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# Acutely Administered Clozapine Does Not Modify Naloxone-Induced Withdrawal Jumping in Morphine-Dependent Mice

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BALLARD, T. M. AND K. H. MCALLISTER. *Acutely administered clozapine does not modify naloxone-induced withdrawal jumping in morphine-dependent mice.* PHARMACOL BIOCHEM BEHAV **62**(2) 285–290, 1999.—A direct comparison of the effects of clozapine and haloperidol upon naloxone-induced withdrawal jumping was investigated in morphine-dependent mice, as this syndrome may provide a behavioral baseline to differentiate between the two neuroleptics. Neither clozapine (0.03–3.0 mg/kg SC, $n$ = 9–10) nor haloperidol (0.01–0.1 mg/kg SC, $n$ = 9–10) affected withdrawal jumping precipitated by 0.1 or 15.0 mg/kg IP naloxone in morphine-dependent mice. Measurement of locomotor activity immediately prior to naloxone administration revealed a dose-dependent reduction in activity by both compounds, indicating pharmacological effects at the time of naloxone-induced withdrawal. Clonidine (0.02–0.5 mg/kg SC, $n$ = 9–10) also had no affect upon withdrawal jumping, although reductions in locomotor activity prior to naloxone administration were detected. There is no difference in the effects of acutely administered clozapine and haloperidol upon naloxone-precipitated withdrawal jumping in morphine-dependent mice. © 1998 Elsevier Science Inc.

Morphine withdrawal Jumping Naloxone Clozapine Haloperidol Clonidine Mice

THE studies described below investigated whether there is a difference between the effects of clozapine and haloperidol upon jumping in mice following naloxone-induced withdrawal from morphine dependence. Rodents abruptly withdrawn from a state of morphine dependence following a single administration of an opiate antagonist display multiple withdrawal symptoms, including jumping, a behavior involving complex changes in dopamine (DA) neurotransmission. For instance, DA depletion attenuates withdrawal-induced jumping, which is restored by the repletion of DA with 3-(3, 4-dihydroxyphenyl)-L-alanine (20). Furthermore, DA levels are increased in the cortical-striatal area within 2 min of naloxone administration to morphine-dependent mice, with those mice displaying withdrawal jumping showing a 20% greater increase in DA than mice not showing jumping (15).

Although there is evidence that DA agonists may potentiate withdrawal jumping (11,12), the effects of dopamine antagonists are less consistent. For instance, haloperidol has no effect upon a high baseline of withdrawal jumping (3,7,11,23), and does not exacerbate a low baseline of jumping (34) in naloxone-treated morphine-dependent rats. In a single study of the effects of atypical neuroleptics, clozapine exacerbated naloxone-induced withdrawal escape jumping in morphine-treated guinea pigs, and remoxipride [a compound with a lower propensity for catalepsy (27)] resulted in a slight augmentation of jumping (5). Raclopride, a more typical neuroleptic, had no effect. Notwithstanding the complex pharmacological profile of clozapine (9,13), the inconsistency may also depend upon the distinct modification of DA during naloxone-induced withdrawal in different brain areas (1,4,22). Microdialysis studies have revealed a reduction in DA levels in the nucleus accumbens [NAc; (1,22)] and an increase in DA release in the prefrontal cortex [PFC; (4)] following naloxone administration to morphine-dependent rats. Compared to haloperidol, clozapine induces a marked increase in DA release in the PFC (21). Because typical and atypical neuroleptics have different therapeutic activity [clozapine ameliorates the negative symptoms of schizophrenia (16), and has a low propensity for extrapyramidal side effects (6)], it was of interest to confirm whether clozapine and a typical neuroleptic (halo-

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peridol) have different effects upon morphine withdrawal jumping because this may provide another behavioral baseline to differentiate between the compounds preclinically.

