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Effects of SCH 23390, Raclopride, and Haloperidol on Morphine Withdrawal-Induced Aggression in Male Mice

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RODRÍGUEZ-ARIAS, M., J. PINAZO, J. MIÑARRO AND L. STINUS. *Effects of SCH 23390, raclopride, and haloperidol on morphine withdrawal-induced aggression in male mice.* PHARMACOL BIOCHEM BEHAV **64**(1) 123–130, 1999.— Dopamine seems to play a very important role in aggressive behavior observed in morphine withdrawal. The effect of SCH 23390 (0.5 mg/kg), raclopride (0.3 mg/kg), and haloperidol (0.1 mg/kg) on morphine withdrawal-induced aggression has been studied in this work. Mice were rendered dependent by a daily injection of morphine (2.5 mg/kg) for 14 days. Three different experiments were carried out with the objective to evaluate the antiaggressive effect of the dopamine antagonists on: first, spontaneous morphine withdrawal; second, naloxone-induced withdrawal; and third, naloxone-induced withdrawal after previous administration of the neuroleptics. Thirty minutes after injection of the dopamine antagonists, experimental animals were confronted in a neutral area with anosmic, group-housed conspecifics (standard opponents), and aggression was evaluated by estimation of times allocated to 11 different behavioral categories. Morphine withdrawal produced an increase in aggressive behavior and a decrease in social and nonsocial behaviors. The three neuroleptics counteracted this aggression, but when SCH 23390 (selective D_1 antagonist) and haloperidol (mixed D_1/D_2 antagonist) were administered in naloxone-induced withdrawal, the effect was greater in comparison to the spontaneous withdrawal. However, no changes were observed after raclopride administration (selective D_2 antagonist). In conclusion, the alterations in the dopaminergic system produced by opiate withdrawal depend on the type of withdrawal produced, and this produces a change in the antiaggressive potency of the dopamine antagonists. © 1999 Elsevier Science Inc.

Morphine withdrawal Aggression SCH 23390 Raclopride Haloperidol Mice

DOPAMINE seems to play a very important role in motor and aggressive symptoms of morphine withdrawal (14,23). There is a clear distinction between somatic and motivational states because there seems to be no correlation between the onset of physical withdrawal symptoms and the measures obtained from motivational tests. In rodents, morphine withdrawal is characterized by several physical symptoms (such as ptosis, swallowing, diarrhea, jumping, rearing, hyperactivity, wet dog shakes, or teeth chattering) and an increase in agonistic behaviors (15,19). The motivational state of aversion in morphine withdrawal could develop in the absence of any physical withdrawal signs and lower doses of naloxone are necessary to produce it (18).

Separate brain sites are responsible for the physical and motivational signs of opiate withdrawal. The locus coeruleus area, and secondarily the periaqueductal gray matter play an important role in the precipitation of the physical signs of opiate withdrawal. Furthermore, the spinal cord could mediate the expression of some autonomic components of opiate withdrawal (29). The neurobiological basis for the motivational aspects of opiate withdrawal are, at least in part, involved in the nucleus accumbens and the ventral tegmental area (source of the dopamine projection to the nucleus accumbens) (17,20,23).

Because it has been suggested that an increase of dopaminergic neurotransmission is responsible for the subjective

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pleasure aspects of drug action, it is reasonable to hypothesize that a decrease in dopaminergic neurotransmission may be responsible for some of the unpleasant subjective symptoms associated with drug withdrawal syndromes (11). Many studies have found a decrease in mesolimbic dopamine levels in the first 24 h of spontaneous withdrawal (9–11), which remained significant for 3 weeks (33). At the same time, a sensitization to morphine has been found, because readministration of this drug during the third and fifth day of withdrawal in morphine-dependent rats increased dopamine release between 100 to 160% over basal levels (1).

Although many authors have found a decrease in dopamine during naloxone-induced morphine withdrawal (1,10), other studies failed to find it. Crippens and Robinson (9) suggested that morphine withdrawal symptoms cannot be caused solely by variation in the extracellular concentration of dopamine in the striatum. It has to be pointed out that only physical signs were quantified in this study, it being possible, therefore, that there was no dissociation between the motivational symptoms of withdrawal and extracellular dopamine concentrations.

Taken together, these data indicate that repeated opiate administration results in a profound, long-lasting impairment of the activity of the DA system (1) and produces modifications at a postsynaptic dopaminergic level (4,26). It has been hypothesized that opiate administration provides an exogenous excitatory input that tonically stimulates DA neurons and gradually replaces the tone provided by endogenous excitatory or disinhibitory inputs that are thus adaptively turned off. As a result of this, the drug would become the main if not the only determinant of the basal activity of DA neurons so that withdrawal from the drug results in a profound depression of the activity of these neurons (1,11).

Dopaminergic agonists as well as antagonists do not have a clear action on morphine withdrawal. Amphetamine, apomorphine, or L-dopa increase aggression in rats with morphine withdrawal at doses that do not affect naive animals (14,21). However, Tidey and Miczek (32) found the D_1 agonist SKF 38393 decreases the display of aggressive behavior in morphine-withdrawn mice without altering walking and rearing. Moreover, the D_2 agonist quinpirole also decreases aggressive behavior, but at doses that also decrease motor activity. Furthermore, Harris and Aston-Jones (17) found that activation of the D_2 dopaminergic receptors within the accumbens prevents somatic signs of naloxone-induced opiate withdrawal, and their blockade elicits somatic withdrawal symptoms.

