30 min.

2.4. Drugs

The following drugs were used: morphine sulphate (Temad, Iran), naloxone hydrochloride ampoules (Tolidaru, Iran), apomorphine hydrochloride, SCH23390, sulpiride (Sigma, Poole, UK), quinpirole and SKF38393 (research Biochemical USA) and bromocriptine (Ciba-Geigy). The drugs were injected subcutaneously (s.c.) in a volume of 5 ml/kg. The control groups received saline. The doses of drugs used were those active in previous studies (Zarrindast et al., 1999, 2000).

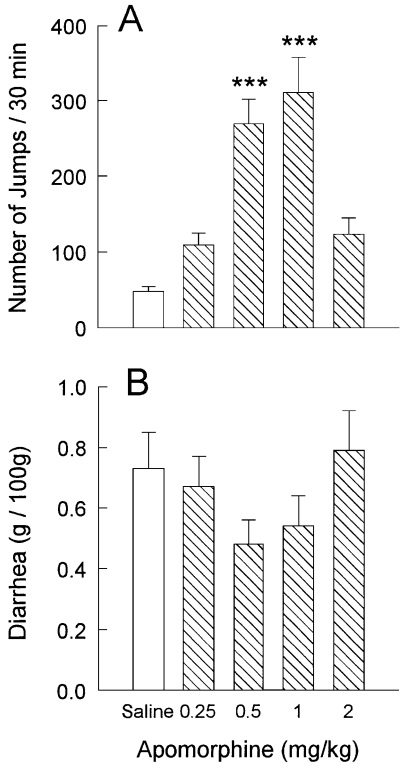

Fig. 1. Effects of apomorphine on the expression of naloxone-induced jumping and diarrhoea in morphine-dependent mice. Mice were made dependent as described in Materials and methods. All the dependent animals received naloxone (2 mg/kg) to induce jumping. The animals received saline or different doses of apomorphine (0.25, 0.5, 1 and 2 mg/kg) subcutaneously (s.c.) 15 min before naloxone administration. Each group comprised 10 mice. Data are means ± S.E.M. *** $P < 0.001$ different from the saline control group.

2.5. Statistical analysis

Analyses of variance (ANOVAs) followed by Newman–Keuls test were used for analysis of the data. Differences between means were considered statistically significant if $P<0.05$. Each point is the mean ± S.E.M. for 10 mice.

3. Results

3.1. Naloxone-induced withdrawal jumping in morphine-dependent mice

The mice were divided randomly into two groups. One group received morphine (as described in Materials and methods) to induce dependence. The other group received saline (5 ml/kg) instead of morphine subcutaneously (s.c.). Naloxone (2 mg/kg, s.c.) increased the number of jumps in morphine-dependent mice (74.3 ± 7.9; $n=10$) as compared with jumps in nondependent (saline-treated) mice (0.54 ± 0.09; $n=10$, $P<0.0001$). The results showed that naloxone can induce jumping in morphine-dependent mice. We considered jumping behaviour and diarrhoea as signs of abstinence in the other experiments of our study. Hyperactivity and Straub-tail reaction were seen after morphine injections. Loss of weight (8–9%) and death (1%) occurred with chronic administration of morphine sulphate.