The effects of the clozapine and haloperidol were assessed on a low and a high baseline of withdrawal jumping precipitated by two doses of naloxone in morphine-dependent mice. Furthermore, the effect of each drug on horizontal locomotor activity was assessed prior to naloxone administration to confirm that the dose range under investigation produced pharmacological effects. The $\alpha_2$-adrenoceptor agonist clonidine was tested within the same experimental paradigm for comparative purposes. While systemically administered clonidine reliably attenuates the autonomic changes observed during morphine withdrawal (7,10,23,33), it either has no effect (7,10,23) or slightly increases (30,33) or decreases (8) the frequency of jumping in rats, or has no effect (17) or decreases (32) withdrawal jumping in morphine-dependent mice.

## METHOD

### *Animals*

Two hundred thirty-four male OF-1 mice (Novartis, Basel), weighing 25–30 g, were housed in groups of 8–10 in Makrolon Type IV cages. The studies were undertaken in accordance with the Tierschutzgesetz (9.3.78) and Tierschutzverordnung (27.5.81), Switzerland governing the experimental use of animals.

### *Apparatus*

Four activity meters (Motron products, Sweden) were housed individually in custom-made, light- and sound-attenuating boxes. Makrolon Type II boxes (22 × 16 × 14 cm) were used for each mouse, and a lid was placed on top to prevent the mouse jumping out. The photocells measuring vertical movement were positioned at a height (11 cm) that detected jumping, but not rearing.

### *Drugs*

All drugs were dissolved in 0.9% saline from the salt form, with the exception of haloperidol (Janssen Pharmaceuticals), which was obtained in ampoules (5.0 mg/ml) and further diluted with saline. Doses of clozapine (Novartis Pharma AG), haloperidol, clonidine (SIMS, Florence), and naloxone (DuPont) are expressed as weight of the base, morphine (Research Biochemicals International, Zurich) as the weight of the salt (sulphate). All drugs were administered in an injection volume of 10 ml/kg.

### *Morphine Dependence*

Morphine solutions were freshly made prior to each injection. Mice were injected SC three times daily, with an interval of 4–5 h between the first and second, and second and third injections and 14 h between the third and first injection. The dose of morphine was increased according to the schedule in Table 1.

TABLE 1
SCHEDULE OF MORPHINE ADMINISTRATION
(mg/kg SC)

| Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|
| 20.0 | 80.0 | 160.0 | 320.0 |
| 40.0 | 80.0 | 320.0 | Test |
| 40.0 | 160.0 | 320.0 | — |

### *Naloxone-Induced Withdrawal*

On the fourth day of morphine administration, the subjects were transferred to the experimental room, where they received a final injection of morphine. Two hours later, the test drug was administered SC, and 50 min later each mouse was introduced into one of the four activity boxes for a 10-min period, during which horizontal activity was measured. On removal from the box naloxone was administered IP to each subject prior to immediate replacement in the same activity chamber for another 10-min period, during which vertical activity (i.e., jumping) was measured. Locomotor activity during this period was not measured. The treatments were counterbalanced across activity chambers.

Preliminary experiments investigating a dose range of naloxone, revealed that a 15.0 mg/kg dose resulted in consistent median levels of withdrawal jumping with relatively low variance. This dose was used in Experiments 1–3. Similar doses of naloxone have been used to precipitate withdrawal in a previous study (5). A dose of 0.1 mg/kg was used in Experiments 4–6 in the investigation of the test compounds upon a low baseline of jumping.

### *Experiments 1–3: Investigation of the Effects of Clozapine, Haloperidol, and Clonidine on Naloxone (15.0 mg/kg)-Induced Withdrawal Jumping*

In each experiment, four treatment groups were administered either clozapine (saline, 0.03, 0.3, or 3.0 mg/kg, $n = 10$), haloperidol (saline, 0.01, 0.05, or 0.1 mg/kg, $n = 10$), or clonidine (saline, 0.02, 0.1, or 0.5 mg/kg, $n = 9$–10) SC 1 h prior to the administration of naloxone (15.0 mg/kg).

