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Effects of morphine and cocaine in mice with stable high aggressive and nonaggressive behavioral strategy

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Abstract

The social group experience of mice with opposite aggressive and nonaggressive behavioral strategies was examined to modulate reinforcing effects of morphine and cocaine. Highly aggressive and nonaggressive male mice cohoused for long period in three-member groups were tested to self-administrate the drugs and to develop conditioned place preferring by them. Mouse triads formed by principle of descending aggression were used as a model of linear hierarchical group. The level of mouse aggression was identified previously within the stock group and during encounter with unknown intruder that continued to be stable over the time of experiment. Highly aggressive mice self-administered morphine and cocaine at higher unit concentrations (1.5 and 1.5 mg/ml) as compare with nonaggressive animals (0.5 and 0.25, 0.5, 1.0 mg/ml). Both morphine (2.5, 5.0, 10.0, and 20.0 mg/kg) and cocaine (2.5, 5.0, and 10.0 mg/kg) induced conditioned place preference in nonaggressive mice at all doses. In contrast, morphine had no effect in highly aggressive mice, while cocaine induced place conditioning at the highest doses (10 mg/kg) only. Our results illustrate that social experience in a stable group alter mouse sensitivity to the rewarding properties of drugs of abuse and social state should be taken into account in the experiments when social interactions are present.

Keywords: Morphine; Cocaine; Self-administration; Conditioned place preference; Reinforcing properties; Social experience; Mice

1. Introduction

Acquisition of drug dependence is critically controlled by various external factors, such as stress, social surroundings, cultural factors, as well as genetic factors (Stolerman, 1992; Zvartau et al., 1997). Rewarding properties of abused drugs are seen as the primary factors underlying the development of drug addiction (Yanagita, 1992; Markou et al., 1993). These effects are strongly modulated by stress (Woolverton, 1992; Deroche et al., 1995; Shaham and Stewart, 1995; Kuzmin et al., 1996; Deroche et al., 1997), social deprivation (Woolverton and Johnson, 1992; Phillips et al., 1994), and genetic background (Semenova et al., 1995; Deroche et al., 1997). Various behavioral characteristics such as irritability, anxiety-like responding, motor activity (Hooks et al., 1994; Jahkel et al., 1994), as well as brain levels of various neurotransmitters (West et al., 1995) were reported to correlate with responsiveness to the drugs. Most experimental models that evaluate the drug-taking behavior are based on the use of laboratory animals that under natural conditions are characterized by strong hierarchies of group organization such as rodents (Schenk and Partridge, 1997; McBride and Li, 1998) and monkeys (van Ree et al., 1994; Mello et al., 1995; Rowlett et al., 1998). Social experience as a function of the social position within a stable group should be recognized as a major factor predisposing to the development of drug use-related phenomena (Serova and Naumenko, 1996).

The social group structure is revealed through dominant–subordinate relationships seen in the forms of agonistic confrontations (Uemura and Morimasa, 1994). Agonistic contacts themselves were shown to stimulate drug-taking behavior (Miczek and Mutschler, 1996) while repeated confrontations lead to anxiogenic-like behaviors (Keeney and Hogg, 1999) and increased drug consumption (Wilde and Vogel, 1994). Cohousing in a stable group promotes development of adaptive learned behavioral strategy and stress reduction (Devoino et al., 1991).

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Despite these adaptations, differences in the drug-taking behavior between animals of different social position are observed in the stable group. For instance, in monkeys, social state was shown to modify effects of ethanol that correlated with altered neurotransmitter balance in dominants and subordinates (Winslow and Miczek, 1985). Thus, we hypothesized that mice with the opposite behavioral strategies (e.g., high aggressive and nonaggressive) would respond differently to the reinforcing effects of cocaine and morphine.

In the present study, animals were grouped in triads comprising highly aggressive, less aggressive, and nonaggressive mice. Such triads were used as a primitive model of a small society where the influence of the factors of social position on the drugs' reinforcing effects can be studied.