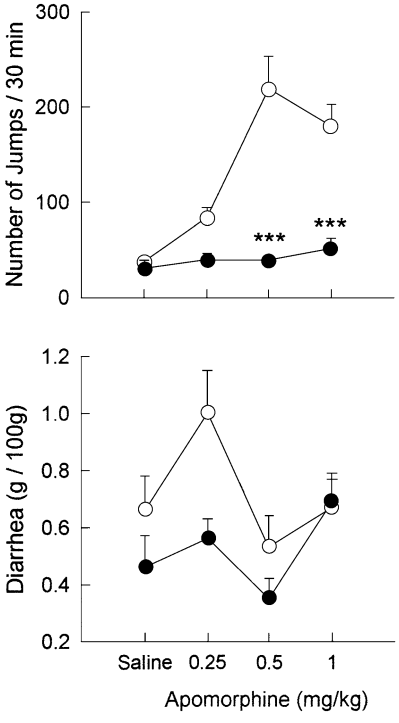

Fig. 2. Effects of sulpiride on the influence of apomorphine on expression of naloxone-induced jumping and diarrhoea in morphine-dependent mice. Mice were made dependent as described in Materials and methods. All the dependent animals received naloxone (2 mg/kg) to induce jumping or diarrhoea. The animals received different doses of apomorphine (0.25, 0.5 and 1 mg/kg) or apomorphine plus sulpiride (50 mg/kg). Apomorphine was administered 15 min and sulpiride 60 min before naloxone injection. Each group comprised 10 mice. Data are means ± S.E.M. $***P<0.001$ different from respective apomorphine control groups.

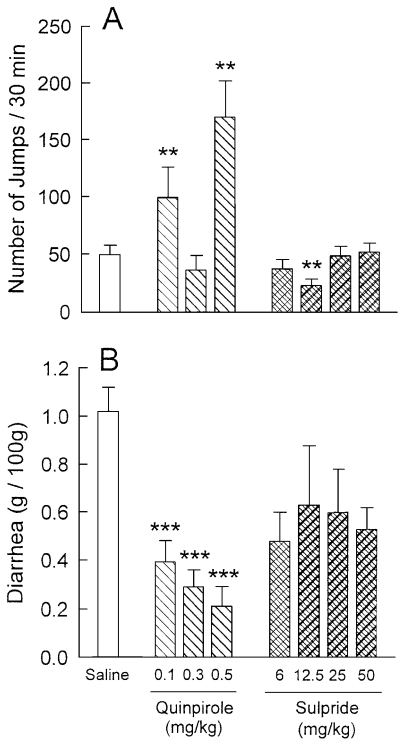

Fig. 3. Effects of quinpirole or sulpiride on the expression of naloxone-induced jumping and diarrhoea in morphine-dependent mice. All the dependent animals received naloxone (2 mg/kg) to induce jumping. The animals received different doses of quinpirole (0.1, 0.3 and 0.5 mg/kg) or sulpiride (6, 12.5, 25 and 50 mg/kg). Apomorphine was administered 15 min and sulpiride 60 min before naloxone injection. Each group comprised 10 mice. Data are means ± S.E.M. $**P<0.01$, $***P<0.0001$ different from respective saline control group.

3.2. Effect of dopamine receptor agonists and antagonists on expression of naloxone-induced jumping behaviour and diarrhoea in morphine-dependent mice

The dose–response curve for the dopamine receptor agonist, apomorphine, on the expression of naloxone-induced jumping and diarrhoea is shown in Fig. 1. All animals received morphine (s.c.) three times daily for 3 days in order to induce dependence on morphine as described earlier. Different doses of apomorphine were injected 15 min before naloxone on day 4, and then the number of jumps was recorded. The subcutaneous (s.c.) administration of apomorphine (0.25, 0.5, 1 and 2 mg/kg) before the expression of withdrawal increased naloxone-induced jumping [one-way ANOVA, $F(4,45)=15.6$,

$P<0.0001$, $n=10$ in each group] in morphine-dependent animals. The maximum effect of the drug was obtained with 0.5 mg/kg. The severity of diarrhoea was unchanged [$F(4,45)=1.5$, $P>0.05$, $n=10$ in each group].

The effects of apomorphine in the presence of the dopamine D_2 receptor antagonist sulpiride is shown in Fig. 2. Two-way ANOVA shows that administration of sulpiride (50 mg/kg) 60 min before apomorphine (0.25, 0.5 and 1 mg/kg) decreased the apomorphine response on jumping [factor apomorphine, $F(3,72)=11.9$, $P<0.0001$; factor sulpiride, $F(1,72)=45.7$, $P<0.0001$; factor apomorphine × sulpiride, $F(3,72)=10.7$, $P<0.0001$; $n=10$ in each group].