### *Experiments 4–6: Investigation of the Effects of Clozapine, Haloperidol, and Clonidine on Naloxone (0.1 mg/kg)-Induced Withdrawal Jumping*

In each experiment, four treatment groups were administered either clozapine (saline, 0.03, 0.3, or 3.0 mg/kg, $n = 9$), haloperidol (saline, 0.01, 0.05, or 0.1 mg/kg, $n = 9$–10), or clonidine (saline, 0.02, 0.1, or 0.5 mg/kg, $n = 10$) SC 1 h prior to the administration of naloxone (0.1 mg/kg).

### *Statistical Analysis*

Nonparametric statistical analyses were employed (25). Horizontal locomotor activity and number of jumps were analyzed using the Kruskal–Wallis one-way analysis of variance, and significant effects were further investigated using the Mann–Whitney *U*-test (two-tailed). The Fisher exact probability test was used to compare the proportions of subjects showing jumping compared to controls. Differences were considered statistically significant if the calculated probability was less than 5% ($p < 0.05$).

## RESULTS

### *Experiment 1: Effect of Clozapine on Naloxone (15.0 mg/kg)-Induced Withdrawal Jumping*

Clozapine significantly and dose dependently reduced locomotor activity ($H = 21.61$, $p < 0.001$). Mann–Whitney *U*-tests revealed that the highest dose of clozapine (3.0 mg/kg) significantly ($U = 1.0$, $p < 0.001$) reduced locomotor activity

(Fig. 1A). There was no significant effect of clozapine upon naloxone-induced jumping behavior ($H = 5.36$, $p = 0.2$) (Fig. 1B), nor was there a significant effect upon the proportion of mice jumping compared to controls (saline 9/10, 0.03 mg/kg 10/10, $p = 0.5$; 0.3 mg/kg, 8/10, $p = 0.39$; 3.0 mg/kg, 9/10, $p = 0.53$).