On the other hand, dopaminergic antagonists such as haloperidol markedly decrease morphine withdrawal-induced aggression (16,22). However, other authors have found that haloperidol, raclopride, and clozapine increase morphine withdrawal symptoms produced by naloxone (7). Moreover, the injection of nonselective DA antagonists such as alpha-fluphenthixol or selective D_2 antagonists such as eticlopride in the nucleus accumbens produces opiate-like withdrawal symptoms in dependent rats (17).

The objective of this study was to throw light on the role of different dopaminergic antagonists, both selective such as SCH 23390 (D_1) and raclopride (D_2) or nonselective such as haloperidol (D_1/D_2), in withdrawal-induced aggression of morphine-dependent male mice. Aggression was evaluated in two different circumstances: during either spontaneous or naloxone-induced withdrawal. We analyzed the effects of neuroleptic treatments upon the expression of aggressive and social behaviors triggered by spontaneous morphine withdrawal (first experiment). A parallel experiment was conducted during naloxone-induced opiate withdrawal (second experiment). Finally, the effects of neuroleptics on the induction of naloxone-induced withdrawal was studied (third experiment).

METHOD

Subjects

In the three experiments a total of 450 OF.1 albino male mice, aged 42 days (Laboratories CRIFFA, Barcelona) were used. All animals were housed under standard laboratory conditions: constant temperature (21° C), a reversed light schedule (white lights off; 0730 to 1930 h), and food and water available ad lib, except during behavioral testing. Half were individually housed during 28 days in transparent plastic cages ($24 \times 13.5 \times 13$ cm) and employed as experimental animals. The remainder were housed in groups of five to be used as standard opponents and made temporally anosmic by intranasal lavage with a 4% zinc sulphate solution on the day before testing (31). This kind of opponent was used because it is able to face attack but never initiates such behavior, because it cannot perceive a pheromone present in the urine of the experimental animals, which is considered to be a cue for eliciting aggressive behavior in mice with a normal sense of smell (5,25).

The animals in the present study have been used in accord with national, regional, and local laws and regulations. The procedures used are equivalent to those recommended by the documents "Policy on Human Care and Use of Laboratory Animals" (USPHS) and "Guide for the Care and Use of Laboratory Animals" (NIH), both from the USA.

Procedure

Drug treatments. Morphine hydrochloride, 2.5 mg/kg (Laboratories Alcaliber, Toledo, Spain), Naloxone Clorhydrate, 1 mg/kg (Abello, Madrid, Spain), SCH 23390, 0.5 mg/kg (Research Biochemicals International), Raclopride, 0.3 mg/kg (Janssen-Pharmaceutical), haloperidol®, 0.1 mg/kg (Laboratories Latino), and physiological saline (NaCl 0.9%) were used in this experiment. Drugs were diluted in physiological saline (0.1 mg/ml) and administered IP. The injection volume was proportional to the weight of the mouse (1 ml of dissolution per 100 gr of weight). The pH was between 6 and 6.5 in all the drug solutions used.

The selection of doses was performed on the basis of their efficacy in reducing isolation-induced aggression. The dose of 0.1 mg/kg for haloperidol was chosen because it presented a high antiaggressive action (91% reduction of attack behavior) and its impairment of motor activity was limited (24,28). With respect to raclopride, although the 0.6 mg/kg dose presented a higher antiaggressive action, we chose 0.3 mg/kg because it presented a similar decrease in aggression, and in addition, its selective action over the D_2 receptor was higher (2). Finally, the SCH 23390 dose was chosen because this presented comparable antiaggressive potency (86% of attack reduction) with respect to the other two neuroleptics (27,28).

Induction of morphine dependence. After the 28th day of isolation and during the following 14 days, morphine dependence was induced by a daily (0800 h) injection of morphine 2.5 mg/kg (morphine group, MOR). Control mice received 14 injections of vehicle (vehicle group, V). It has to be pointed out that no tissue damage was observed in any experimental animal.

Social encounters. The behavior of the mice was evaluated 30 min after the last injection (vehicle or neuroleptic), except in the third experiment in which the behavioral evaluation started 10 min after the naloxone injection. For 10 min an experimental animal and a standard opponent confronted each other in a neutral cage. All tests were carried out under white illumination between the second (0930) and fifth (1230) hour of the dark phase. Before the encounter, the animals were allowed 1 min of adaptation to the neutral cage while separated by means of a plastic barrier. Encounters were videotaped with a Panasonic VHS camera.

Behavioral analyses. The tapes were analyzed using a microprocessor (Commodore 64 computer) and a custom-developed program (6) that facilitated estimation of times allocated to 11 broad functional categories of behavior. Each category included a collection of different postures and elements. The names of categories are the following: body care, digging, nonsocial exploration, explore from a distance, social investigation, threat, attack, avoidance/flee, defensive/submissive, sexual, and immobility. A detailed description of all elements can be found in Brain et al. (6) and Rodríguez-Arias et al. (28). In additional, attack latency was evaluated in all the experiments.

Statistical analyses. The data were initially analyzed using the Kruskal–Wallis test. In the behavioral categories in which this test was significant, differences between vehicle and experimental groups in accumulated times were then examined by the two-tailed Mann–Whitney *U*-test.