The effects of the dopamine D_2 receptor agonist, quinpirole, and the dopamine D_2 receptor antagonist, sulpiride, on the expression of naloxone-induced jumping behaviour and diarrhoea in morphine-dependent mice is shown in Fig. 3. Quinpirole was injected 15 min and sulpiride 60 min prior to naloxone on day 4, and then the number of jumps was recorded.

One-way ANOVA indicated a significant difference between jumping of the animals in the presence or absence of quinpirole (0.01, 0.3 and 0.5 mg/kg) and sulpiride (6, 12.5, 25 and 50 mg/kg) [$F(7,72)=8.9$, $P<0.0001$, $n=10$]. Further analysis showed that quinpirole increased and a dose of sulpiride (12.5 mg/kg) decreased jumping. One-way ANOVA also showed a significant difference between diarrhoea induced in the animals in the presence or absence of quinpirole and sulpiride [$F(7,72)=3.4$, $P<0.05$, $n=10$]. Post hoc analysis showed that quinpirole but not sulpiride decreased diarrhoea.

The effects of the dopamine D1 receptor agonist, SKF38393, and the dopamine D1 receptor antagonist, SCH23390, on the expression of naloxone-induced jumping behaviour and diarrhoea in morphine-dependent mice is shown in Fig. 4. SKF38393 was injected 15 min and SCH23390 15 min prior to naloxone on day 4, and then the number of jumps was recorded.

One-way ANOVA indicated that administration of SKF38393 (8 and 16 mg/kg) and SCH23390 (5, 10 and 25 μg/kg) did not alter jumping in the animals [$F(5,54)=1.0$, $P>0.05$, $n=10$]. However, a significant difference was found between diarrhoea in the animals in the presence or absence of SKF38393 and SCH23390 [$F(5,54)=6.0$, $P<0.001$, $n=10$]. Further analysis showed that both drugs decreased diarrhoea.

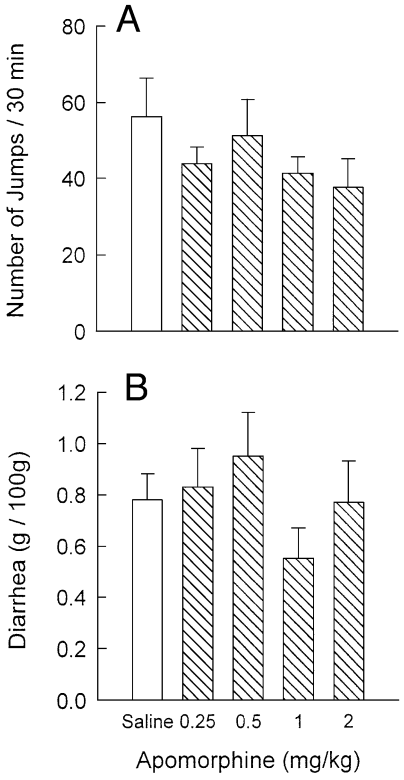

Fig. 5. Effects of apomorphine on the development of morphine dependence in mice. Animals were made dependent as described in Materials and methods. The animals received saline or different doses of apomorphine (0.25, 0.5, 1 and 2 mg/kg, s.c.) 30 min after the second and third daily dose of morphine, on days 2 and 3 (during development of dependence on morphine). Naloxone (2 mg/kg) was used on day 4 to elicit jumping and diarrhoea. Each group comprised 10 mice. Data are means ± S.E.M. Apomorphine did not alter jumping or diarrhoea.