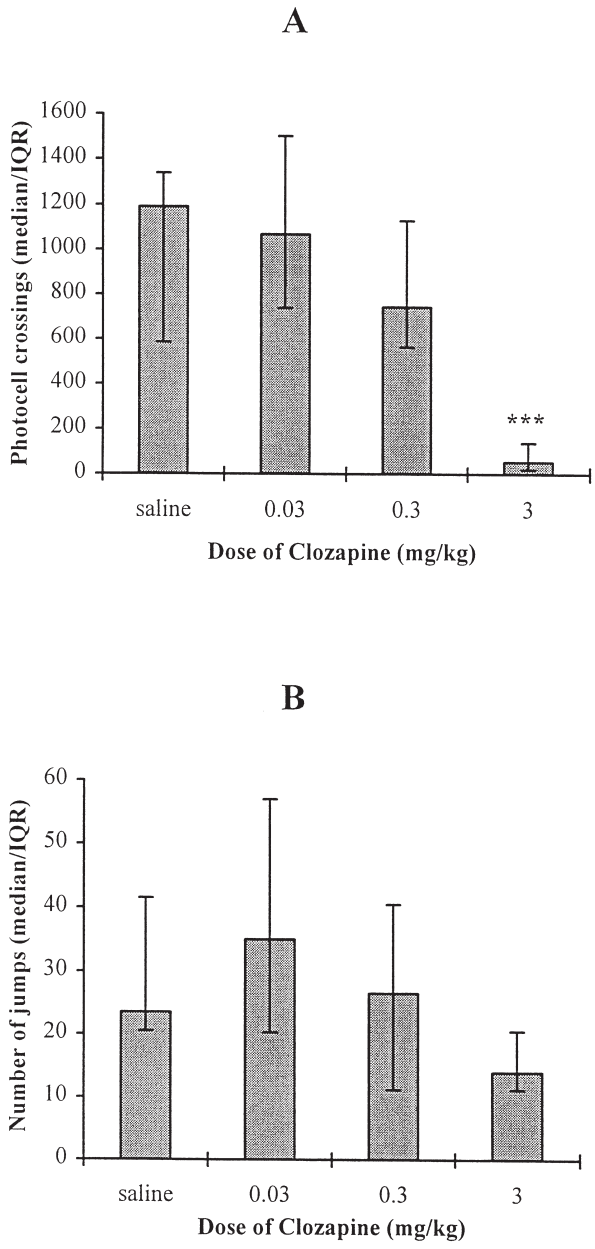


FIG. 1. The effect of clozapine administration (0, 0.03, 0.3, or 3.0 mg/kg SC, $n = 10$) to morphine-dependent mice, 2 h following the last morphine injection (320.0 mg/kg SC). Horizontal locomotor activity (number of photocell crossings) was measured 50 min after clozapine administration, for a 10-min period (A); immediately followed by administration of naloxone (15.0 mg/kg IP) and measurement of number of withdrawal jumps in a 10-min period (B). The data is expressed as median values with interquartile ranges (IQR). (***$p < 0.001$, Mann–Whitney $U$-test).

*Experiment 2: Effect of Haloperidol on Naloxone (15.0 mg/kg)-Induced Withdrawal Jumping*

Haloperidol significantly and dose dependently reduced locomotor activity ($H = 15.26$, $p < 0.01$). Mann–Whitney $U$-tests revealed that animals administered 0.05 ($U = 13.0$, $p < 0.01$) and 0.1 ($U = 2.0$, $p < 0.001$) mg/kg haloperidol showed significant reductions compared to controls (Fig. 2A). Haloperidol did not significantly affect naloxone-induced