2. Methods

2.1. Subjects

Three-month-old male Swiss mice (25–30 g) bred at the State Breeding Farm "Rappolovo" (St. Petersburg, Russia) were kept in stock groups of 7–8 animals at the beginning of the experiment under a 12:12-h light–dark cycle (L: 9:00 a.m.–9:00 p.m.) at 22 ± 1 °C. Food (standard rodent lab dry pellets; "Volossovo," St.Petersburg, Russia) and water were available ad libitum. This mouse strain is profiled behaviorally as intermediate emotional (Griebel et al., 2000; Belzung et al., 2001; Lucki et al., 2001) and is widely used in pharmacological and neurochemical studies. Following a quarantine period, mice were housed in triads comprising highly aggressive, less aggressive, and nonaggressive mice. Experimental manipulations with drugs were started 2 weeks after the group behavior stabilized. Stability of the group behavior in each triad was checked weekly and after each treatment session using the resident–intruder paradigm (see below). Animals, whose social strategy during the experiment was changed, were excluded from the data analysis. All experiments were conducted between 11:00 a.m. and 3:00 p.m.

Experimental procedures were approved by the Ethics Committee of Pavlov Medical University and were performed in accordance with the recommendations and policies of the U.S. National Institutes of Health "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985).

2.2. Behavioral phenotyping procedures

After the transfer to the laboratory's animal facility, mice were screened to characterize the levels of aggressiveness that was tested under two different experimental situations. In the first situation, an unknown intruder was placed into the group home cage (Haemisch and Gartner, 1994; Petitto et al., 1999). Animals that attacked the intruder were removed from the stock group immediately and placed into the individual cages. Two hours later, remaining animals were placed on a new territory with fresh sawdust bedding, a procedure that is known to induce the fighting between familiar members (Benton and Brain, 1979). Identified aggressors were removed from the group. These two procedures were repeated daily until all aggressive mice from the initial stock group were removed. The order of these provocative situations was changed each time.

Subsequently, previously identified aggressive and remaining nonaggressive mice were grouped in triads according to the principle of descending aggression (Benton and Brain, 1979). As a result, each three-member group consisted of a highly aggressive mouse, moderately aggressive mouse (the one that showed aggression in the absence of the highly aggressive mouse only), and a mouse that never showed aggressive behavior.

All members of the triad were taken from the same initial stock group. During the selection, aggressive mice were unavoidably subjected to short-term (3–4 days) isolation. Unlike longer term isolation, such short-term isolation was expected not to produce significant alterations that would compromise the results of the subsequent behavioral testing (Oehler et al., 1985).

Two weeks later, a final resident–intruder test was carried out to confirm aggression levels before starting the drug treatments. Each member of a triad was isolated for 1 h and its behavior towards unknown nonaggressive intruder was tested. The sequence and duration of all observed behavioral elements were recorded (Poshivalov et al., 1988). The elements were combined into behavioral categories: (a) aggression (throws towards the partner, fighting, bites, boxing, threats, tail rattling, and circulation around the partner), (b) defense (lateral and vertical defense postures, pose on the back, and freezing), (c) sociability (sniffing and grooming of the partner), (d) ambulation, and (i) static behaviors (sitting without sniffing, passive contact with the partner). Elements such as sitting with sniffing and rears were calculated separately. Other behavioral elements (digging up, self-grooming, scratching, and eating) were pooled together for "other behavior" category. The behavioral differences between high aggressive and nonaggressive mice were analyzed by nonparametric Mann–Whitney test. Relative duration of behavioral elements or categories was calculated as percentage of a ratio of element (category) duration to test time (240 s).

2.3. Intravenous self-administration

2.3.1. Apparatus

The custom-made apparatuses for intravenous self-administration consisted of four identical test cages (8 × 8 × 8 cm) for simultaneous testing of two pairs of mice (see below). The test cages were made from opaque plastic

and were covered with opaque lid during the test. Each cage had a one hole (diameter 1 cm) in frontal wall and a vertical slot (width 5 mm) in the back wall. Both openings were for nose poking and fixing of mouse's tail, respectively. The nose-poke responses (NPR) were recorded by means of infrared sensors interfaced to an operating computer controlling the activation of the two-syringe infusion pumps. The volume and duration of infusions were held constant at 1.6 μl and 1.0 s, respectively.

