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Morphine withdrawal-facilitated aggression is attenuated by morphine-conditioned stimuli

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Abstract

There is a considerable body of evidence indicating that stimuli associated with drug administration may become conditioned and evoke drug-like effects. The purpose of this study was to evaluate the ability of morphine-paired stimuli to affect an expression of morphine withdrawal-facilitated aggression. Individually housed aggressive adult mice were subjected to the repeated subcutaneous administration of morphine (twice a day, 8 days, increasing doses 10–80 mg/kg). Morphine treatment cessation facilitated an aggressive behaviour of animals during the second day of withdrawal. Subcutaneous but not intraperitoneal injection of saline attenuated the aggressive behaviour in morphine-withdrawn mice. These results suggest that the site of drug injection may serve as a conditioned stimulus.

Keywords: Morphine; Aggression; Withdrawal; Conditioning; Mice

There is a number of experimental studies showing that stimuli associated with drug administration may become conditioned and evoke drug-like effects (Pert et al., 1990; Tye and Iversen, 1977; Walter and Kuschinsky, 1989). Drug-associated stimuli can mimic the states produced by the drugs themselves and thereby increase the probability of drug-related effects, e.g., reinstate drug self-administration (Stewart et al., 1984), induce drug-like alterations in locomotor activity (Pert et al., 1990; Pertuzzi et al., 1997), serve as second-order reinforcers (Burns et al., 1994), provoke craving and precipitate relapse (Childress et al., 1998; O'Brien et al., 1992), and produce drug-like subjective effects in humans (Muntaner et al., 1989; O'Brien et al., 1988).

The classical conditioning of drug effects can be shown by placing experimental animals into the environment in which they had repeatedly received a drug treatment or by presenting the specific stimuli (e.g., light, sound, odor) previously paired with a drug. Such drug-conditioned responses have been shown for variety of psychoactive substances such as psychostimulants (Pert et al., 1990), opiates (Walter and Kuschinsky, 1989), etc.

Experimental reports provide evidence for both conditioned drug withdrawal and conditioned suppression of drug withdrawal. In morphine-dependent rats, withdrawal signs (e.g., "wet dog"-like shakes) occur more frequently in the environment associated with morphine injections (Caille et al., 1998; Trost, 1973). Similar results were obtained with the antagonist-precipitated withdrawal (Goldberg and Schuster, 1970). On the other hand, auditory, olfactory, and social stimuli previously paired with the injection of morphine cause reduction in withdrawal signs when presented during the withdrawal (Lal et al., 1976; Miksic et al., 1976).

One of the behavioural changes during morphine withdrawal is heightened aggressive behaviour (Kantak and Miczek, 1986, 1988). These data were obtained for the spontaneous withdrawal and both the prior fighting experience and the social status of the animal were established as important determinants of aggression. At the same time, there is some evidence that aggressive bursts may be paired with environmental stimuli (Martinez et al., 1995; Vekovischeva et al., 1998), and therefore,

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may be sensitive to the conditioning. The present study addressed morphine withdrawal-facilitated aggression to examine if morphine-paired injection site may become a conditioned stimulus.

1. Methods

1.1. Subjects

Forty-eight adult male Swiss mice bred at State Breeding Farm "Rappolovo" (St. Petersburg) and weighing 25–30 g were used. Mice were kept in plastic cages with metal lids and unlimited access to standard rodent food chow and filtered tap water under 12-h/12-h light–dark cycle (lights on at 08:00 h). Experimental procedures were approved by the Ethics Committee of Pavlov Medical University and were performed in accordance with the recommendations and policies of the US National Institutes of Health Guidelines for the Use of Animals.

1.2. Procedure

Immediately after the arrival from the breeding centre mice were housed in groups of five. Animals that exhibited aggressive behaviours (bites, attacks, threats) toward their cage mates (approximately 20–30% from the total number of mice admitted to the study) were removed and housed individually for 7 days (Days 1–7). On Day 8, resident mice were screened for attack behaviour using a social interaction test (see below). Only mice that displayed aggression toward a nonaggressive group-housed intruder mice were used in the experiment (approximately 60–70% from the total number of mice selected for individual housing).