EXPERIMENT 1: EFFECTS OF DOPAMINERGIC ANTAGONISTS ON SPONTANEOUS MORPHINE WITHDRAWAL-INDUCED AGGRESSION

One hundred and fifty male mice were employed in this experiment. As previously described, half of them were housed five by five as standard opponents. The remaining mice were housed individually and employed as experimental groups. After the 28th day of isolation and during the following 14 days, morphine dependence was induced by a daily (0800 h) injection of morphine 2.5 mg/kg (morphine group, MOR). Control mice received 14 injections of vehicle (vehicle group, V). Then all animals underwent a spontaneous withdrawal period of 48 h. On the second day of withdrawal, all mice received first an injection of vehicle (V) followed 10 min later by a second injection of either vehicle (the V/V/V group, $n = 15$ and the MOR/V/V group, $n = 15$), or SCH 23390, 0.5 mg/kg (the MOR/V/SCH group, $n = 15$), or raclopride, 0.3 mg/kg (the MOR/V/RAC group, $n = 15$), or haloperidol, 0.1 mg/kg (the MOR/V/HAL group, $n = 15$). The intraspecific aggression test started 30 min after this last injection.

Results

Table 1 illustrates medians (with ranges) of cumulated times allocated to the 11 broad categories described above. The Kruskal–Wallis test showed statistical differences between groups in: threat ($p < 0.001$); attack ($p < 0.002$); digging ($p < 0.009$); nonsocial exploration ($p < 0.001$); explore from a distance ($p < 0.001$); social investigation ($p < 0.05$), and immobility ($p < 0.001$).

Time spent in threat and attack were significantly increased during opiate withdrawal (MOR/V/V vs. V/V/V, threat $U = 12$, $p < 0.002$, and attack $U = 44$, $p < 0.02$), and reduced during neuroleptic treatments. MOR/V/SCH, MOR/V/RAC, and MOR/V/HAL groups were indentical to the V/V/V group and different from the MOR/V/V ($U = 20$, 17, and 38, for threat; $U = 32$, 26, and 39 for attack $p < 0.02$, respectively).

Digging was not affected by opiate withdrawal but was reduced by SCH treatment ($U = 61$, $p < 0.05$). Time spent in nonsocial exploration was significantly decreased by opiate withdrawal (the MOR/V/V vs. the V/V/V group, $U = 58$, $p < 0.05$) and restored by raclopride and haloperidol treatment ($U = 52$, $p < 0.05$, and $U = 55$, $p < 0.02$, respectively, when compared to MOR/V/V). On the contrary, SCH treatment did not attenuate the withdrawal effect.

Explore from a distance was reduced during opiate withdrawal and was not restored either by raclopride or haloperidol treatment; the groups MOR/V/V, MOR/V/RAC, and MOR/V/HAL presented a significant decrease in this behavior compared to V/V/V group ($U = 14$, 15.5, and 29, respectively, $p < 0.002$ in all cases). However, SCH treatments attenuated withdrawal effects (MOR/V/SCH vs. MOR/V/V, $U = 39$, $p < 0.02$).

Social investigation was drastically reduced during opiate withdrawal and was not restored by any neuroleptic treatment when compared to V/V/V (MOR/V/V $U = 45$, $p < 0.02$, MOR/V/SCH $U = 63$, $p < 0.05$, MOR/V/RAC $U = 59$, $p < 0.05$, MOR/V/HAL $U = 61$, $p < 0.05$).

Immobility was not affected by opiate withdrawal, but animals treated with SCH 23390 (MOR/V/SCH) and haloperidol (MOR/V/HAL) presented a significant increase in time spent in immobility compared to vehicle group (V/V/V) ($U = 0$ and 5, $p < 0.002$, respectively). These two groups also showed a significant increase in this behavior compared to the MOR/V/RAC and MOR/V/V groups ($p < 0.01$, $p < 0.02$) and the MOR/V/SCH group also spent significantly more time in this behavior than the MOR/V/HAL group ($p < 0.05$).

EXPERIMENT 2: EFFECTS OF DOPAMINERGIC ANTAGONISTS ON AGGRESSION IN NALOXONE-INDUCED MORPHINE WITHDRAWAL

One hundred and fifty male mice were used in this experiment. As previously described, half of them were housed five by five as standard opponents. The remaining mice were housed individually and employed as experimental groups. After the 28th day of isolation and during the following 14 days morphine dependence was induced by a daily injection (0800) of morphine 2.5 mg/kg (morphine group, MOR). Control mice received 14 injections of vehicle (vehicle group, V). On the following day all animals received first a naloxone injection (1 mg/kg) followed 10 min later by a second injection of either vehicle (the V/Nal/V group, $n = 15$ and the MOR/Nal/V group, $n = 15$), or SCH 23390, 0.5 mg/kg (the MOR/SCH/Nal group, $n = 15$) or raclopride, 0.3 mg/kg (the MOR/Nal/ RAC group, $n = 15$), or haloperidol, 0.1 mg/kg (the MOR/Nal/HAL group, $n = 15$). The intraspecific aggression test started 30 min after this last injection.

Results

Table 2 illustrates medians (with ranges) of cumulated times allocated to the 11 broad categories described previously. The Kruskal–Wallis test showed statistical differences between groups in: threat ($p < 0.001$); attack ($p < 0.001$); latency of attack ($p < 0.002$); body care ($p < 0.01$); nonsocial exploration ($p < 0.001$); explore from a distance ($p < 0.001$); social investigation ($p < 0.003$), and immobility ($p < 0.001$).