2.3.2. Procedure

Preliminary test (pretest) was conducted for the each mouse to record the operant level of nose poking. Mice were placed into test cages for 10 min, their tails were fixed but needles were not inserted. Based on these pretest results, mice were grouped in pairs so that both animals in a pair exhibited approximately equal levels of nose poking. The pairs were formed independently among highly aggressive and nonaggressive mice.

Within 1 h after the pretest, these pairs were placed again into the experimental boxes, and the needles (OD = 0.4 mm) were inserted into the lateral tail veins of both animals of the pair. Intravenous deliveries of drug or its vehicle were made contingent upon each nose poke of the one animal per pair (''active'' mouse). Each nose poke of the active mouse resulted in an infusion of the drug solution or saline to both the active mouse and the passive (yoked control) mouse. Nose pokes of the yoked control were counted but had no programmed consequence (Kuzmin et al., 1996). Each drug session lasted 30 min. Mice were returned to their home cage after the experiment. Each mouse was exposed for drugs only once. The experimental boxes were thoroughly deodorized with 3% H_2O_2 after each animal.

2.3.3. Data analysis

The data analysis was based on the comparison of both active and passive mouse NPR in each pair. R-criterion was calculated for each pair of the experimental animals accordingly to the formula: $R = \log(A_T/P_T) - \log(A_{BL}/P_{BL})$, where A_T-the total number of active mouse NPR during the 30-min test, P_T-the total number of passive mouse NPR during the test, A_{BL}-the total number of active mouse NPR for 10-min pretest, and P_{BL}-the total number of passive mouse NPR for the pretest (baseline). Additionally, the number of mouse pairs with R-criterion higher or lower than limit fixed by standard deviation interval from mean of R-criterion in a saline self-administration group was calculated for each drug concentration. Appropriate two-way analyses of variance (ANOVAs) were performed using SAS-STAT software (version 6.11, SAS Institute, Cary, NC), the two factors being the drug doses and behavioral strategy (highly aggressive or nonaggressive). The individual comparisons were performed using post hoc Student–Newman–Keuls test (only when ANOVA revealed significant effects).

Additionally, differences in absolute values of total numbers of nose pokes between active and passive mice were calculated for each pair (delta-criterion). The cumulative doses of self-injected drugs were calculated.

2.4. Conditioned place preference

2.4.1. Apparatus

Procedure of place conditioning with pretest was used (Schechter and Calcagnetti, 1998). The experimental plastic chamber was divided into two equal size (30 × 30 × 30 cm) compartments by sliding doors. The compartments differed by the wall color (white and brown) and floor texture (metal grid in white and plastic solid floor in brown compartments). The both compartments were equipped with infrared sensors recording the time spent inside.

2.4.2. Procedure

The procedure consisted of preconditioning, conditioning, and postconditioning periods. During pre- and postconditioning periods, each mouse got possibility to move freely 15 min between the both compartments. The time spent in white compartment was recorded automatically. The preconditioning procedure was repeated during three consecutive days. That compartment where animal spent the most of time was considered to be a preferred compartment. The time spent in the preferred compartment on the third time was taken as a baseline for data analyses.

During conditioning period, the door between the compartments was closed. Each daily session consisted of two 30-min (for morphine) or 20-min (for cocaine) trials. During the first trial, animals were injected with the saline and immediately placed into the preferred compartment. Then, an hour later after the first trial, they were injected with a drug or saline (control group) and placed into the nonpreferred compartment. The conditioning procedure was repeated daily for four consecutive days.

The postconditioning test was performed 48 h after the last conditioning procedure. The difference (''time shift'') in time spent in the nonpreferred compartment during post- versus preconditioning tests was calculated as the measure of drug reward. The shuttle boxes were deodorized with 3% H_2O_2 after each animal.