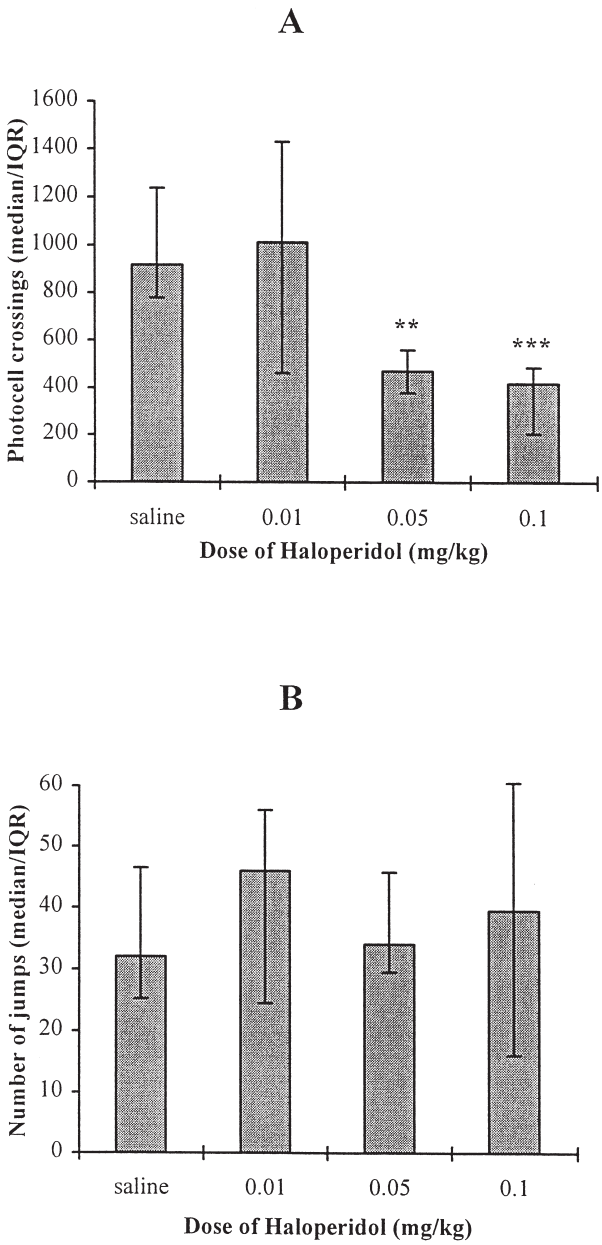


FIG. 2. The effect of haloperidol administration (0, 0.01, 0.05, or 0.1 mg/kg, $n = 10$) to morphine-dependent mice on (A) horizontal locomotor activity (number of photocell crossings) and (B) number of naloxone-induced withdrawal jumps (see legend of Fig. 1 for further details). The data is expressed as median values with interquartile ranges (IQR). (**$p < 0.01$, ***$p < 0.001$, Mann–Whitney $U$-test).

jumping behavior ($H = 0.43$, $p = 0.9$) (Fig. 2B). Haloperidol also did not significantly affect the proportion of mice jumping at any dose tested (saline 10/10, 0.01 mg/kg, 10/10, $p = 1$; 0.05 mg/kg, 10/10, $p = 1$; 0.1 mg/kg, 10,10, $p = 1$).

*Experiment 3: Effect of Clonidine on Naloxone (15.0 mg/kg)-Induced Withdrawal Jumping*

Clonidine significantly and dose dependently reduced locomotor activity ($H = 23.92$, $p < 0.001$). Mann–Whitney *U*-tests revealed that animals administered 0.1 ($U = 12.0$, $p < 0.01$) and 0.5 ($U = 0$, $p < 0.001$) mg/kg clonidine differed significantly from the control group (Fig. 3A). There was no significant ($H = 5.58$, $p = 0.1$) effect of clonidine on naloxone-induced jumping behavior (Fig. 3B). In addition, 0.02 (10/10, $p = 0.47$), 0.1 (10/10, $p = 0.47$), and 0.5 (9/10, $p = 0.53$) mg/kg clonidine did not affect the proportion of mice jumping compared to controls (saline 8/9).

*Experiment 4: Effect of Clozapine on Naloxone (0.1 mg/kg)-Induced Withdrawal Jumping*

As in Experiment 1, it was found that clozapine significantly and dose dependently reduced horizontal locomotor activity ($H = 19.98$, $p < 0.001$, Fig 4). The highest dose (3.0 mg/kg) produced a significant ($U = 0$, $p < 0.001$) reduction in locomotor activity. Naloxone induced a very low baseline of withdrawal jumping, i.e., in the control group, three out of nine mice jumped 2, 4, and 38 times, respectively, which provides a suitable baseline for assessing the ability of test drugs to augment withdrawal jumping. Clozapine did not increase jumping, as only two to three out of nine mice displayed two to three jumps each at each dose tested ($H = 0.76$). There was no significant effect on proportion of mice jumping following doses of 0.03 (two out of nine, $p = 0.35$), 0.3 (three out of nine, $p = 0.38$), and 3.0 (two out of nine, $p = 0.35$) mg/kg clozapine, compared to the control group.

*Experiment 5: Effect of Haloperidol on Naloxone (0.1 mg/kg)-Induced Withdrawal Jumping*

Haloperidol significantly ($H = 27.25$, $p < 0.001$) reduced locomotor activity at all doses tested, 0.01 ($U = 11.0$, $p < 0.01$), 0.05 ($U = 6.0$, $p < 0.01$), 0.1 ($U = 0$, $p < 0.001$) mg/kg compared to saline-treated mice (Fig. 5). In Experiment 2, 0.01 mg/kg haloperidol did not significantly reduce locomotor activity; however, as shown in Fig. 2A, this group had a larger interquartile range compared to the present experiment. There was no significant difference ($H = 3.22$) in total number of jumps between the control group and haloperidol-treated mice (3–5 out of 10 mice made 1–15 jumps). 0.01 (3 out of 10, $p = 0.35$), 0.05 (5 out of 9, $p = 0.11$), and 0.1 (3 out of 10, $p = 0.35$) mg/kg haloperidol did not significantly affect the proportion of mice jumping compared to controls (2 out of 10 jumping).

