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Original Article

The Effects of Dopamine Receptor Agents on Swim Stress-Induced Inhibition of Naloxone-Induced Jumping Behavior in Morphine-Dependent Mice

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Abstract

In the present study, interactions of dopamine receptor agonists and antagonists with water swimming stress (WSS) on naloxone-induced jumping in morphine-dependent mice were examined. Mice were rendered dependent as described in the methods section. The opioid receptor antagonist, naloxone (1 mg/kg), was injected to elicit jumping (as a withdrawal sign). The first group exposed to WSS in the presence or absence of dopamine receptor drugs, before naloxone injection, in order to test the interaction of dopamine receptor mechanisms with WSS on expression of jumping behavior. When the animals were exposed to WSS for periods of 0.5, 1 or 3 min, 15 min prior to naloxone injection, WSS administration for a period of 3 min decreased the expression of jumping, but not diarrhea induced by naloxone. The D1 receptor agonist, SKF38393 (1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride; 8 and 16 mg/kg), D1 receptor antagonist, SCH 23390 (R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1Hbenzazepine=7-ol maleate; 0.0025 and 0.005 mg/kg), D2 receptor agonist, quinpirole (0.3 and 0.5 mg/kg) and D2 receptor antagonist, sulpiride (50 mg/kg), potentiated the inhibition of jumping induced by WSS. Quinpirole, but not other dopamine receptor agents, increased diarrhea. In the second group of animals, effects of the dopamine receptor drugs; during development of morphine dependence, in the presence of WSS administration were tested. Administration of apomorphine (1 and 2 mg/kg) or SKF 38393 (8 mg/kg) in the presence of WSS, during the development of morphine dependence increased jumping, while quinpirole (0.5 mg/kg) decreased diarrhea. In contrary, neither sulpiride nor SCH 23390 did not alter jumping or diarrhea induced by naloxone. It could be concluded that dopamine receptor mechanism(s) and/or WSS could be related the development of morphine dependency.

Key words: Jumping; Swim-stress; Morphine; Naloxone; Dopamine receptor agents; Mouse.

Introduction

Chronic use of opioids may induce drug dependence (1) and behavioral reinforcing effects (2). Central catecholamines seem to have an important role in the expression of the somatic signs of withdrawal and the abstinence syndrome of opioids (3). Several effects of morphine, such as locomotion (4) and change in

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temperature (5), may be mediated through the dopaminergic system. Furthermore, morphine inhibits yawning (6) or penile erection (7) are induced by dopamine D2 receptor stimulation. The action of morphine at opiate receptors has been reported to decrease the number (8) and activity (9) of D2 receptors. Chronic morphine treatment has been reported to cause development of hyperactivity within the dopaminergic system (10). Behavioral signs induced during morphine withdrawal are similar to those elicited during activation by dopamine D2 receptors (11). 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 (12). Several biochemical changes have also been described in noradrenergic neurons of the lucus coeruleus (LC) after chronic morphine treatment (13).

Furthermore, various studies have shown that stress produces a reduction in various dopamine affected behaviors, including locomotor activity in an open field (14), avoidance and escape behavior in maze (15) and swimming activity (16). As previously reported, reduced central noradrenergic function has been involved as a factor in reduced behavioral activity after stress (17, 18). Noradrenaline levels were suppressed by stress in the dorsal cortex and lucus coeruleus of mice. While, stress produced lower dopamine levels in the hypothalamus, dopamine levels demonstrated a marked increase in the amygdala of mice. Furthermore, stress induced an increase in dopamine turnover in the lucus coeruleus of mice.

In the present study, the influence of water swimming-stress (WSS) in the presence or absence of dopamine receptor agents on the expression of jumping as a withdrawal sign, and development of morphine dependence in mice has been investigated.

Experimental

Materials

Animals

Male NMRI mice (20-30g) were used In this study. They were housed in plastic cages in an animal room maintained at 22±3 °C with a light cycle of 12h light/12h darkness (lights on at 7:30 am.). Standard food and water were freely available at all times except during the experiments. Each animal was used only once.

Drugs

Morphine sulphate (Temad, Iran), naloxone hydrochloride ampoules (Tolidaru, Iran), SCH 23390, sulpiride, apomorphine hydrochloride (Sigma, Poole, UK), quinpirole and SKF 38393 (Research Biochemical USA) were used. The doses of drugs used were those found to be active in a previous study [19].