2.4.3. Data analysis

Statistical analysis was conducted using SAS-STAT software (release 6.11; SAS Institute). Because some of the data were not distributed normally (Wilks–Shapiro's test), a combination of the rank and general linear model (GML) procedures were used. Briefly, data were ranked and the ranks were later subjected to two-way ANOVA (GML procedure for unbalanced design with unequal group size) followed by Student–Newman–Keuls test. Effects of drug doses and behavioral strategy (highly aggressive or nonag-

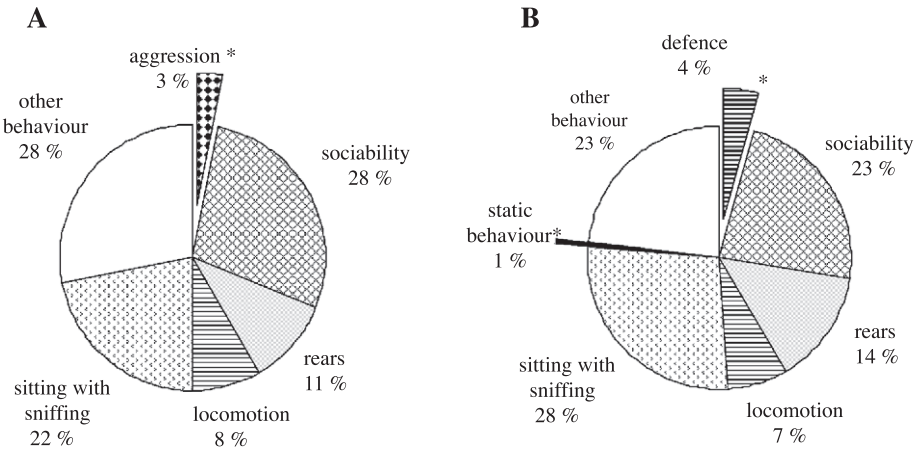

Fig. 1. The behavior of highly aggressive (A) and nonaggressive (B) mice in resident–intruder paradigm after 1 h isolation. The relative duration of behavioral elements or their pooled categories are presented as temporal share of whole behavior observed during the 4-min test. Asterisk (*) denotes significant differences found between animals of opposite behavioral strategies ($P < .05$, Mann–Whitney test).

gressive) were evaluated. Null hypothesis was rejected at the $P < .05$ level.

2.5. Nociceptive tests

Tail-pinch (Bianchi and Franceschini, 1954) and hot plate test were performed (Eddy and Leimbach, 1953; Cannon et al., 2003). For the hot plate test, mice were placed on a 57 ± 0.5 °C metal surface and the latency for a hindpaw lift or lick was recorded. Cut-off time was 30 s. For the tail pinch test, mice were placed on the open surface and an alligator clip exerting force equal to 225 g of weight was placed on the tail towards the tip (approximately 3–4 cm from the tip). The mouse reaction was evaluated by points (0 = no reaction, 1 = going over, 2 = going over and attempts to bite the clip or vocalization, and 3 = flicking, long-drawn vocalization, gnawing the clip, and active attempts to avoid the fixation). Both tests were created for 8–10 males of each (high aggressive mouse and nonaggressive) mouse groups. The measurements were repeated seven times with 15-min intervals. Repeated measures ANOVA was used to analyze the data.

2.6. Drugs

Morphine hydrochloride (Moskovsky Endokrynny Zavod, Russia) and cocaine hydrochloride (St. Petersburg Central Pharmacy, Russia) were dissolved in saline (0.9% NaCl). Both drugs were used at the doses of 2.5, 5.0, and 10.0 mg/kg and administered intraperitoneally in a volume of 10 ml/kg in the conditioned place preference procedure. The following concentrations of drugs were used to characterize the dose–response curve for morphine 0.5, 1.0, and 1.5 mg/ml and cocaine 0.25, 5.0, and 10.0 mg/ml in the IV self-administration procedure. Additional smallest concentration of morphine (0.25 mg/ml) was tested especially in nonaggressive mice after they successfully self-administrated a higher concentration (0.5 mg/ml), while additional

Table 1
IV self-administration of morphine in highly aggressive and nonaggressive male mice