*Experiment 6: Effect of Clonidine on Naloxone (0.1 mg/kg)-Induced Withdrawal Jumping*

As in Experiment 3, clonidine significantly and dose dependently reduced locomotor activity ($H = 18.48$, $p < 0.001$; Fig. 6). Mann–Whitney *U*-tests revealed that animals administered 0.1 ($U = 16.0$, $p < 0.05$) and 0.5 ($U = 12.0$, $p < 0.01$) mg/kg clonidine were significantly different from controls. There was no difference in number of jumps or proportion of mice jumping in each group (saline, 0.02, 0.1, 0.5 mg/kg 0/10 animals jumping).

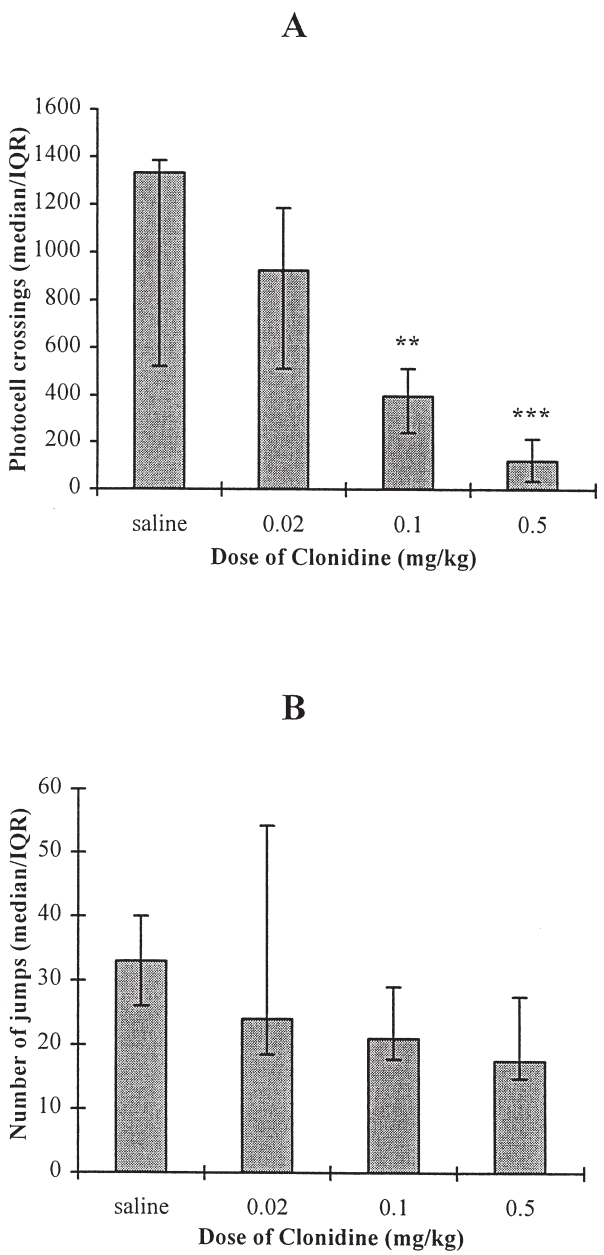


FIG. 3. The effect of clonidine administration (0, 0.02, 0.1, or 0.5 mg/kg, $n = 9$–10) to morphine-dependent mice on (A) horizontal locomotor activity (number of photocell crossings) and (B) number of naloxone-induced withdrawal jumps (see legend of Fig. 1 for further details). The data is expressed as median values with interquartile ranges (IQR). (**$p < 0.01$, ***$p < 0.001$, Mann–Whitney *U*-test).