Methods

Stress procedure

Mice were subjected to swim stress (0.5,1 and 3 min swimming at 20°C). The swimming tank (28cm diameter, 25cm height) was filled up with water up to a height of 15 cm. After swimming, the animals were dried by a towel and placed near the heater.

Induction of dependence

The mice were rendered dependent on morphine, based on the method used previously (19). Morphine sulphate was injected subcutaneously (s.c.) three times daily at 8, 12 and 16 h (with 4 intervals), based 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 all groups of mice. A dose of 50 mg/kg of morphine sulphate was also injected on the 4^{th} day (2 h before naloxone injection). Weight loss (8-9%) and death (1%) were observed during chronic administration of morphine sulphate.

Naloxone-induced Jumping and Diarrhea

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 (1 mg/kg). Then animals were placed individually in a Perspex observation cylinder

(15 cm diameter, 50 cm height) lined with pre-weighed 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 diarrhea induced after naloxone administration was expressed as the weight in grams of faecal material/100g body weight in 30 min.

Drug Treatment

The animals received 10 injections of morphine in order to develop dependence to morphine. The number of jumps induced by naloxone was compared to those that received 10 injections of saline instead of morphine. Drugs were injected either before naloxone administration (effect of drugs on the expression) or during the development of dependency to morphine (effect of drugs on the development).

Experiment 1: Effect of water swimming-stress (WSS) on the expression of naloxone-induced jumping.

All the animals were rendered dependent on morphine. One group of animals received no WSS. Other groups of animals were exposed to WSS for periods of 0.5, 1 and 3 min, 15 or 30 min before naloxone administration and compared with the non-exposed-WSS control group. The number of jumps (Figure 1A) and diarrhea (Figure 1B) after naloxone administration were recorded in order to test the effect of WSS on expression of morphine withdrawal signs.

Experiment 2: Effect of dopamine receptor agents, in the presence of WSS, on the expression of naloxone-induced withdrawal signs.

The morphine dependent animals received either saline (5 ml/kg) or SKF 38393 (8 and 16 mg/kg), SCH 23390 (0.0025 and 0.005 mg/kg), quinpirole (0.3 and 0.5 mg/kg) and sulpiride (25 and 50 mg/kg) 30 min, and WSS 15 min before naloxone injection. The number of jumps or diarrhea were recorded for 30 min after naloxone injection (Table 1).

Experiment 3: Effects of WSS on the development of naloxone-induced jumping and diarrhea in the morphine dependent mice.

The morphine dependent animals were forced to swim for different periods of time (0.5, 1 and 3 min), on day 2 and day 3; 15 min either after the first morphine injection (2 Stress), or first and second morphine injections (4 Stress) or first, second and third morphine injections (6 Stress), during development of morphine dependence. The number of jumps (Figure 2A) or diarrhea (Figure 2B) were recorded for a period of 30 min, on day 4 after naloxone injection and compared with the non-exposed-WSS control group.

Experiment 4: Effects of apomorphine in the presence or absence of WSS on development of morphine dependence.

The first group of morphine dependent animals received either saline (5 ml/kg) or different doses of apomorphine (0.25, 0.5, 1 and 2 mg/kg), 30 min after injections of morphine, on day 2 and day 3 during development of morphine dependence. The second group of morphine dependent animals received WSS (for a period of 3 min), 15 min, and saline or different doses of apomorphine (0.25, 0.5, 1 and 2 mg/kg) 30 min after morphine injections, on day 2 and day 3, during development of morphine dependence. The number of jumps (Figure 3A) or diarrhea (Figure 3B) were recorded on the fourth day, after naloxone administration in order to test effect of apomorphine on inhibition of naloxone-induced withdrawal signs by WSS.

Experiment 5: Effect of dopamine receptor agents, in the presence of WSS, on the development of morphine dependency.

The animals received either saline (5 ml/kg) or SKF38393 (8 and 16 mg/kg), SCH 23390 (0.0025 and 0.005 mg/kg), quinpirole (0.3 and 0.5 mg/kg) or sulpiride (25 and 50 mg/kg) 30 min, and WSS 15 min after morphine injections, on the day 2 and 3, during development of morphine dependence. The number of jumps (Figure 4A) or diarrhea (Figure 4B) wererecorded on day 4 after naloxone injection.

Statistical analysis

Data were analyzed by using one-way or two-way analysis of variance (ANOVA), followed by Newman-Keuls post-hoc tests. The results were considered significant at $p<0.05$. Data obtained are reported as mean ± SEM for 10 mice.