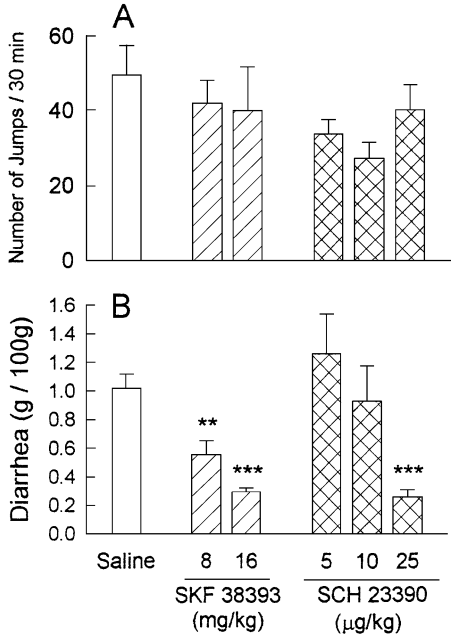

Fig. 4. Effects of SKF38393 or SCH23390 on the expression of naloxone-induced jumping and diarrhoea in morphine-dependent mice. All the dependent animals received naloxone (2 mg/kg) to induce jumping. The animals received different doses of SKF38393 (8 and 16 mg/kg) or SCH23390 (0.005, 0.01 and 0.025 μg/kg). SKF38393 and SCH23390 were administered 15 min before naloxone injection. Each group comprised 10 mice. Data are means ± S.E.M. $^{**}P<0.01$, $^{***}P<0.0001$ different from respective saline control group.

3.3. Effect of dopamine receptor agonists and antagonists on development of morphine dependence

All animals received morphine (s.c.) three times daily for 3 days in order to induce dependence on morphine as described earlier. Different doses of apomorphine, bromocriptine, quinpirole or SKF38393, sulpiride and SCH23390 were administered 30 min after morphine administration of the second and third doses of morphine on day 2 and day 3. The number of jumps was recorded on day 4 after naloxone injection. One-way ANOVA showed that administration of different doses of apomorphine (0.25, 0.5, 1 and 2 mg/kg; during development of morphine dependence) did not alter jumping [$F(4,45)=0.99$, $P>0.05$, $n=10$] or diarrhoea [$F(4,45)=1.04$, $P>0.05$, $n=10$](Fig. 5). One-way ANOVA showed a significant difference between jumping [$F(9,90)=3.2$, $P<0.01$] or diarrhoea [$F(9,90)=3.5$, $P<0.001$, $n=10$] induced by naloxone in the presence or absence of bromocriptine (4, 8 and 16 mg/kg), quinpirole (0.1, 0.3 and 0.5 mg/kg) and sulpiride (12.5, 25 and 50 mg/kg). Further analysis showed that only a dose of 0.5 and 0.3 mg/kg of quinpirole, but not the other drugs, decreased jumping and diarrhoea, respectively (Fig. 6).