Threat and attack were significantly increased by opiate withdrawal (MOR/Nal/V vs. V/Nal/V, $U = 0$ and 8, $p < 0.002$,

TABLE 1

	V/V/V	MOR/V/V	MOR/V/SCH	MOR/V/RAC	MOR/V/HAL
Body care	14 (6–30)	17 (9–39)	26 (0–54)	19 (9–36)	12 (9–29)
Digging†	13 (6–47)	13 (8–25)	9‡ (3–14)	15 (8–31)	9 (4–25)
Nonsoc. Exp.*	308 (204–383)	270‡(177–324)	280 (180–358)	347§# (305–433)	329# (198–393)
Exp. Distance*	11 (3–27)	4¶ (2–27)	6# (3–13)	4¶ (1–7)	5¶ (2–12)
Soc. Invest.†	158 (42–288)	88§ (52–177)	129‡ (43–224)	127‡ (21–190)	122‡ (38–204)
Threat*	56 (0–89)	122¶ (58–171)	54# (2–124)	50# (0–113)	57# (8–146)
Attack†	35 (0–81)	70§ (8–151)	29# (0–99)	33# (0–76)	30# (0–117)
Immobility*	0 (0–9)	0 (0–3)	7# 5¶# (18–174)	4 (0–13)	37¶# (2–104)
Attack latency	197 (62–600)	93 (12–600)	318 (5–600)	92 (25–600)	270 (14–600)

Medians (with ranges) of cumulated times (in seconds) spent in different behaviors and attack latency found for the groups V/V/V (14 daily injections of vehicle and the second day after received first an injection of vehicle followed 10 min later by a second injection of vehicle); MOR/V/V (14 daily injections of morphine 2.5 mg/kg, and the second day after, first an injection of vehicle followed 10 min later by a second injection of vehicle); MOR/V/SCH (14 daily injections of morphine, 2.5 mg/kg and the second day of withdrawal, first an injection of vehicle followed 10 min later by an injection of SCH 23390, 0.5 mg/kg); MOR/V/RAC (14 daily injections of morphine, 2.5 mg/kg, and the second day of withdrawal, first an injection of vehicle followed 10 min later by an injection of Raclopride, 0.3 mg/kg); and MOR/V/HAL (14 daily injections of morphine, 2.5 mg/kg, and the second day of withdrawal, first an injection of vehicle followed 10 min later by an injection of haloperidol, 0.1 mg/kg).

Kruskall–Wallis test shows significant variance $*p < 0.001$ $†p < 0.05$.

Differs on two-tailed Mann–Whitney U-test from vehicle group (V/V/V) $‡p < 0.05$, $§p < 0.02$, $¶p < 0.002$, and from morphine group (MOR/V/V) $\#p < 0.02$.

respectively), and reduced by the neuroleptic treatments. Basal levels of threat and attack were restored by neuroleptic treatments (identical to V/Nal/V); moreover, when compared to MOR/Nal/V, these behaviors decreased significantly in the MOR/Nal/SCH, MOR/Nal/RAC, and MOR/Nal/HAL groups ($U = 0$, 17, and 0, respectively, in threat; $U = 13$, 15, and 4, respectively, in attack $p < 0.02$). Furthermore, the MOR/Nal/SCH group showed a significant decrease in threat and attack compared to the MOR/Nal/RAC group ($U = 50$, $p < 0.02$, and $U = 58$, $p < 0.05$, respectively). On the other hand, only in attack, haloperidol-treated animals (MOR/Nal/HAL) showed a significant decrease compared to the animals of the MOR/Nal/RAC group ($U = 64$, $p < 0.05$).

Attack latency was significantly decreased by opiate withdrawal (the MOR/Nal/V group vs. V/Nal/V, $U = 39$, $p < 0.002$), and restored by neuroleptic treatments. Moreover, the MOR/NAl/SCH and MOR/Nal/HAL groups presented a significant increase in attack latency compared to the MOR/Nal/V groups ($U = 33$ and 39, $p < 0.02$, respectively) and with the MOR/Nal/RAC group ($U = 58$, $p < 0.05$).

Body care was not affected by opiate withdrawal but was increased by SCH (MOR/Nal/SCH) and raclopride (MOR/Nal/RAC) treatment ($U = 56$, $p < 0.05$, and $U = 53$, $p < 0.02$, respectively). Haloperidol-treated animals (MOR/Nal/HAL) were not affected.

Nonsocial exploration was significantly decreased by opiate withdrawal (MOR/Nal/V vs. V/Nal/V, $U = 36$, $p < 0.002$). This behavior was restored by all neuroleptic treatments (no difference compared to V/Nal/V). Moreover, they induced a significant increase in social exploration compared to the MOR/Nal/V (SCH $U = 56$, $p < 0.02$, raclopride and haloperidol $U = 17$ and 16, $p < 0.02$, respectively).

Explore from a distance was significantly reduced by opiate withdrawal (MOR/Nal/V) and was not restored by SCH or raclopride treatment ($U = 29$, $p < 0.002$, $U = 62$, $p < 0.05$, $U = 15$, $p < 0.002$) compared to the V/Nal/V.