Results and discussion

Naloxone-induced jumping in morphine-dependent mice

The animals were divided into two groups. The first group received three doses of morphine for three days

, in order to induce dependence. The second group received saline (5 ml/kg), instead of morphine, subcutaneously (s.c.). Naloxone (1 mg/kg, s.c.) increased the number of jumps in morphine-dependent mice (73.5±6.8; n=10), compared with the non-dependent (control saline-treated) mice (0.70±0.6; n=10, $p<0.05$). Jumping and diarrhea were considered as withdrawal in the other experiments. Hyperactivity and Straub-tail were seen after morphine administration. Weight loss (8-9%) and death (1%) were observed with chronic injection of morphine sulphate.

In agreement with our previous report (20), the present data showed that chronic administration of morphine (for 3 days) and administration of naloxone on fourth day induced jumping behavior and diarrhea in mice.

Effect of water swimming-stress (WSS) or dopamine receptor agents in the presence of WSS on expression of naloxone-induced jumping behavior and diarrhea in morphine-dependent mice

Figure1 indicates the effect of WSS on the expression of naloxone-induced withdrawal signs.

All animals received morphine, (s.c.) three times daily for 3 days in order to induce dependence on morphine, as described earlier. One-way ANOVA showed that when animals were forced to swim for different periods of times (0.5, 1 and 3 min), 15 min [$F(3,36)=5.9$, $p<0.01$] or 30 min [$F(3,36)=4.18$, $p<0.05$] before naloxone injection, 3 min WSS decreased jumping but not diarrhea.

Our present results show that administration of water swimming-stress (WSS) before naloxone, reduced the expression of jumping. It has been reported that endogenous opioid released into the ventral tegmental area in response to stress, modulates mesocorticolimbic dopamine (21). Therefore, the possibility may exist that response induced by WSS is due to such mechanism.

Table 1 indicates the effect of dopamine receptor drugs on inhibition of expression of naloxone-induced jumping by WSS. The morphine-dependent animals were forced to swim for a period of 3 min, 15 min prior to naloxone injection. Dopamine receptor agents were used 30 min before naloxone administration, and the number of jumps were recorded following naloxone injection. One-Way ANOVA revealed that administration of different doses of dopamine D1 receptor agonist, SKF 38393 (8 and 16 mg/kg), dopamine D1 receptor antagonist, SCH 23390 (0.0025 and 0.005 mg/kg), dopamine D2 receptor agonist, quinpirole (0.3 and 0.5 mg/kg) and dopamine D2 receptor

Table 1. Effect of dopamine receptor agents on the expression of naloxone-induced

++Treatment(mg/kg,i.p.)	Number of jumps/30 min (mean±S.E.M)	Diarrhea (g/100g) (mean±S.E.M)
Saline (5 ml/kg)	6.2±3.24	0.17±0.05
SKF 38393 8	0.0±0.0**	0.19±0.03
SKF 38393 16	0.0±0.0**	0.45±0.13
Quinpirole 0.3	0.0±0.0**	0.76±0.18**
Quinpirole 0.5	0.0±0.0**	0.87±0.16***
Sulpiride 25	0.0±0.0**	0.16±0.06
Sulpiride 50	0.0±0.0**	0.14±0.03
SCH 23390 0.0025	0.0±0.0**	0.21±0.03
SCH 23390 0.005	0.0±0.0**	0.27±0.04

withdrawal signs in the presence of swimming-stress (WSS). The morphine dependent animals received WSS for a period of 3 min, 15 min and saline or dopamine receptor agents 30 min before naloxone injection. The number of jumps were recorded after naloxone administration. Each group comprised 10 mice. Data are presented as mean±S.E.M. *$p<0.05$, **$p<0.01$, ***$p<0.001$ different from the saline control group.