On Days 9–22 (2 weeks), selected mice were housed individually. On Day 23, mice were subjected to the social interaction test and baseline level of aggression for each animal was assessed. On Days 23–30, mice were assigned to the different experimental groups ($n = 11–12$ in each group) used in the following experiments.

1.2.1. Experiment I: The time course of aggressive behaviour during the morphine withdrawal

Experimental group of animals ($n = 12$) was exposed to repeated morphine treatment for 8 days increasing doses of morphine according to the following schedule: Day 23, 10 mg/kg (18:00 h); Day 24, 20 mg/kg; Day 25, 30 mg/kg; Day 26, 40 mg/kg; Day 27, 50 mg/kg; Day 28, 60 mg/kg; Day 29, 70 mg/kg; Day 30, 80 mg/kg (09:00 h). The control group ($n = 12$) received physiological saline subcutaneously twice a day (at 09:00 and at 18:00 h). Social interaction tests were conducted 24, 48, 72, 96, and 120 h after the last morphine/saline injection (i.e., Days 31, 32, 33, 34, and 35 of the experiment).

1.2.2. Experiment II: The effect of subcutaneous vs. intraperitoneal saline injection on the expression of morphine withdrawal-facilitated aggression

Experimental groups were repeatedly injected subcutaneously with saline (Groups I and II) twice a day (at 09:00 and at 18:00 h) or morphine (Groups III and IV) according to the above schedule and 48 h after the last morphine injection (Day 32) received: Group I ($n = 11$, saline, subcutaneous), Group II ($n = 11$, saline, intraperitoneal), Group III ($n = 11$, saline, subcutaneous), and Group IV ($n = 11$, saline, intraperitoneal).

1.3. Social interaction test

Behavioural observations were made during the light period of the day–night cycle, between 10:00 and 12:00 h. Tests were carried out in the home cages of experimental mice. A group-housed nonaggressive male mouse (intruder) was placed into the home cage of an experimental subject (resident). During the 4 min of observation, durations and sequences of 40+ items of resident's behaviour (acts and postures) were recorded using the customized PC-based data acquisition system. After the social interaction test was completed, the intruder was returned to its home cage.

The behaviours were classified into two broad classes: social behaviours and individual (nonsocial) behaviours. (1) Social behaviour: (a) agonistic behaviours included aggressive behaviour (attacks/bites, threats, tail-rattling) and defensive behaviour (upright and sideways postures, pushing, retreat); (b) social activities encompassed social investigation (sniffing of nose, body, anogenital region, following, grooming of the partner) and others social contacts (crawl over, crawl under, huddling, passive contact). (2) Nonsocial or individual behaviour: (a) motor activities comprised walking, rotation, rearing, jumping, digging, and push digging; (b) maintenance allied eating, self-grooming, shaking, scratching, stretching; (c) static postures included sitting and lying.

1.4. Drugs

Morphine hydrochloride ("Endocrinnyj Zavod", Moscow, Russia) was dissolved in physiological saline. Injection volume was 1 ml/100 g of body weight. Nonpyrogenic needles 25GX5/8″ (Terumo Europe, Leuven, Belgium) were used for injections.

1.5. Data analysis

For the social interaction test, the durations ([cumulative time of the element expression/session duration] × 100%) and frequencies ([number of times the element was expressed/total number of behavioural counts per session] × 100%), of each behavioural item or group of items as well as the total number of transitions between behavioural

elements were calculated. For the sake of clarity and brevity, results of the analysis are represented using only relative durations of the selected clustered elements (i.e., aggression: attacks, bites, threats, tail rattling; sociability: sniffing and grooming of the partner, following, crawl over, crawl under; nonsocial motor activity: walking, rearing, retreat; static items: sitting, sitting with sniffing) rather than all elements item by item.