Social investigation was drastically reduced by opiate withdrawal (MOR/Nal/V vs. V/Nal/V, $U = 23$, $p < 0.002$), but was restored by neuroleptic treatment. The MOR/Nal/SCH, MOR/Nal/RAC, and MOR/Nal/HAL groups presented a significant increase compared to MOR/Nal/V group ($U = 52$, 54, and 60, $p < 0.02$, respectively).

Immobility was not affected by opiate withdrawal, but animals treated with neuroleptics presented a significant increase in time spent in this behavior compared to vehicle group (V/Nal/V) (respectively for MOR/Nal/SCH, MOR/Nal/RAC, and MOR/NAl/HAL $U = 0$, 39, and 0, $p < 0.002$) and with the MOR/Nal/V group (MOR/Nal/SCH and MOR/Nal/HAL, $U = 0$, $p < 0.002$ and MOR/Nal/RAC, $U = 44$, $p < 0.02$). Additionally, the two groups treated with SCH and Haloperidol also showed a significant increase in this behavior compared to the MOR/Nal/RAC ($U = 0$, $p < 0.002$), the SCH-treated animals spending significantly more time in this behavior than the haloperidol-treated group ($U = 59$, $p < 0.05$).

EXPERIMENT 3: EFFECTS OF DOPAMINERGIC ANTAGONISTS ON AGGRESSION WHEN ADMINISTERED PRIOR TO A NALOXONE-INDUCED MORPHINE WITHDRAWAL

As described previously, half of the 150 male mice employed were housed in groups of five as standard opponents. The remaining mice were housed individually and used as experimental groups. After the 28th day of isolation and during the following 14 days, morphine dependence was induced by a daily injection (0800 h) of morphine 2.5 mg/kg (MOR). Control mice received 14 injections of vehicle (V). On the following day, all animals received first an injection of either vehicle (the V/V/Nal group, $n = 15$, and the MOR/V/Nal group, $n = 15$), or SCH 23390, 0.5 mg/kg (the MOR/SCH/Nal group, $n = 15$) or raclopride, 0.3 mg/kg (the MOR/RAC/Nal group, $n = 15$), or haloperidol, 0.1 mg/kg (the MOR/HAL/Nal group, $n = 15$), and 20 minutes after this administration all animals received a naloxone injection (1 mg/kg). The intraspecific aggression test commenced 10 min after this last injection; in this way the test was performed 30 min after the neuroleptic administration as in the two previous experiments.

TABLE 2

	V/Nal/V	MOR//Nal/V	MOR/Nal/SCH	MOR/Nal/RAC	MOR/Nal/HAL
Body care†	11 (4–23)	17 (2–45)	25‡ (3–183)	20§ (10–41)	9(3–66)
Digging	10 (3–33)	10(4–21)	9 (4–26)	14 (6–20)	11 (5–25)
Non. Soc. Exp.*	342 (205–406)	264¶ (182–301)	295# (211–395)	332# (245–429)	345# (218–408)
Exp. Distance*	8 (5–14)	4¶ (1–14)	6‡ (1–13)	3¶ (0–9)	4 (1–14)
Soc. Invest.†	169 (82–337)	78¶ (34–153)	116# (67–216)	156# (28–226)	129# (49–254)
Threat*	33(0–80)	125¶ (96–180)	17# (0–96)	55# (14–157)	26# (0–92)
Attack*	34 (0–73)	85¶ (47–145)	5# (0–124)	22# (4–107)	14# (0–71)
Immobility*	0 (0–5)	0 (0–4)	73¶ (24–167)	4¶ (0–22)	58¶ (24–72)
Attack latency*	285 (56–600)	73¶ (6–280)	494# (46–600)	127 (24–428)	292# (16–600)

Medians (with ranges) of cumulated times (in seconds) spent in different behaviors and attack latency found for the groups V/Nal/V (14 daily injections of vehicle and the following day received first a naloxone injection, 1 mg/kg, followed 10 min later by a second injection of vehicle); MOR/Nal/V (14 daily injections of morphine 2.5 mg/kg, and the following day, first a naloxone injection, 1 mg/kg, followed 10 min later by a second injection of vehicle); MOR/Nal/SCH (14 daily injections of morphine, 2.5 mg/kg, and the following day first a naloxone injection, 1 mg/kg, followed 10 min later by an injection of SCH 23390, 0.5 mg/kg); MOR/Nal/RAC (14 daily injections of morphine, 2.5 mg/kg, and the following day first a naloxone injection, 1 mg/kg, followed 10 min later by an injection of Raclopride, 0.3 mg/kg); and MOR/Nal/HAL (14 daily injections of morphine, 2.5 mg/kg, and the following day first a naloxone injection, 1 mg/kg, followed 10 min later by an injection of haloperidol, 0, 1 mg/kg).

Kruskall–Wallis test shows significant variance $*p < 0.001$ $†p < 0.05$.

Differs on two-tailed Mann–Whitney U-test from vehicle group (V/Nal/V) $‡p < 0.05$, $§p < 0.02$, $¶p < 0.002$, and from morphine group (MOR/Nal/V) $\#p < 0.02$.

Results

Table 3 illustrates medians (with ranges) of cumulated times allocated to the same behavioral categories: Kruskal–Wallis test showed statistical differences between groups in: threat ($p < 0.001$); attack ($p < 0.001$); attack latency ($p < 0.001$; body care ($p < 0.02$); explore from a distance ($p < 0.005$); social investigation ($p < 0.001$) and immobility ($p < 0.001$).