## DISCUSSION

Clozapine significantly and dose dependently reduced locomotor activity, indicating that within the procedure being used, the compound was exerting pharmacological effects. Clozapine neither increased nor decreased withdrawal jumping induced by 15.0 mg/kg naloxone. Although the lower dose slightly increased the number of jumps (Fig. 1B), this was not significantly different. Clozapine did not augment withdrawal

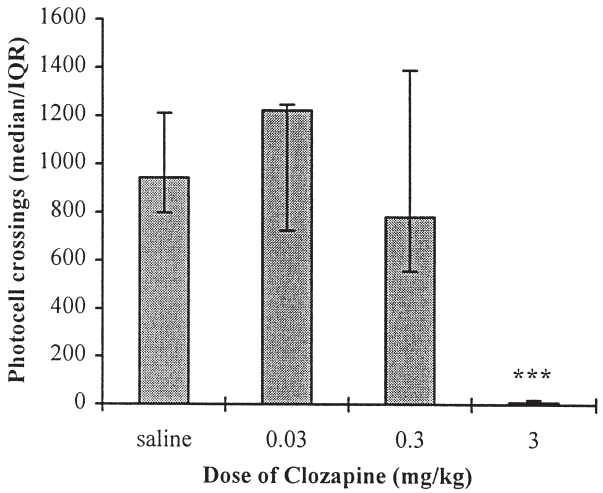


FIG. 4. The effect of clozapine administration (0, 0.03, 0.3, or 3.0 mg/kg SC, $n = 9$) to morphine-dependent mice, 2 h following the last morphine injection (320.0 mg/kg SC). Horizontal locomotor activity (number of photocell crossings) was measured 50 min after clozapine administration, for a 10-min period. The data is expressed as median values with interquartile ranges (IQR). (***$p < 0.001$, Mann–Whitney *U*-test).

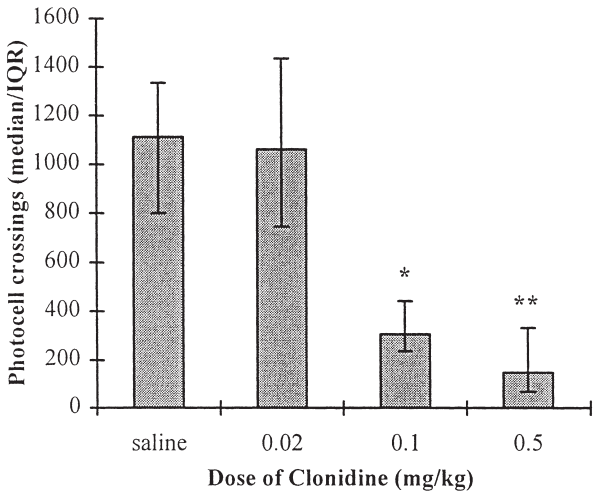


FIG 6. The effect of clonidine administration (0, 0.02, 0.1, or 0.5 mg/kg, $n = 10$) to morphine-dependent mice on horizontal locomotor activity (number of photocell crossings) (see legend of Fig. 4 for further details). The data is expressed as median values with interquartile ranges (IQR). (*$p < 0.05$, **$p < 0.01$, Mann–Whitney *U*-test).

jumping induced by 0.1 mg/kg naloxone. Furthermore, the compound did not effect jumping behavior in mice administered a middle dose (1.0 mg/kg) of naloxone, which induced jumping in approximately 50% of mice (preliminary data). These results differ from those in a previous study (5). Although the reason for this difference may be due to the use of guinea pigs and a procedure using only a single high dose of morphine (5), mice and guinea pigs display similar morphine withdrawal signs following acute administration of naloxone (29). It has also been demonstrated that a single dose of morphine is adequate to initiate dependence in both mice (12,18) and rats (24).