Social status	Morphine concentration (mg/ml)	Number of pairs	Criterions of reinforcing morphine effect		Cumulative dose (mg)
			R-criterion	Delta-criterion	
Highly aggressive males	Saline	14	− 0.19 ± 0.10	− 26.14 ± 18.36	–
	0.5	10	− 0.30 ± 0.21	− 35.70 ± 25.91	0.06 ± 0.01
	1.0	8	− 0.01 ± 0.15	− 5.63 ± 37.38	0.14 ± 0.05
	1.5	10	0.17 ± 0.16 *	44.60 ± 49.28	0.33 ± 0.13#
	2.0	6	− 0.24 ± 0.17	− 47.33 ± 29.77	0.06 ± 0.02
Nonaggressive males	Saline	14	− 0.16 ± 0.11	− 39.93 ± 19.93	–
	0.25	9	− 0.31 ± 0.12	− 4.67 ± 12.59	0.03 ± 0.01
	0.5	11	0.21 ± 0.14 *	28.36 ± 12.88 *	0.05 ± 0.01
	1.0	9	− 0.07 ± 0.17	− 2.11 ± 20.55	0.07 ± 0.02
	1.5	6	− 0.30 ± 0.20	− 60.00 ± 47.23	0.09 ± 0.03

The experimental data, presented as average ± S.E., refer the level of self-administration calculated by means of R- and D-criterions. Cumulative dose (average ± S.E.) means amount of cocaine that was received during self-administration session. Description of the criterions (R and Delta) is presented in Methods and Results sections.

* Denotes statistically significant ($P < .05$) differences between saline and drug groups according to Student–Newman–Keuls test.

\# Denotes statistically significant ($P < .05$) differences between aggressive and nonaggressive mice according to Student–Newman–Keuls test.

highest concentration of 2.0 mg/ml was used in high aggressive mice only after they shown self-administration at 1.5 mg/kg.

3. Results

3.1. Behavioral phenotyping

The behavior of highly aggressive and nonaggressive mice differed in the resident–intruder paradigm (Fig. 1). The behavior of highly aggressive mice was characterized by high levels of aggression (3% of test time), while the behavior of nonaggressive ones was characterized by high rates of defensive (4%) and static behavioral elements such as passive contact with partner or sitting without sniffing. Mann–Whitney's test indicated that the animals of opposite social positions were significantly different ($P<.05$). Behavioral categories such as sociability, locomotion, sitting with sniffing, rears, and other pooled behavioral elements were equally presented for both mouse groups.

3.2. Morphine IV self-administration

Nose-poke activity of highly aggressive (59.69 ± 2.96, $n=190$) and nonaggressive mice (55.88 ± 2.96, $n=178$) did not differ during the 10-min pretest period (Mann–Whitney's test).

Summary on the morphine IV self-administration is presented in Table 1. Two-way ANOVA revealed no significant influence of morphine concentration [R-criterion: $F(5,97)=0.89$, ns; Delta-criterion: $F(5,97)=1.0$, ns] or the behavioral strategy [R-criterion: $F(1,97)=0.08$, ns; Delta-criterion: $F(1,97)=0.31$, ns]. However, there was found a significant interaction between these two factors [R-criterion: $F(3,97)=3.04$, $P<.05$; Delta-criterion: $F(3,97)=2.95$, $P<.05$]. The cumulative dose of self-injected morphine depended significantly on the morphine concentration [$F(4,69)=9.13$, $P<.0001$] but not on the behavioral strategy factor [$F(1,69)=1.68$, ns].

Table 3
Morphine place conditioning in highly aggressive and nonaggressive male mice

Social status	Dose (mg/kg)	N	Shift of time spent in morphine-paired compartment
Highly aggressive males	Saline	10	29.6 ± 49.6
	2.5	8	31.4 ± 77.1
	5	10	47.5 ± 33.0
	10	10	50.4 ± 32.1
	20	10	112.0 ± 33.2
Nonaggressive males	Saline	10	-13.2 ± 36.0
	2.5	11	103.5 ± 29.1 *,#
	5	12	172.0 ± 53.1 *,#
	10	10	163.6 ± 31.6 *,#
	20	9	165.1 ± 51.3 *,#

The experimental data, presented as average ± S.E., show the difference (shift of time) in time spent in nonpreferred compartment during post- versus preconditioning tests. For more details see Methods and Results sections.

* Denotes statistically significant ($P<.05$) differences between saline and drug groups according to Student–Newman–Keuls test.

# Denotes statistically significant ($P<.05$) differences between aggressive and nonaggressive mice according to Student–Newman–Keuls test.