The threat and attack was significantly increased by opiate withdrawal and were reduced by all neuroleptics. The MOR/V/Nal animals presented a significant increase in threat and attack compared to V/V/Nal group ($U = 9$ in threat and $U = 14$ in attack, $p < 0.002$). All the neuroleptic-treated animals presented a significant decrease in threat and attack compared to MOR/V/Nal animals ($U = 34$, $p < 0.02$ for MOR/SCH/Nal and for MOR/RAC/Nal, and $U = 26$, $p < 0.02$ for MOR/HAL/Nal in threat; and $U = 19$, 23, and 13, $p < 0.02$, respectively, in attack). In addition, SCH ($U = 62$ in threat and $U = 62$ in attack, $p < 0.05$), and haloperidol-treated animals ($U = 47$ in threat, and $U = 49$ in attack, $p < 0.002$) significantly decreased these behaviors compared to the Morphine/Racl group.

Attack latency was significantly reduced by the opiate and restored by SCH and haloperidol treatment. The MOR/V/Nal and MOR/RAC/Nal groups presented a significant decrase compared to V/V/Nal animals ($U = 46$ and 49, $p < 0.02$, respectively). In addition, animals treated with SCH, showed a significant increase with respect to MOR/V/Nal ($U = 27, p < 0.02$) and MOR/RAC/Nal groups ($U = 27$ and 28, $p < 0.002$, respectively).

Body care was not affected by opiate withdrawal. The MOR/SCH/Nal group spent more time in this behavior compared to vehicle group V/V/Nal ($U = 53$ $p < 0.02$).

Explore from a distance was decreased by the opiate and restored by SCH and haloperidol treatment. The MOR/V/Nal and MOR/RAC/Nal groups presented a significant decrase in explore from a distance compared to the V/V/Nal group ($U = 27, p < 0.002$, and $U = 55, p < 0.02$).

Social investigation was significantly deceased by opiate withdrawal and restored by raclopride treatment. The MOR/V/Nal, MOR/SCH/Nal and MOR/HAL/Nal groups presented significant differences compared to the V/V/Nal group ($U = 16$, $p < 0.002$, $U = 51$, $p < 0.02$, $U = 45$, $p < 0.02$). Raclopride-treated mice were identical to the V/V/Nal group and presented a significant increase compared to MOR/V/Nal animals ($U = 49$ $p < 0.02$).

Immobility was not affected by opiate withdrawal, but animals treated with SCH and haloperidol (MOR/SCH/Nal, and MOR/HAL/Nal groups) presented a significant increase in time spent in this behavior compared to vehicle group (V/V/Nal group), ($U = 0$ and 9, $p < 0.002$, respectively). Moreover, these groups also displayed a significant increase in immobility compared to MOR/V/Nal ($U = 0$ and 12, $p < 0.02$, respectively) and MOR/RAC/Nal groups ($U = 0$ and 16, $p < 0.002$, respectively).

COMPARISON INTEREXPERIENCES

The aggression levels observed in the three vehicle groups were similar, presenting comparable medians in attack and threat behaviors. This fact suggests that the level of aggression is not affected by the naloxone administration.

The level of aggression produced by spontaneous or naloxone-induced withdrawal was similar—the three groups showing a significant increase in aggressive behaviors compared to vehicles. The morphine-treated animals, which received a daily morphine injection for 14 days (MOR/V/V, MOR/Nal/V, and MOR/V/Nal) and then experienced an opiate withdrawal, presented the highest levels of attack (70, 85, and 79 s) and threat (122, 125, and 96 s) compared to animals that received 14 vehicle injections (V/V/V, V/Nal/V, and V/V/Nal groups, attack 35, 34, and 9 s, and threat 56, 33, and 23 s, respectively). In addition, only in animals belonging to MOR/V/V, MOR/Nal/V, and MOR/V/Nal groups physical signs, such as piloerection and paw tremor were observed. Piloerection was the most frequent sign presented in 30% of the withdrawn animals.

To determine possible differences between spontaneous and naloxone-induced withdrawal and discern the neuroleptic effects as a function of different withdrawal procedures, a comparison was made by analyzing the results obtained in each group with the Mann–Whitney U-test in behaviors in

TABLE 3

	V/V/Nal	MOR/V/Nal	MOR/SCH/Nal	MOR/RAC/Nal	MOR/HAL/Nal
Body care†	10 (3–43)	12 (7–34)	24 (6–43)§	22 (11–43)	14 (0–51)
Digging	13 (3–43)	12 (5–18)	8 (3–16)	12 (5–26)	9 (6–37)
Nonsoc. Exp.	318 (259–428)	281 (111–361)	295 (194–398)	319 (196–418)	352 (226–427)
Exp. Distance†	6 (3–24)	3¶ (1–8)	6 (2–11)	3 (1–6)§	4 (2–12)
Soc. Invest.*	159 (110–299)	88¶ (46–150)	122 (31–243)§	150# (49–328)	115 (48–199)§
Threat*	23 (0–71)	96¶ (0–189)	2(±) (0–126)	36§# (0–98)	18# (0–47)
Attack*	9 (0–53)	79¶ (0–145)	4# (0–90)	20# (0–56)	8# (0–38)
Immobility*	0 (0–4)	0 (0–15)	117¶# (23–173)	1 (1–16)	85¶# (0–194)
Attack latency*	339 (22–600)	80 (12–600)§	506# (52–600)	76 (18–600)§	196 (32–600)