To reduce the overall variability before the statistic analysis, the data are represented as percent of baseline for each group. Then, an analysis of variance (ANOVA) was carried out using SAS-STAT software (ver. 6.11, SAS Institute, Cary, NC). Repeated measures design was applied wherever needed (Experiment I). Following the rank transformation, data were subjected to the multivariate ANOVA. For Experiment I, independent variables were "withdrawal" (repeated morphine vs. repeated saline) and "day" (days after morphine/saline treatment cessation). For Experiment II, independent variables were "withdrawal" (repeated morphine vs. repeated saline) and "route" (subcutaneous vs. intraperitoneal route of acute saline injection). Duncan's and *t* tests were used for the post hoc pairwise group comparisons.

2. Results

There were no differences in the baseline behaviour among all treatment groups. Analysis of behavioural baseline data of all experimental groups did not find significant differences between them neither for duration [attacks, $F(1,60) = 1.89$, NS; threats, $F(1,60) = 0.12$, NS; tail rattling,

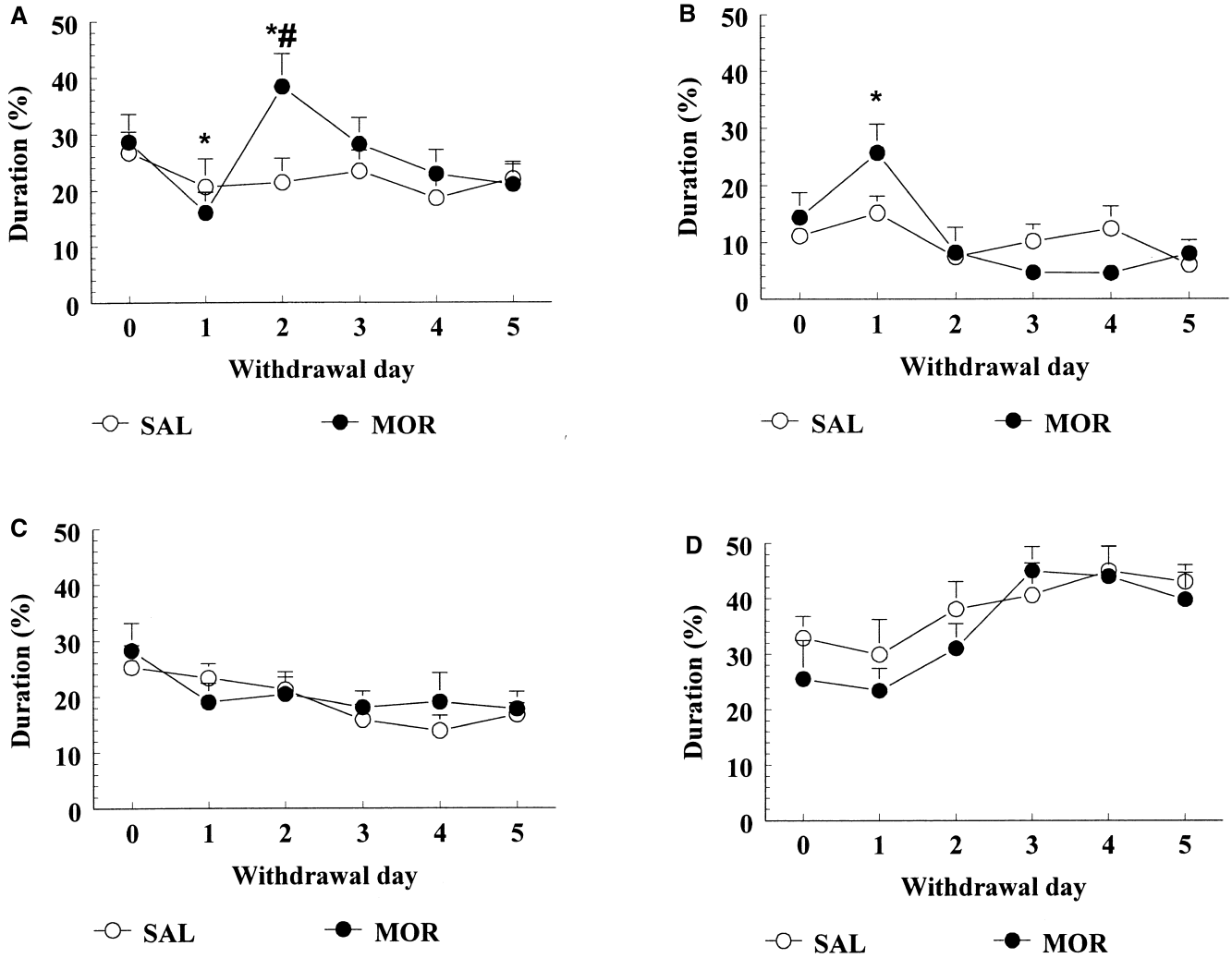

Fig. 1. Behavioural effects of morphine withdrawal in aggressive isolated male mice. Tests were conducted 24 h (Day 1), 48 h (Day 2), 72 h (Day 3), 96 h (Day 4), and 120 h (Day 5) after the last morphine (MOR) or saline (SAL) injection. Data are represented as mean (+S.E.M., $n = 12$ per group) relative duration (% from the test duration). The zero point on the *X* scale corresponds baseline data. "Aggression" (A) comprises attacks/bites, sideways threats and tail rattling items; "sociability" (B) comprises sniffing and grooming of the partner, following, crawl over, crawl under; "nonsocial motor activity" (C) comprises walking, rearing, retreat; "static items" (D) comprises sitting, sitting with sniffing. * $P < .05$ (Duncan's test) compared to baseline data, $^{\#}P < .05$ compared to SAL group.