3.3. Cocaine IV self-administration

Summary for cocaine IV self-administration is presented in Table 2. Two-way ANOVA revealed significant main effects of cocaine concentration [R-criterion: $F(4,87)=7.25$, $P<.001$; Delta-criterion: $F(4,87)=9.50$, $P<.001$], behavioral strategy [R-criterion: $F(1,87)=10.10$, $P<.01$; Delta-criterion: $F(1,87)=16.76$, $P<.001$], as well as interaction between these factors [R-criterion: $F(4,87)=11.10$, $P<.001$; Delta-criterion: $F(4,87)=16.77$, $P<.001$] on values of R-

Table 2
IV self-administration of cocaine in highly aggressive and nonaggressive male mice

Social status	Cocaine concentration (mg/ml)	Number of pairs	Criterions of reinforcing morphine effect		Cumulative dose (mg)
			R-criterion	Delta-Criterion	
Highly aggressive males	Saline	8	-0.23 ± 0.20	-33.63 ± 21.93	–
	0.25	10	0.16 ± 0.22#	-6.30 ± 14.84#	0.02 ± 0.01#
	0.5	8	-0.53 ± 0.16#	-74.00 ± 21.69#	0.03 ± 0.01#
	1.0	13	0.11 ± 0.09	-5.25 ± 17.06#	0.14 ± 0.02#
	1.5	8	0.39 ± 0.08 *,#	93.34 ± 27.37 *,#	0.35 ± 0.06#
Nonaggressive males	Saline	9	-0.29 ± 0.17	-109.10 ± 64.39	–
	0.25	8	0.87 ± 0.11 *	143.13 ± 24.64 *	0.06 ± 0.01
	0.5	7	0.65 ± 0.19 *	75.00 ± 25.45 *	0.10 ± 0.02
	1.0	8	0.38 ± 0.11 *	99.125 ± 36.03 *	0.25 ± 0.07
	1.5	8	-0.13 ± 0.16	-14.25 ± 9.11 *	0.04 ± 0.01

The experimental data, presented as average ± S.E., refer the level of self-administration calculated by means of R- and D-criterions. Cumulative dose (average ± S.E.) means amount of cocaine that was received during self-administration session. Description of the criterions (R and Delta) is presented in Methods and Results sections.

# Denotes statistically significant ($P<.05$) differences between aggressive and nonaggressive mice according to Student–Newman–Keuls test.

* Denotes statistically significant ($P<.05$) differences between saline and drug groups according to Student–Newman–Keuls test.

criterion. Cumulative dose of self-injected cocaine depended significantly on the cocaine concentration [$F(3,70) = 23.58$, $P < .001$] as well as the behavioral strategy [two-factor interaction: $F(3,70) = 25.30$, $P < .001$].

3.4. Conditioned place preference

There was no initial preference to either of the compartments in aggressive (565.7 ± 17.5 s, $n = 44$) and nonaggressive mice (593.6 ± 15.8 s, $n = 51$) during the preconditioning test. The animals spent 64.5 ± 6.0% of the total preconditioning time (900 s) in the white compartment during the last pretest session. These data are summarized in Tables 3 and 4.

3.4.1. Morphine-conditioned place preference

Conditioning with saline did not affect preference for either of the compartments. The percentage of mice with saline place conditioning or place aversion did not exceed 20%. When time spent in the morphine-associated compartment was analyzed, two-way ANOVA revealed significant effects of the dose [$F(4,100) = 2.65$, $P < .05$] and behavioral strategy [$F(1,100) = 5.35$, $P < .05$]. Post hoc tests suggested that nonaggressive mice spent more time in the morphine-associated compartment than highly aggressive mice.

3.4.2. Cocaine-conditioned place preference

Conditioning with saline did not produce place preference (14 and 20% for highly aggressive and nonaggressive mice, respectively) or aversion (14% and 10%, respectively). Two-way ANOVA indicated that the time spent in cocaine-associated compartment depended significantly on the dose [$F(3,68) = 8.09$, $P < .001$], behavioral strategy [$F(1,68) = 6.77$, $P < .05$], and there was significant interaction between these factors [$F(3,68) = 3.9$, $P < .05$]. Cocaine induced place preference in nonaggressive mice at all dose levels (2.5–10 mg/kg). In contrast, cocaine induced place preference in highly aggressive mice at the highest dose (10 mg/kg) only.