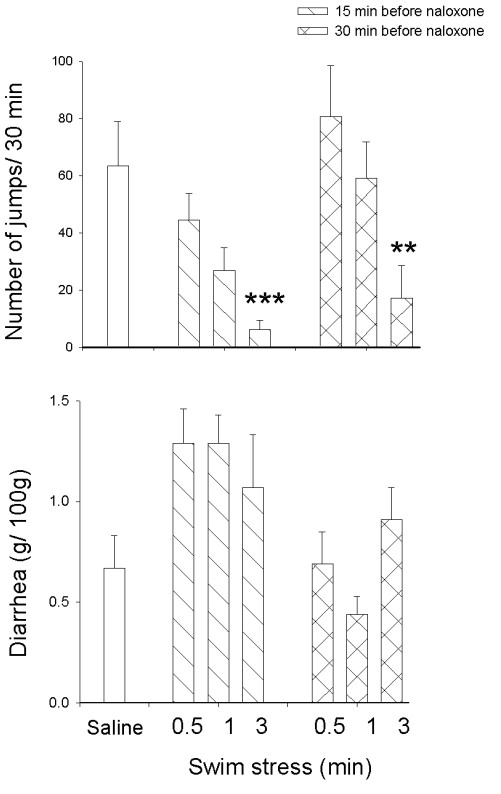

Figure 1. Effect of WSS on the expression of naloxone-induced jumping and diarrhea in morphine dependent mice. Mice became dependent as described in the Material and methods section. All the dependent animals received naloxone (1 mg/kg) to induce jumping. Animals were exposed to WSS (for periods of 0.5, 1 and 3 min), 15 or 30 min before naloxone administration and compared with the non-exposed WSS control group. Each group comprised of 10 mice. Data are presented as means±S.E.M. **p<0.01, ***p<0.001 different from the non-exposed WSS control group.

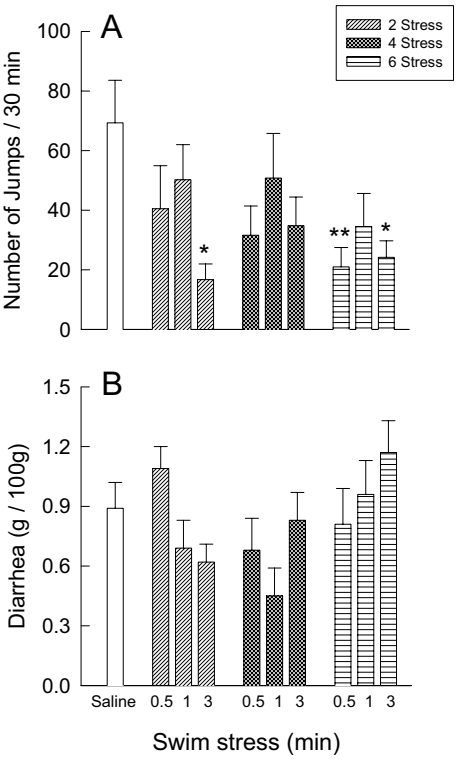

Figure 2. Effect of WSS on the development of naloxone-induced jumping and diarrhea in morphine dependent mice. The animals were forced to swim for different periods of time (0.5, 1 and 3 min), on days 2 and 3; either 15 min after the first morphine injection (2 Stress), or first and second morphine injections (4 Stress) or first, second and third morphine injections (6 Stress), during the development of morphine dependence. The number of jumps were recorded on day 4 after naloxone injection and compared with the non-exposed WSS control group. Each group comprised of 10 mice. Data are presented as mean±S.E.M. * p<0.05, ** p<0.01 different from the non-exposed WSS.

antagonist, sulpiride (25 and 50 mg/kg), 30 min before naloxone injection potentiated the inhibition of naloxone-induced jumping by WSS [$F(8,81)=3.66$, $p<0.01$].

One-Way ANOVA also showed that administration of quipirole (0.3 and 0.5 mg/kg), but not SKF 38393 (8 and 16 mg/kg), SCH23390 (0.0025 and 0.005 mg/kg) or sulpiride (50 mg/kg), in the presence of WSS, increased diarrhea [$F(8,81)=8.1$, $p<0.0001$].

The complex behaviors, such as tolerance, dependence, sensitization and craving, that characterize the addicted state, appear to result from nueroadaptations at the receptor/effector level. It has been shown that chronic morphine treatment results in the development of central supersensitivity of dopaminergic receptors (22, 23). The enhancement of dopaminergic transmission by dopamine receptor agonists could produce withdrawal symptoms, such as jumping "wet dog" shakes and hypothermia, but inhibits other withdrawal symptoms such as body weight loss.