Medians (with ranges) of cumulated times (in seconds) spent in different behaviors and attack latency found for the groups V/V/Nal (14 daily injections of vehicle and the following day received first an injection of vehicle followed 10 min later by a second injection of naloxone, 1 mg/kg); MOR/V/Nal (14 daily injections of morphine 2.5 mg/kg, and the following day, first an injection of vehicle followed 10 min later by a second injection of naloxone, 1 mg/kg); MOR/SCH/Nal (14 daily injections of morphine, 2.5 mg/kg, and the following day, first an injection of SCH 23390, 0.5 mg/kg, followed 10 min later by an injection of naloxone, 1 mg/kg); MOR/RAC/Nal (14 daily injections of morphine, 2.5 mg/kg, and the following day first an injection of Raclopride, 0.3 mg/kg, followed 10 min later by an injection of naloxone, 1 mg/kg); and MOR/HAL/Nal (14 daily injections of morphine, 2.5 mg/kg, and the following day, first an injection of haloperiodol, 0.1 mg/kg followed 10 min later by an injection of naloxone, 1 mg/kg.

Kruskall-Wallis test shows significant variance $*p < 0.001$ $\dagger p < 0.05$.

Differs on two-tailed Mann–Whitney *U*-test from vehicle group (V/V/Nal) $\ddagger p < 0.05$, $\S p < 0.02$, $\P p < 0.002$ and from morphine group (MOR/V/Nal) $\# p < 0.02$.

which the Kruskal–Wallis test was significant, i.e., in SCH and HAL groups.

Groups treated with SCH 23390 (MOR/V/SCH, MOR/Nal/SCH, and MOR/SCH/Nal)

Threat and Attack. Animals belonging to the first experimental group (spontaneous withdrawal) spent significantly more time in this behavior compared to the second and third experimental groups ($p < 0.02$ for threat and $p < 0.05$ and $p < 0.002$ for attack, respectively).

Attack Latency. The spontaneous withdrawal group needed a shorter time to initiate attack compared to the group of the third experiment ($p < 0.05$).

Groups treated with Haloperidol (MOR/V/HAL, MOR/Nal/HAL, MOR/HAL/Nal)

Threat and Attack. Animals belonging to the spontaneous withdrawal group spent significantly more time in these behaviors compared to the groups belonging to the second and third experiments ($p < 0.05$ and $p < 0.02$ for threat, respectively, and $p < 0.02$ and $p < 0.01$ for attack, respectively).

Immobility. Animals of the third experiment spent more time in these behaviors compared to those of the first experiment ($p < 0.05$).

GENERAL DISCUSSION

Spontaneous or naloxone-induced withdrawal in morphine-dependent mice produces an increase in the aggressive behaviors (threat and attack) and a decrease in nonsocial exploration, explore from a distance, and social investigation behaviors.

Although experimental schedules were very different, control groups (V/V/V, V/Nal/V, and V/V/Nal) were identical (age, isolation, and handling), and all the withdrawal groups presented a significant increase in aggressive behaviors. Thus, we can suggest that opiate withdrawal induces a specific state of aggressiveness that could only be attributed to the abstinence to morphine.

Likewise, in all experiments the three neuroleptics produced a level of aggression similar to the vehicle groups and brought about a decrease in aggressive behaviors in comparison with the morphine groups (MOR/V/V, MOR/Nal/V, and MOR/V/Nal). Our results are in agreement with others obtaining an antiaggressive effect of neuroleptics, especially haloperidol in morphine withdrawal (22). However, other studies failed to observe that neuroleptics affected withdrawal symptoms in morphine-dependent monkeys, or even in some cases produced them (12,13).

Nevertheless, when a more detailed analysis is performed, subtle differences can be observed, depending on the procedure used. When SCH and haloperidol are administered in spontaneous withdrawal (first) the level of aggression is higher in comparison with the naloxone-induced withdrawal (second and third). These data indicate that aggressive behavior diminishes more notably when those neuroleptics (SCH and haloperidol) are administered during naloxone-induced withdrawal and less when administered in spontaneous withdrawal.

Naloxone-precipitated withdrawal presents marked differences with respect to spontaneous withdrawal. The former is more abrupt and desadaptative (3), and there is no agreement with regard to the changes produced in the dopaminergic system after naloxone-induced withdrawal (9,10). The mesolimbic dopaminergic system is considered to play an important role for the dysphoric state associated with morphine withdrawal (10) and it seems clear that neuroleptics can exert their antiaggressive effect in a different way, depending on the status of the dopaminergic systems.

However, in naloxone-induced withdrawal, there are differences between the three drugs, depending on the dopamine receptor that is blocked. The exclusively D_2 receptor blockade (raclopride) is less efficient than the blockade of the D_1 (SCH 23390) or the D_1 and D_2 receptors (haloperidol).