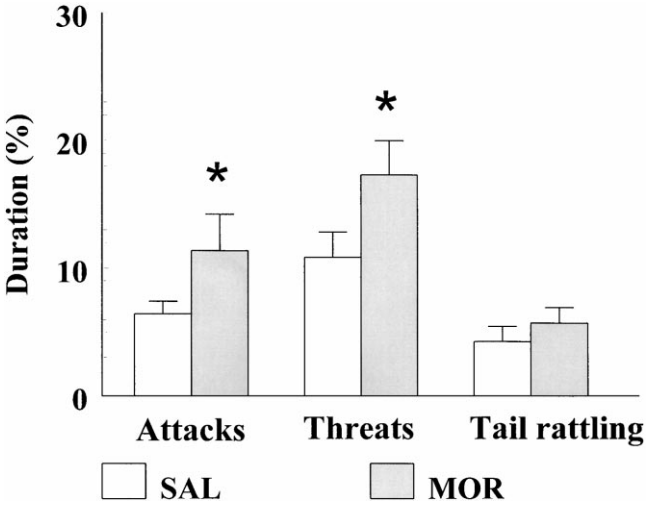

Fig. 2. Alterations in separate constituents of aggressive pattern 48 h after cessation of repeated morphine administration. Data are represented as mean (+S.E.M., $n=12$ per group) relative duration (% from the test duration) of attacks, threats and tail rattling. * $P<.05$ (t test) compared to SAL group.

$F(1,60)=0.0$, NS] nor for frequency of aggressive events [attacks, $F(1,60)=2.88$, NS; threats, $F(1,60)=1.55$, NS; tail rattling, $F(1,60)=0.81$, NS].

2.1. Experiment I: The time course of aggressive behaviour during the morphine withdrawal

The morphine withdrawal increased an aggressive behaviour in resident mice toward drug-naive nonaggressive intruder mice. This effect was significantly influenced by time [$F(1,17)=3.75$, $P<.01$] for Withdrawal × Day interaction. As shown in Fig. 1, on Withdrawal Day 1 there were no differences in the level of aggression between morphine and saline group but the aggression of morphine group significantly suppressed as compare to baseline level. On Withdrawal Day 2 (48 h after the last morphine injection), the elevation of the total duration of aggressive events (attacks, threats, and tail rattling) in morphine-withdrawn mice was the most pronounced and significantly differed from the level of aggression in the repeated saline-treated mice [$F(1,17)=19.33$, $P<.01$]. Fig. 2 indicates the individual components of the aggressive burst that significantly altered by morphine withdrawal. The duration of attacks and threats in withdrawn aggressive mice was significantly increased [$F(1,17)=3.47$, $P<.05$, and $F(1,17)=2.58$, $P<.05$, respectively], while changes in the duration of tail rattling [$F(1,17)=0.24$, NS] and in the frequency of aggressive behaviours [$F(1,17)=1.67$, NS] did not reach the level of statistical significance.