Two dopamine receptor subtypes, named 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 (24). Gene cloning studies have split these into further subgroups (25, 26). The dopamine D1 family is now known to include dopamine D1 and D5, while the D2 family has been split into D2, D3 and D4 subtypes**.** These subtypes

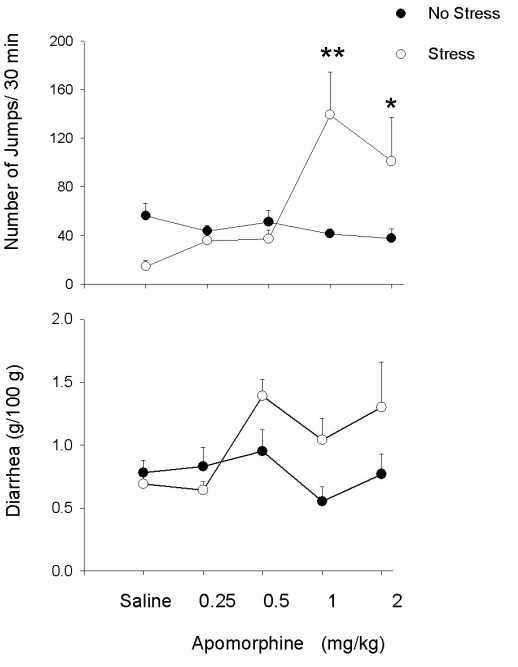

Figure 3. Effect of apomorphine in the presence or absence of WSS on the development of naloxone-induced withdrawal signs. The animals received saline (5 ml/kg) or different doses of apomorphine (0.25, 0.5, 1 and 2 mg/kg) 30 min after the second and third doses of morphine injections, on days 2 and 3, in the presence (○) or absence of WSS (●) (as in figure 2). The number of jumps were recorded on day 4 after naloxone injection. Each group comprised of 10 mice. Data are presented as mean±S.E.M. *p<0.05, **p<0.01 different from the saline control group

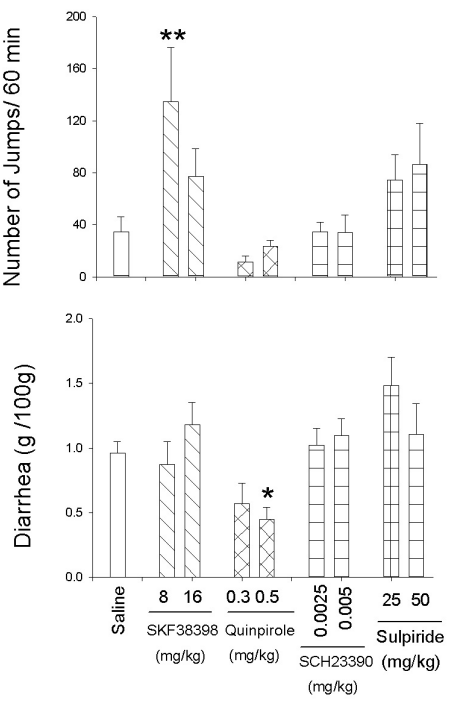

Figure 4. The effect of dopamine receptor agents in the presence or absence of WSS on the development of naloxone-induced withdrawal signs. The animals were forced to swim for different periods of 3 min, 15 min and under saline or different doses of dopamine D1 receptor agonist, SKF 38393 (8 and 16 mg/kg), dopamine D1 receptor antagonist, SCH 23389 (0.0025 and 0.005 mg/kg), dopamine D2 receptor agonist, quinpirole (0.3 and 0.5 mg/kg) and dopamine D2 receptor antagonist, sulpiride (25 and 50 mg/kg), 30 min after the second and third doses of morphine injections, on days 2 and 3. The number of jumps were recorded on day 4 after naloxone injection. Each group comprised of 10 mice. Data are presented as mean±S. E.M. *p<0.05, **p <0.01 different from the saline control group.

of dopamine receptors are distinct molecular entities (27, 28) with different distributions (29, 30, 31).

The present study shows that administration of the D1 dopamine receptor agonist, SKF38393 (32, 33), and the dopamine D1 receptor antagonist, SCH23390 (34, 35), the dopamine D2 receptor agonist, quinpirole (36) and sulpiride, a dopamine D2 receptor antagonist (37- 40) in the presence of WSS, and 30 min before naloxone injection, potentiate WSS-induced inhibition of naloxone-induced jumping. This indicates that dopamine receptor mechanism may be involved in WSS-induced inhibition of jumping. One may suggest that postsynaptic activation of both D1 and D2 receptors increases the WSS response. While presynaptic blockade with sulpiride releases endogenous dopamine, in turn postsynaptic D1 stimulation potentiates WSS-induced inhibition of jumping. Furthermore, SCH 23390 may block 5HT receptors, and causes potentiation of the WSS response. In the absence of WSS, the expression of diarrhea has been shown to decrease by quinpirole (19), while the present data indicated that the drug in the presence of WSS even increases diarrhea. There is a report showing that dopamine D2 receptor activation may induce an opposite effect to that of morphine on the expression of withdrawal signs (11). The locus coeruleus has been the most widely studied and it has been proposed to play a principal, causal role in the expression of many withdrawal signs (41). Mesolimbic dopamine system is linked to the nucleus accumbens and is thought to play a role in motivational/reinforcement/reward phenomena