In the first experiment, there are no significant differences in the antiaggressive effect of the three neuroleptics (threat and attack behavior). However, in the second and third, raclopride shows a significant decrease in its antiaggressive action in comparison to SCH 23390 and haloperidol. When the raclopride action in the three experiments are analyzed, no

significant differences are observed. One possible explanation of these differences regarding the action of the three neuroleptics could be that naloxone modifies the effect of these drugs, increasing the antiaggressive action of SCH 23390 and haloperidol. We have previously assessed the interaction between naloxone and these three neuroleptics at the same doses used (data not shown). Coadministration of naloxone and SCH 23390 only produces a small decrease in threat compared to the administration of D_1 antagonist alone. The interaction of the opiate antagonists and haloperidol (0.1 mg/kg) did not affect its antiaggressive actions. Finally the coadministration with raclopride decreases time spent in attack compared with raclopride administration alone. As a consequence, these results do not indicate that naloxone administration in the second and third experiment is the cause of the higher antiaggressive action observed in SCH 23390 and haloperidol in these experiments.

Another measure related to aggressiveness is latency of attack. This latency is reduced in spontaneous and naloxone-induced withdrawal groups, but in general returns to the levels of vehicle groups when neuroleptics are administered.

On the other hand, nonsocial exploration decreases in opiate withdrawal, which could be related to the typical decrease in motor activity seen in opiate withdrawal (30). Neuroleptic treatments (SCH, raclopride, and haloperidol) restore this behavior to normal levels. Likewise, explore from a distance and social investigation present a significant decrease in opiate withdrawal, when compared to vehicle group. Neuroleptic treatments partly restore social investigation to the normal ranges, which could be considered as an anxiolytic action (34). However, this action is unexpected, due to the fact that dopaminergic antagonists usually decrease these behaviors; the administration of SCH 23390 and raclopride has been reported to decrease the social behavior in familiar as well as unfamiliar animals (8).

Immobility was increased in SCH 23390 and haloperidol-treated mice, while it was unchanged by raclopride. Moreover, haloperidol produces a significant increase in immobility in the neuroleptic pretreatment situation (third experiment) in comparison with spontaneous withdrawal (first experiment). In recent experiments, it has been shown that haloperidol reduces withdrawal symptoms and locomotion in morphine withdrawal induced by naloxone (3). The increase observed in immobility of the animals treated with SCH 23390 or Haloperidol does not seem to be responsible for its antiaggressive action. Other behaviors that need an important motor component, such as nonsocial exploration, are not decreased by these drugs; even treatment with SCH 23390 and Haloperidol restore this behavior to normal levels in withdrawn mice.

These results show the antiaggressive effect of SCH, raclopride, and haloperidol in the aggression produced by either spontaneous or naloxone-induced morphine withdrawal. The fact that SCH 23390 and haloperidol-treated animals spend less time in aggressive behaviors than those treated with raclopride in the second and third experiment, seems to suggest that naloxone-induced withdrawal affects the action of these two neuroleptics. Moreover, administration of the dopamine blockers before or after the naloxone injection does not seem to modify their antiaggressive action. Although in all the experiments, the three neuroleptics efficiently counteract the withdrawal-induced aggression, in naloxone-induced withdrawal, SCH 23390 and haloperidol showed a greater antiaggressive action.

Raclopride presents quite a different situation because its antiaggressive actions are similar in the three experimental conditions used. This fact can be interpreted in a function of the different dopaminergic receptors affected by neuroleptics. When the drug blocks the D_1 (SCH 23390) or the D_1/D_2 receptors (haloperidol) the antiaggressive effects are enhanced in naloxone-induced withdrawal, without manifesting any changes in immobility. However, when a D_2 antagonist is used (raclopride) neither changes in antiaggressive nor motor effects are observed. Positive effects are noted only when the D_1 receptors are blocked, but not when the drug affects the D_2 receptors. It could be suggested that the opiate tone modulates the D_1 dependent behaviors, but not others depending on the D_2 receptor.

The antiaggressive effects of neuroleptics may be mediated mainly through the mesolimbic system. The reduction of withdrawal-induced aggression due to neuroleptic treatment may be a consequence of their action on the mesolimbic dopaminergic system. This effect could directly decrease the aversive motivational effect of the withdrawal, and consequently decrease the state of aggressiveness. Another possible explanation is a direct antiaggressive action in the same way that neuroleptics decrease other kinds of aggression (such as isolation-induced aggression). In a previous study, we assessed the antiaggressive effects of the three neuroleptics (with similar doses) used in this experiment in nondependent mice injected only with vehicle (data not shown). In these mice, belonging to the same strain and isolated for the same period of time, the three neuroleptics decreased aggression, although only SCH 23390 and haloperidol achieved it in a significant way. Raclopride decreased threat significantly, but although time spent in attack behavior was reduced to half, it did not reach statistical significance. Thus, because these drugs also reduced aggressive behavior in the paradigm of isolation-induced aggression, further investigation is needed to clarify the specific or nonantiaggressive effect of these neuroleptics in morphine withdrawal-induced aggression.

In conclusion, in addition to clear evidence that morphine withdrawal induces a specific state of aggression, and that neuroleptics efficiently counteract it, we can deduce that the alterations in the dopaminergic system produced by opiate withdrawal varies, depending on the type of withdrawal produced. The fact that the antiaggressive action of the D_2 blockade receptor does not suffer any modification, but the D_1 blockade changes its power of action depending on the type of withdrawal, could suggest that spontaneous and naloxone-induced withdrawal affect D_1 or D_2 dopamine receptors in a different way.

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