Extinction of withdrawal-facilitated aggression was observed over next 3 days of withdrawal (Fig. 1). Sociability was affected by morphine withdrawal [$F(1,17)=2.59$, $P<.05$] due to enhancement on first day of one. Nonsocial motor activity [$F(1,17)=1.52$, NS], as well as the static behaviour [$F(1,17)=0.46$, NS] in morphine-withdrawn mice did not differ from saline withdrawn animals (Fig. 1).

2.2. Experiment II: The effect of subcutaneous vs. intraperitoneal saline injection on the expression of morphine withdrawal-facilitated aggression

The route of the test saline injections influenced the expression of morphine withdrawal-facilitated aggression. Global ANOVA suggested a significant Withdrawal × Route interaction for the duration of attacks [$F(1,43)=7.72$, $P<.01$], threats [$F(1,43)=8.09$, $P<.01$], and the total duration of aggressive events [$F(1,43)=13.01$, $P<.01$]. As to the frequency data, a significant Withdrawal × Route interaction was found for attacks only [$F(1,43)=3.93$, $P<.05$]. The tail rattling was not significantly changed, both in the duration [$F(1,43)=2.36$, NS] and in the frequency [$F(1,43)=3.0$, NS].

In morphine-withdrawn mice, intraperitoneal injections of saline did not affect an elevation of the aggressive behaviour on Day 2 of the morphine withdrawal. The total duration of aggressive bursts was significantly increased [$F(1,20)=8.50$, $P<.05$] in morphine-treated vs. saline-treated mice (Fig. 3) as it was in Experiment I. Among the individual components of aggressive behaviour (Table 1), the attacks' duration [$F(1,20)=5.14$, $P<.05$] and the tail rattling duration [$F(1,20)=7.60$, $P<.05$] were significantly heightened.

Subcutaneous saline injection attenuated the total duration of aggressive behaviour (Fig. 3) of morphine-with-

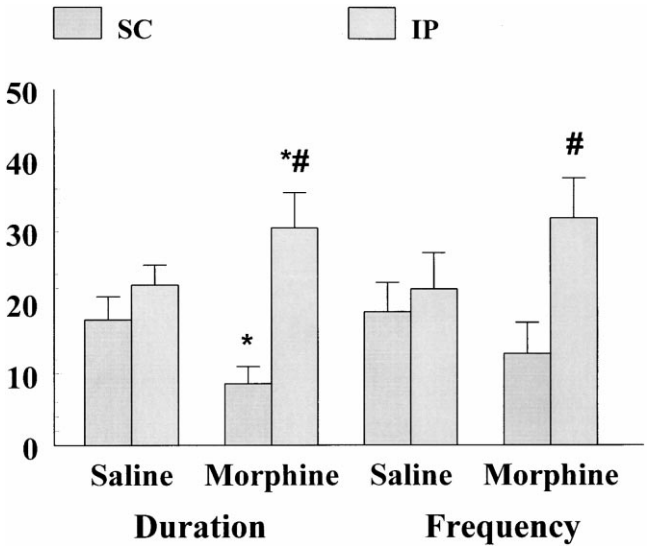

Fig. 3. Effects of acute subcutaneous (SC) and intraperitoneal (IP) saline injections on aggressive behaviours in mice subcutaneously treated with repeated saline ("Saline") vs. repeated morphine ("Morphine"). Tests were conducted 48 h after cessation of repeated morphine administration. Data are represented as mean (+S.E.M., $n=11$ per group) relative duration (% from the test duration) and frequency (% from the total number of behavioural counts per session). * $P<.05$ (t test) compared to saline group, # $P<.05$ (t test) when compared intraperitoneal vs. subcutaneous injection.