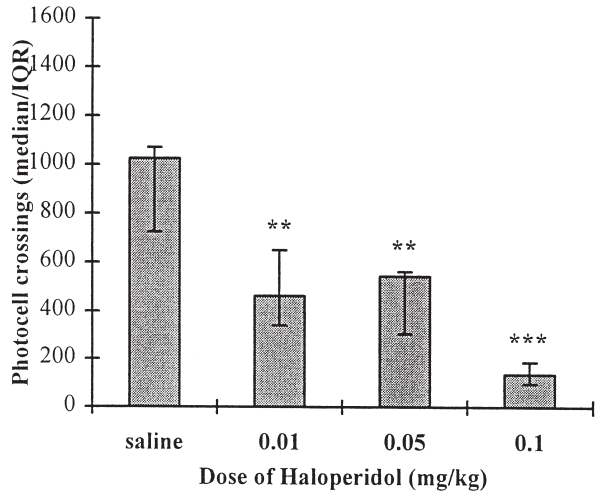


FIG. 5. The effect of haloperidol administration (0, 0.01, 0.05, or 0.1 mg/kg, $n = 9$–10) to morphine-dependent mice on horizontal locomotor activity (number of photocell crossings) (see legend of Fig. 4 for further details). The data is expressed as median values with interquartile ranges (IQR). (**$p < 0.01$, ***$p < 0.001$, Mann–Whitney *U*-test).

Haloperidol also significantly and dose dependently reduced horizontal locomotor activity, confirming that an appropriate dose range was chosen for a pharmacological effect. In agreement with previous studies (3,7,11,23,34), haloperidol did not have any effect on naloxone-induced jumping.

Clonidine significantly and dose dependently reduced locomotor activity. This effect parallels the sedative effect reflected in some animals by a reduction in exploratory activity, which has been noted following peripheral and central administration of clonidine in morphine-dependent rats prior to naloxone (10). Although there appeared to be a slight decrease in the frequency of jumping following the high dose of naloxone, the dose–response curve was shallow, and the effect not statistically significant. Furthermore, there was no effect on jumping following the low dose of naloxone. Although some studies have recorded slight increases (30,33) or small (8) or large (32) decreases in withdrawal jumping, the majority have also reported no effect (7,10,17,22).

The experiments described above failed to demonstrate differences between clozapine and haloperidol on naloxone-induced withdrawal jumping, and furthermore, failed to demonstrate an effect per se, even though motor-debilitating doses were used. The reduction in locomotor activity in morphine-dependent mice is presumably related to DAergic blockade, as morphine-induced hyperactivity is accompanied by increased striatal DA turnover (2,19,28). Therefore, the lack of effect on withdrawal jumping implies that either these drugs do not antagonise DA receptors involved in jumping, or that jumping per se cannot be reduced by DA antagonists. An explanation for this is the possibility that DA may interact with other neurotransmitters to mediate withdrawal jumping, particularly as there is evidence for serotonergic and noreadrenergic involvement in withdrawal jumping (7,23,32,34).

Despite the lack of differences between clozapine and haloperidol given acutely, it would be interesting to examine the effects of the drugs given in higher doses [the experiments in

guinea pigs used a single high dose of clozapine (5)] or chronically. Compared to chronic clozapine administration, chronic haloperidol may increase $D_2$ receptor density and basal DA release in the striatum and NAc (14,35). Chronic haloperidol modifies both A9 and A10 DAergic neural activity, whereas clozapine appears to selectively modifies A10 neural activity (26). Furthermore, chronic administration of clozapine produces a change in FosB-like immunoreactivity in the PFC (31). Nevertheless, the experimental design would have to take into account a potential interaction of the neuroleptics with the development of morphine tolerance over the experimental period.

Within the parameters of the experiments described above, neither haloperidol nor clozapine modified naloxone-precipitated withdrawal jumping in morphine-dependent mice. Withdrawal jumping in mice does not result in a baseline of behavior that distinguishes between acute administration of typical and atypical neuroleptics.

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