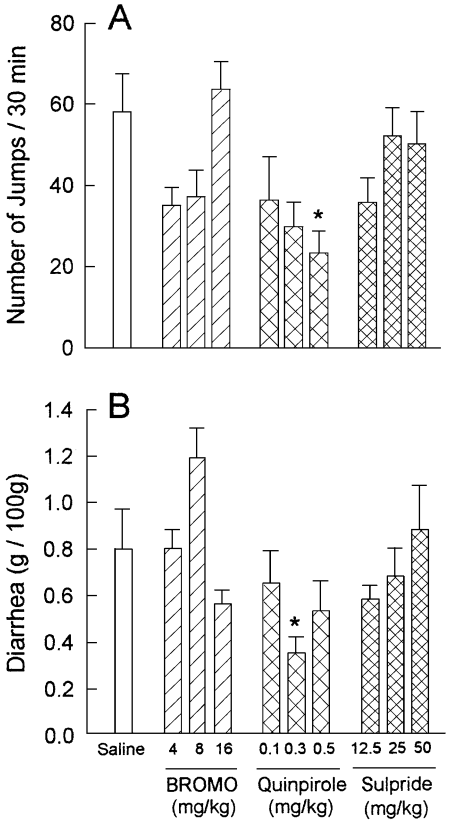

Fig. 6. Effects of D2 dopamine receptor agonists and antagonist on the development of morphine dependence in mice. The dependent mice received different doses of bromocriptine (BROMO; 4, 8 and 16 mg/kg, s.c.), quinpirole (0.1, 0.3 and 0.5 mg/kg) or sulpiride (12.5, 25 and 50 mg/kg). The drugs were injected 30 min after the second and third daily dose of morphine, on days 2 and 3 (during development of dependence on morphine). Naloxone (2 mg/kg) was used on day 4 to test jumping and diarrhoea. Each group comprised 10 mice. Data are means ± S.E.M. * $P<0.05$ different from saline control group.

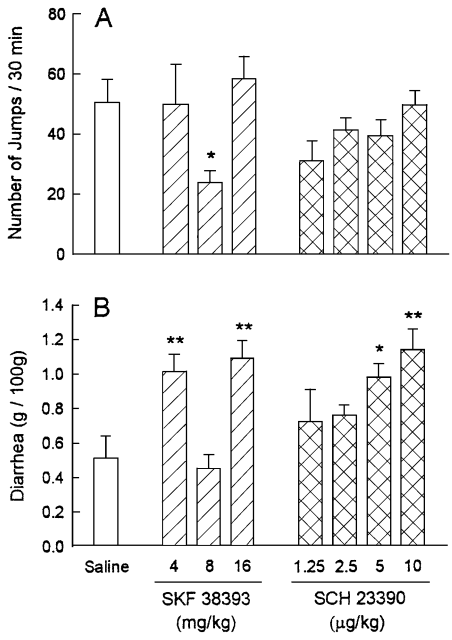

Fig. 7. Effects of D1 dopamine receptor agonist and antagonist on the development of morphine dependence in mice. The dependent mice received different doses of SKF38393 (4, 8 and 16 mg/kg) or SCH23390 (1.25, 2.5, 5 and 10 μg/kg). The drugs were injected 30 min after the second and daily third dose of morphine, on days 2 and 3 (during development of dependence on morphine). Naloxone (2 mg/kg) was used on day 4 to test jumping and diarrhoea. Each group comprised 10 mice. Data are means ± S.E.M. * $P<0.05$, * * $P<0.01$ different from saline control group.

The effects of SKF38393 and SCH23390 on the development of morphine dependence in mice is shown in Fig. 7.

One-way ANOVA indicated a significant difference between jumping [$F(7,72)=2.6$, $P<0.05$, $n=10$] and diarrhoea [$F(7,72)=5.3$, $P<0.0001$, $n=10$] induced by naloxone in the animals treated with either saline or SKF38393 (4, 8 and 16 mg/kg) and SCH23390 (1.25, 2.5, 5 and 10 μg/kg) during the development of morphine dependence. Further analysis showed that a dose of SKF38393 (8 mg/kg) decreased jumping, while both of the drugs increased diarrhoea.

4. Discussion

This study was designed to investigate the involvement of dopamine receptor subtypes in morphine dependence. Several neurotransmitters seem to be involved in morphine tolerance and dependence (Bhargava, 1994; Bourin, 1999). There is considerable evidence implicating the mesolimbic dopaminergic system as a major neural substrate for the reinforcement and dependence produced by opioids (see Introduction).

As expected and consistent with our previous reports (Rezayat et al., 1994), subchronic administration of morphine (for 3 days) and administration of naloxone on the fourth day induced jumping behaviour and diarrhoea in mice.