Table 1
Acute subcutaneous/intraperitoneal saline effects in mice subcutaneously treated with repeated morphine vs. repeated saline

Acute injection	Repeated injections	Items of aggressive behaviour		
		Attacks/bites	Threats	Tail rattling
Duration				
Saline, subcutaneous	Saline, subcutaneous	5.72 ± 1.39	8.71 ± 1.28	3.14 ± 0.87
Saline, intraperitoneal	Saline, subcutaneous	9.74 ± 2.07	9.15 ± 1.7	2.58 ± 0.5
Saline, subcutaneous	Morphine, subcutaneous	2.35 ± 0.74 *,#	4.12 ± 1.00 *,#	2.12 ± 1.14#
Saline, intraperitoneal	Morphine, subcutaneous	11.74 ± 2.81	13.21 ± 2.08	5.55 ± 1.07 *
Frequency				
Saline, subcutaneous	Saline, subcutaneous	4.74 ± 1.30	10.88 ± 1.98	3.07 ± 1.22
Saline, intraperitoneal	Saline, subcutaneous	8.62 ± 2.33	11.00 ± 2.47	2.27 ± 0.84
Saline, subcutaneous	Morphine, subcutaneous	2.52 ± 0.08 *,#	7.23 ± 1.95#	3.07 ± 1.62
Saline, intraperitoneal	Morphine, subcutaneous	9.28 ± 2.66	17.45 ± 3.31	5.25 ± 2.45

Data are represented as mean (+S.E.M., $n=11$ per group) relative duration (% from the test duration) and frequency (% from the total number of behavioural counts per session).

* $P<.05$ (t test) compared to saline group.

\# $P<.05$ (t test) when compared intraperitoneal vs. subcutaneous injection.

drawn mice [$F(1,20)=9.80$, $P<.01$]. More detailed analysis of aggressive items (Table 1) found a significant decrease for the duration [$F(1,20)=12.05$, $P<.01$] and frequency of attacks [$F(1,20)=7.85$, $P<.05$], as well as for the duration of threats [$F(1,20)=5.95$, $P<.05$], after subcutaneous saline injection in morphine-withdrawn mice.

3. Discussion

In line with the previous reports, the present study found morphine withdrawal to facilitate an aggressive behaviour. Miksic et al. (1976) observed aggressive responses in rats withdrawn for 72 h after 15-day period of morphinization (a maintenance dose of 400 mg/kg/day was reached in 10 days and was continued for 5 additional days). In a more detailed study, Kantak and Miczek (1986) assessed aggressive behaviour facilitated by spontaneous (natural) and antagonist-precipitated morphine withdrawal and found significant increases in attack bites and threats after the removal of morphine pellet in resident mice. Naloxone injection (precipitated withdrawal) prevented the facilitation of aggressive behaviour of morphine-withdrawn mice. Despite of procedural differences (doses, route, and duration of morphine administration), our results are consistent with the observations that 48 h (Day 2) after the last morphine administration, the facilitation of aggression reaches the maximum (Tidey and Miczek, 1992a,b). Conversely, 24 h after the last morphine injection (Day 1), an aggressive behaviour is suppressed (Fig. 1), which may be, at least in part, due to severe somatic withdrawal state (Sukhotina and Bespalov, 2000) expressed as significant elevation in ''wet dog''-like shaking activity and various other withdrawal signs (ptosis, piloerection, tremor, genital grooming/ejaculation, vocalization). In the present study, the social interaction test revealed that the pronounced decrease of locomotor activity as well as the significant enhancement of the self-grooming, shakes, and rearing frequencies were most prominent on Day 1 of morphine withdrawal. The facilitation of aggression on Day 2 in morphine-withdrawn mice: (1) reached approximately 130–140% compared to baseline data (Fig. 1); (2) developed while somatic withdrawal symptoms diminished, and (3) significantly exceeded the level of aggression in the saline withdrawn group of animals. Such increase in aggressiveness can certainly be viewed as a behavioural sign of morphine withdrawal. Therefore, in further experiments on conditioned suppression of withdrawal-related aggression, behavioural observations were focusing on Day 2 of morphine withdrawal.