(42). Moreover, the decrease in dopaminergic transmission by dopamine receptor antagonists may inhibit all the withdrawal symptoms, and only jumping may be mediated by the noradrenergic system (43).

Effect of dopamine agents in the presence of WSS on development of naloxone-induced jumping behavior and diarrhea in morphine-dependent mice.

Figure 2 indicates the effect of WSS on the development of naloxone-induced jumping. The animals were forced to swim for different periods of time (0.5, 1 and 3 min), 15 min after either the first (2 Stress) or first and second (4 Stress) or first, second and third (6 Stress) injections of morphine on days 2 and 3, during the development of morphine dependence. The number of jumps were recorded on day 4 after naloxone injection. One-way ANOVA showed that 2 WSS for a period of 3 min decreased jumping, but not diarrhea. Six WSS for 0.5 and 3 min also decreased jumping. The present findings show that exposure to WSS during development of morphine dependency reduces naloxone-induced jumping. It has been proposed that WSS releases the endogenous substance (44). Whether this modulates the dopamine system (21) and in turn accounts for inhibition of morphine dependence should be tested.

Figure 3 indicates the effect of dopamine D1/D2 receptor agonist, apomorphine, in the presence or absence of WSS on the development of morphine dependence. The animals were forced to swim for a period of 3 or 15 min and saline or different doses of apomorphine (0.25, 0.5, 1 and 2 mg/kg) were injected 30 min after the second and third doses of morphine on days 2 and 3. The number of jumps were recorded on day 4 after naloxone injection. Two-way ANOVA showed a significant difference between the effect of apomorphine (1 and 2 mg/kg) in the presence or absence of WSS, during the development of morphine dependence, on jumping [$F(4,90)=6.76$, $p<0.0001$] or diarrhea [$F(4,90)=2.85$, $p>0.05$]. Post-hoc analysis indicated that WSS, could increased the response of apomorphine on naloxone-induced jumping, but not diarrhea.

The present data indicate that when apomorphine was used in the presence of WSS, during the development of dependence, more jumps were induced by naloxone. It seems likely that administration of WSS during the development of morphine dependence results in up-regulation of dopamine receptors. The possibility may exist that WSS releases endogenous opioids, similar to that of chronic morphine administration, inducing up-regulation of cAMP (45) or central supersensitivity of dopaminergic receptors (43). Based on our data the D1 receptor agonist, SKF 38393, which increases cAMP levels when administered during the development of morphine dependence in the presence of WSS, is able to increase jumping. Furthermore, an increase in dopaminergic activity, assessed by dopamine turnover, has been indicated in the lucus coeruleus of mice (46). These observations show that during chronic administration of WSS, an up-regulation of dopamine D1 receptors could be resulted.

Figure 4 shows the effect of dopamine receptor agents in the presence of WSS on the development of morphine dependence. The animals were forced to swim for different periods of 3 or 15 min, and saline or different doses of dopamine receptor agonists or antagonist were injected 30 min after the second and third doses of morphine on days 2 and 3. The number of jumps were recorded on day 4 after naloxone injection. One-way ANOVA showed that SKF 38393 increased jumping [$F(2,27)=3.37$, $p<0.05$], while quinpirole decreased diarrhea [$F(2,27)=3.4$, $p<0.05$]. SCH 23390 and sulpiride did not alter naloxone-jumping or diarrhea. The results indicate that D1 receptor up-regulation could be the main factor in WSS-induced inhibition of naloxone-induced jumping and/or potentiation of WSS response.

The present results show that administration of quinpirole in the presence of WSS during the development of morphine dependence, increases diarrhea, which further shows the involvement of dopaminergic system inhibition on withdrawal signs by WSS.

It is concluded that dopaminergic system and/or WSS may could influence the morphine withdrawal signs.

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