Two types of dopamine receptors, D1 and D2, have been distinguished on the basis of pharmacological and biochemical data. The dopamine D1 stimulates adenylate cyclase while dopamine D2 inhibits it (Kebabian and Calne, 1979). Gene cloning studies have split these into further subgroups (Sibley and Monsma, 1992; Givelli et al., 1993). The dopamine D1 family now includes dopamine D1 and D5, while the D2 family has been split into D2, D3 and D4. These subtypes of dopamine receptors are distinct molecular entities (Nielsen et al., 1984; Dumbrille-Ross et al., 1985) with different distributions (Altar et al., 1985; Dowson et al., 1985; Dubois et al., 1986).

Our present results show that administration of the D1/D2 dopamine receptor agonist, apomorphine (Seeman, 1980; Creese et al., 1983; Stoof and Kebabian, 1984), and the dopamine D2 receptor agonist, quinpirole (Bach et al., 1980), before naloxone injection increased jumping and decreased diarrhoea in subchronic morphine-treated mice. The results may indicate that the dopamine D2 receptor subtype is involved in jumping behaviour. This hypothesis can be further supported by our data showing that sulpiride, a dopamine D2 receptor antagonist (Di Chiara et al., 1976; Costal et al., 1980; Kendler et al., 1982; Stoof and Kebabian, 1984), decreased the response to apomorphine. Therefore, in agreement with others (Druhan et al., 2000), the dopamine D2 receptor activation seems to induce an opposite effect to that of morphine on the expression of withdrawal signs. Despite the opioid receptor down-regulation in response to chronic morphine exposure in vitro and in vivo (Morris and Herz, 1989; Ronnekleiv et al., 1996), there is a strong up-regulation of the cAMP system (Nestler et al., 1993). Since dopamine D2 receptor activation may decrease cAMP (Kebabian and Calne, 1979), one can therefore expect that the change in cAMP causes an increase in naloxone-induced jumping in morphine-dependent mice. In the present study, a low dose of sulpiride (12.5 mg/kg) by itself decreased jumping in the animals, which may be due to the release of endogenous dopamine and activation of postsynaptic dopamine receptors. The expression of diarrhoea was decreased by quinpirole. Thus, it seems likely that dopamine D_2 subtype stimulation is involved in jumping, while changes in diarrhoea may be due to a peripheral effect. Our present data further show that administration of both the D1 dopamine receptor agonist, SKF38393 (Setler et al., 1978; Stoof and Kebabian, 1982), and the dopamine D1 receptor antagonist, SCH23390 (Iorio et al., 1983; Hyttel, 1984), before naloxone injection decreased diarrhoea but did not alter the expression of jumping in subchronic morphine-treated mice. The data indicate that a dopamine D1 receptor mechanism does not influence jumping. Whether the effect of the agonist and/or antagonist on diarrhoea is elicited through a central or peripheral mechanism needs further investigation.

When apomorphine, quinpirole, SKF38393 or sulpiride was used during the development of dependence, quinpirole decreased naloxone-induced jumping and diarrhoea indicating that dopamine D2 receptor stimulation during dependence on morphine may increase jumping withdrawal signs. Down-regulation of postsynaptic dopamine receptors, on effect on striatal neurons (Georges et al., 1999), or alteration in the up-regulation of the cAMP system, which induced by chronic morphine administration (Nestler et al., 1993), may be involved. However, it should be noted that some investigators (Diana et al., 1999), who used single-cell extracellular recording techniques to quantify the somatic signs of morphine withdrawal, proposed that dopaminergic activity in the mesolimbic system does not participate in the neurobiological mechanisms responsible for somatic withdrawal. Since administration of a dose of SKF38393 during the development of morphine dependence decreased jumping, but increased diarrhoea, there is a possibility that the influence of the drug on diarrhoea be mediated peripherally. Furthermore, SCH23390 also increased diarrhoea. This effect of the D1 dopamine receptor agonist may be due to the blockade of other neurotransmitter systems such as the serotonergic system.

Acknowledgements

The authors wish to thank Dr. Touraj Nayer Nouri for his assistance in preparing this manuscript.

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