Both acute and chronic morphine were earlier reported to possess antiaggressive properties (Miczek et al., 1994). Starting from the dose of 5 mg/kg, morphine selectively decreases aggression of isolated male mice, while at higher doses, morphine inhibits attack behaviour primarily due to the appearance of motor impairment (Poshivalov, 1982). Thus, assuming that repeated morphine injection procedure allows for explicit conditioning of the injection site, one could expect that saline injection to morphine injection site would evoke behavioural effects resembling those of morphine itself, e.g., reverse withdrawal symptoms (Tye and Iversen, 1977). Our data seem to support this contention. Subcutaneous injection procedure significantly diminished the total duration of aggression facilitated by morphine withdrawal. In these experiments, subcutaneous injection delivered saline to the injection site that was previously paired with morphine administration.

Conditioned responses may significantly increase the risk of relapse and their modification may offer important new targets for treatment (O'Brien et al., 1998). Drug-associated stimuli can enhance the probability of drug-related effects, e.g., reinstate drug self-administration (Stewart et al., 1984) and provoke craving and precipitate relapse (Childress et al., 1998; O'Brien et al., 1992).

Stimuli associated with drugs were also shown to decrease the intensity of the withdrawal syndrome triggered

by the cessation of repeated prolonged drug exposure. One of the first studies on conditioned suppression of morphine withdrawal was conducted by Thompson and Schuster (Thompson and Schuster, 1964). Withdrawal from morphine produced profound disruption of operant shock avoidance and ratio food-reinforced behaviours. This behavioural disruption was ameliorated by both morphine administration and administration of saline in conjunction with stimuli associated with morphine. These results were later replicated in a number of experimental settings (e.g., Bespalov et al., 1998; Caille et al., 1998; Lal et al., 1976; Tye and Iversen, 1977). It is noteworthy that the presentation of morphine-associated stimuli to morphine-withdrawn subjects reduces both somatic and nonsomatic measures of withdrawal severity. For example, a reduction of morphine withdrawal rats' aggression by social conditioned stimuli was observed (Miksic et al., 1976). In this study animals for which a social experience was paired with each morphine injection, showed significantly less morphine-withdrawal aggression than rats that either remained socially isolated throughout the addiction period or were socially exposed during between-injection intervals. The results of our study show that an injection ritual also has to be taken into account as a potential conditioned stimulus.

In conclusion, morphine withdrawal facilitates an aggressive behaviour of isolated male mice. The effect was the most pronounced 48 h after the last morphine injection. The injection ritual may be established as a conditioned stimulus after being repeatedly paired with the drug effect. Saline injection to morphine-paired site reduces the morphine withdrawal-facilitated aggression.

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References

Bespalov AY, Beardsley P, Balster RL. Evaluation of the interaction between *N*-methyl-D-aspartate receptor antagonists and discriminative stimulus effects of morphine in rats. Pharmacol, Biochem Behav 1998; 60:507–17.

Burns LH, Everitt BJ, Robbins TW. Glutamate–dopamine interactions in the ventral striatum: role in locomotor activity and responding with conditioned reinforcement. Psychopharmacology (Berlin) 1994; 115:516–28.

Caille S, Cador M, Stinus L. Effects of total noradrenergic and serotoninergic lesion on the expression of the conditioned opiate withdrawal syndrome. Behav Pharmacol 1998;9:S22.

Childress AR, McLellan AT, Ehrman R, O'Brien CP. Classically conditioned responses in opioid and cocaine dependence: a role in relapse? NIDA Res Monogr 1998;84:25–43.

Goldberg SR, Schuster CR. Conditioned nalorphine-induced abstinence changes: persistence in post morphine-dependent monkeys. J Exp Anal Behav 1970;14:33–46.

Kantak K, Miczek K. Aggression during morphine withdrawal: effects of method of withdrawal, fighting experience, and social role. Psychopharmacology (Berlin) 1986;90:451–6.