Table 4
Cocaine place conditioning in highly aggressive and nonaggressive male mice

Social status	Dose (mg/kg)	N	Shift of time spent in cocaine-paired compartment
Highly aggressive males	Saline	7	12.1 ± 30.3
	2.5	7	81.0 ± 53.3
	5	11	108.7 ± 35.6
	10	12	243.0 ± 31.8 *,#
Nonaggressive males	Saline	10	59.0 ± 19.0
	2.5	7	253.5 ± 43.3 *,#
	5	7	245.4 ± 42.7 *,#
	10	7	173.7 ± 49.4 *

The experimental data, presented as average ± S.E., show the difference (shift of time) in time spent in nonpreferred compartment during post- versus preconditioning tests. For more details see Methods and Results sections.

* Denotes statistically significant ($P < .05$) differences between saline and drug groups according to Student–Newman–Keuls test.

# Denotes statistically significant ($P < .05$) differences between aggressive and nonaggressive mice according to Student–Newman–Keuls test.

3.5. Nociceptive tests

Baselines of the nociception were similar in high aggressive and nonaggressive mice in both tests. In the hot plate test, observed latencies were 6.1 ± 0.63 and 5.8 ± 0.46 s, respectively. In the tail-pinch test, all animals had the highest score (3).

4. Discussion

Highly aggressive and nonaggressive mice were clearly distinguished by the behavior displayed in the resident–intruder paradigm after the 2-week period of cohousing. Highly aggressive mice actively attacked the partners while nonaggressive ones displayed defensive behavior. In contrast, other behavioral activities such as nonsocial exploratory behavior (sitting with sniffing, rears), locomotion, and sociability did not differ between opposite mouse groups. It seems that nonaggressive mice acquired defensive behavioral patterns towards unknown partners but maintained high levels of other behavioral activities, which argues against the development of depressive-like behavior in nonaggressive animals.

Repeated encounters with unfamiliar aggressive residents are often used to establish a history of social defeats that leads to the development of suppressed exploratory activity and sociability, main markers of anxiety-like behavior (Avgustinovich et al., 1997). In our case, all behavioral activities, except for an agonistic behavior, observed in both highly aggressive and nonaggressive mice did not differ, which indicates an absence of negative consequences of their cohousing and suggests a development of mice's adaptation to stay together in the home cage. Those groups of mice did not show any differences regarding their visits of the light compartment (Vekovishcheva et al., 2000) and in the initial preference of any compartment of place conditioning chambers. Thus, in the absence of markers of anxiety, the long-term cohousing of highly aggressive and nonaggressive mice together with third member of the group (a moderately aggressive male) might be discussed in light of acquisition of opposite behavioral strategies (e.g., forward or protective), and the animals should be described as dominants and subordinates rather than as winners and losers (Popova et al., 1996). It allows us to discuss the obtained data in terms of adaptive behavioral strategies.

The procedure of self-administration, including tail fixation and needle insertion into the tail vein, may be seen as stressful and painful for the mice. Mouse tail plays a significant role in the behavior, appears to be a target in agonistic confrontations, and social state in the group is

associated with the number of tail bites (Benton and Brain, 1979; Puglisi-Allegra and Oliverio, 1983). It suggests that nose-poke behavior of highly aggressive mice could be suppressed by the manipulations with tail more than in nonaggressive mice adapted to the attacks from the aggressors. However, 10 min nose-poke activity during selection test, used to form active/passive mouse pairs, and 30 min saline self-administration did not produce any differences between the mouse groups. Moreover, the pain reactivity of mice of opposite behavioral strategies appeared similar by the tail-pinch and hot plate nociception tests. Therefore, it seems the differences in first reinforcing effects of morphine and cocaine in highly aggressive and nonaggressive mice could be associated with their distinct responsivity to the drugs rather than with stresslike aspects of self-administration procedure.

Both self-administration and place-conditioning experiments suggested that mice of opposite behavioral groups also differed in their responsiveness to the reinforcing effects of morphine and cocaine. Highly aggressive mice that self-administered higher unit doses of both morphine and cocaine failed to acquire morphine-conditioned place preference and developed cocaine-conditioned place preference only at the highest tested dose. In contrast, nonaggressive animals self-administered lower doses of morphine and cocaine and showed reliable morphine and cocaine place preferences at the wide dose range. The correspondence between the results obtained in both self-administration and conditioned place preference studies supports the notion that behavioral strategy appears to be an adequate marker to select animals for a drug abuse studies.

The failure to find morphine-conditioned place preference in high aggressive mice does not mean that they are insensitive to the drug's rewarding properties. Probably, other experimental protocol would be more successful. Our findings are somewhat in a conflict with the data obtained in rats where morphine-conditioned place preference developed in dominants but not in their submissive partners (Coventry et al., 1997). The lack of morphine effect in the dominants was found when they lost social rank after being defeat suggests a decrease in the hedonic tone (Coventry et al., 1997). Meanwhile, the high aggressive mice of the present study did not display behavioral patterns that would be consistent with the anhedonia explanation (i.e., general behavioral passivity; Alias, 2000).

Aggression levels are under strong genetic control, which is revealed by analyzing the mice of different breeding strains (Simler et al., 1982; Serri and Ely, 1984) and stocks (Serri and Ely, 1984; Devoino et al., 1991; Nikulina and Klimek, 1993). For instance, CBA mice were ranked amongst the most aggressive (Serri and Ely, 1984; Devoino et al., 1991; Vekovishcheva and Zvartau, 1999) while DBA mice demonstrated much less aggression compared with other mouse lines (Vekovishcheva and Zvartau, 1999). At the same time, Semenova et al. (1995) showed that CBA mice self-administered morphine at the highest concentration (1.5 mg/ml) only and developed place preferences only for the maximal morphine dose of 20 mg/kg, while DBA mice self-administered morphine at lower concentrations (0.75 mg/ml) and showed place conditioning within the wide dose range starting from 5 mg/kg. The findings are in accord with the present results supporting the idea that rewarding effects of drugs are influenced by social experience and position within the group.

It is well known that dopamine is critically involved in drug reinforcement mechanisms (Koob and Nestler, 1997), and the negative correlation between dopamine level and self-administration of cocaine was found in rats with individual predisposition to the drug-taking behavior (Glick et al., 1994). At the same time, the level of dopamine is higher in aggressive as compared with nonaggressive mice (Kudriavtseva and Bakshtanovskaia, 1991; Serova and Naumenko, 1996) that results in enhanced locomotor activity of mice with high social state (Hilakivi-Clarke and Lister, 1992; Vekovishcheva et al., 2000). Thus, it is likely that higher dopamine level in aggressive mice is causally linked to attenuated drug self-administration at the lower unit dose levels. In other words, only at higher unit dose levels the drugs may overcome the functional and behavioral consequences of enhanced dopamine levels.

Interestingly, different behavioral strategies in the mouse societies similar to what was used in the present study may be correlated with human traits. Cloninger's (1987) three-dimensional model of personality was introduced in terms that are well acceptable for animals: novelty seeking (or heritable tendency toward intense exhilaration in response to novel stimuli, which leads to frequent exploratory activity in pursuit of potential rewards), harm avoidance (or tendency to respond intensely to signals of aversive stimuli), and reward dependence (or tendency to respond intensely to signal of reward). Our high aggressive mice showed low level of reward dependence and high level of novelty seeking (Hilakivi-Clarke and Lister, 1992; Vekovishcheva et al., 2000), while nonaggressive mice displayed high level of reward dependence and low level of novelty seeking (Vekovishcheva and Zvartau, 1999). In light of the associations of personality traits with the basic stimulus–response characteristics (Cloninger, 1987), aggressors could be described as opportunistic, while nonaggressive mice as scrupulous. In light of personality disorders, they reflect traits of explosive and passive-dependent persons, respectively. These overbold analogies may suggest the existence of differences in drug response in persons with listed traits of personality.

Thus, behavioral mouse strategy in a stable group based on the level of aggression may be considered as the biological factor modulating reinforcing properties of abused drugs. Careful selection of the behavioral background before the implementation of the drug abuse experiments in rodents could be beneficial for the more precise analysis of the obtained results.

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