Kantak K, Miczek K. Social, motor, and autonomic signs of morphine withdrawal; differential sensitivities to catecholaminergic drugs. Psychopharmacology (Berlin) 1988;96:468–76.

Lal H, Miksic S, Drawbaugh R, Numan R, Smith N. Alleviation of narcotic withdrawal syndrome by conditional stimuli. Pavlovian J Biol Sci 1976;11:251–62.

Martinez M, Guillen-Salazar F, Salvador A, Simon VM. Successful intermale aggression and conditioned place preference in mice. Physiol Behav 1995;58:323–8.

Miczek K, DeBold JF, Haney M, Tidey J, Vivian J, Weerts EM. Alcohol, drugs of abuse, aggression and violence. In: Reiss AJ, Roth JA, editors. Violence (social influences). Washington, DC: National Academy Press, 1994. pp. 377–570.

Miksic S, Smith N, Lal H. Reduction of morphine-withdrawal aggression by conditional social stimuli. Psychopharmacology (Berlin) 1976; 48:115–7.

Muntaner C, Cascella NG, Kumor KM, Nagoshi C, Herning R, Jaffe J. Placebo responses to cocaine administration in humans: effects of prior administrations and verbal instructions. Psychopharmacology (Berlin) 1989;99:282–6.

O'Brien CP, Childress AR, Arndt IO, McLennan AT, Woody GE, Maany I. Pharmacological and behavioral treatments of cocaine dependence: controlled studies. J Clin Psychiatry 1988;49:17–22.

O'Brien CP, Childress AR, McLellan AT, Ehrman R. A learning model of addiction. In: O'Brien CP, Jaffe JH, editors. Addictive states. New York: Raven Press, 1992. pp. 157–77.

O'Brien CP, Childress AR, Ehrman R, Robbins SJ. Conditioning factors in drug abuse: can they explain compulsion? J Psychopharmacol 1998; 12:15–22.

Pert A, Post RM, Weiss SRB. Conditioning as a critical determinant of sensitization induced by psychomotor stimulants. NIDA Res Monogr 1990;97:208–41.

Pertuzzi S, Cirulli F, Laviola G. Prior cocaine exposure in different environments affects the behavioural responses of mouse dams. Pharmacol, Biochem Behav 1997;56:541–7.

Poshivalov VP. Ethological analysis of neuropeptides and psychotropic drugs: effects on intraspecies aggression and sociability in isolated mice. Aggressive Behav 1982;8:355–69.

Stewart J, de Wit H, Eikelboom R. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. Psychol Rev 1984;91:251–68.

Sukhotina I, Bespalov A. Effects of the NMDA receptor channel blockers memantine and MRZ 2/579 on morphine withdrawal-facilitated aggression in mice. Psychopharmacology (Berlin) 2000;149:345–50.

Thompson T, Schuster CR. Morphine self-administration, food-reinforced, and avoidance behaviors in rhesus monkeys. Psychopharmacologia 1964;5:87–94.

Tidey JW, Miczek KA. Heightened aggressive behaviour during morphine withdrawal: effects of D-amphetamine. Psychopharmacology (Berlin) 1992a;107:297–302.

Tidey JW, Miczek KA. Morphine withdrawal aggression: modification with D1 and D2 receptor agonists. Psychopharmacology (Berlin) 1992b; 108:177–84.

Trost RC. Differential classical conditioning of abstinence syndrome in morphine-dependent rats. Psychopharmacologia 1973;30:153–61.

Tye NC, Iversen S. Some behavioural signs of morphine withdrawal blocked by conditional stimuli. Nature 1977;255:416–8.

Vekovischeva OY, Sukhotina IA, Zvartau EE. Co-housing in stabilized group is not aversive for dominant and subordinate animals. Russ Physiol J 1998;6:177–90.

Walter S, Kuschinsky K. Conditioning of morphine-induced locomotor activity and stereotyped behaviour in rats. J Neural Transm 1989; 78:231–47.