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Effects of Haloperidol on Communicative and Aggressive Behavior in Male Mice with Different Experiences of Aggression

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KUDRYAVTSEVA, N. N., T. V. LIPINA AND L. A. KORYAKINA. *Effects of haloperidol on communicative and aggressive behavior in male mice with different experiences of aggression.* PHARMACOL BIOCHEM BEHAV **63**(2) 229–236, 1999.—Effects of two doses of haloperidol (0.1 and 0.4 mg/kg, 30 min and 24 h, IP) on communicative and aggressive behavior in C57BL/6J male mice have been studied. Some of the mice were without prior experience of aggression ("recruits"); the others had been victorious in 20 daily aggressive confrontations ("experienced winners"). Communicative behavior was estimated as the behavioral reaction to a standard tester (loser) in the partition test. Haloperidol in either dose significantly reduced communicative behavior in the "recruits," but not in the "experienced winners." Significantly fewer attacks, less total attacking time, and total time of aggressive behavior (aggressive grooming + attacks) were demonstrated by the "experiences winners," than by the "recruits," while the latency of the first attack, the number, the total and average duration of aggressive grooming events were significantly higher. In the "recruits," haloperidol dose dependently increased the latency and decreased the number of attacks, the total attacking time, and the total time of aggressive behavior 30 min and 24 h after injection. However, haloperidol did not affect the average or total time of aggressive grooming. Neither dose significantly affected any measure of aggressive behavior in the "experienced winners." It has been concluded that repeated aggression experience reduces the pharmacological sensitivity of the dopamine receptors. © 1999 Elsevier Science Inc.

Aggression Haloperidol Sensory contact model Mice

LIKE other neuroleptic drugs, haloperidol reduces aggressive behavior in many animal species (7,23,24,30,31) and humans (4,40). However, the expression of its inhibiting effects is as closely related to the temporal patterns of administration as to the existing tone of other pharmacologically modulated mediator systems, first of all, the opioid system. For example, the attack duration and threatening behaviors were significantly reduced in animals acutely treated with haloperidol (24,27,33). The animals chronically treated with the drug show tolerance to the antiaggressive effects of haloperidol (25,27,28). Administered with haloperidol, morphine may counteract the explicit antiaggressive effect of the neuroleptic (38).

The basic question in the interpretation of all these observations is the relationship between the dopaminergic and the opioid systems (38), both being involved in the reinforcing process. Most of the results suggest that the dopaminergic systems mediate the effects of opioids, especially their reinforcing and psychomotor actions [for review, see (6)]. It was proposed that aggression, regarded as a reinforcing process (26,34), would stimulate the brain areas related to the reward system, possibly, the dopaminergic pathways, which could explain why the dopaminergic antagonist haloperidol produces powerful antiaggression effects (24,38). The opiate antagonists naloxone and naltrexone, administered at high doses, suppress aggression similarly (19,22,29,35).

The sensory contact technique, developed as a tool for studying the mechanisms of agonistic behavior (11), allows the effects of drugs to be examined on the background of brain neurochemical activity modulated by agonistic experience. As has been shown, the experience of repeated victory in daily aggressive confrontation is followed by the activation

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TABLE 1

EFFECTS OF HALOPERIDOL 30 MIN AND 24 H AFTER ACUTE INJECTION ON COMMUNICATIVE BEHAVIOR OF MALE MICE WITH DIFFERENT EXPERIENCE OF AGGRESSIVE CONFRONTATIONS IN THE PARTITION TEST

	Recruits			Experienced Winners		
Parameters	Saline	0.1 mg/kg	0.4/mg/kg	Saline	0.1 mg/kg	0.4 mg/kg
Number of approaches						
30 min	11.8	12.7	9.5	12.3	11.6	10.4
	(6–16)	(10–16)	(2–16)	(8–16)	(4–18)	(2–16)
24 h	11.11	10.4	10.3	10.1	9.0	10.6
	(6–16)	(4–15)	(1–17)	(7–13)	(4–14)	(6–16)
Total time spent near the partition						
30 min	72.6	44.4*	44.4*	77.6	75.8	68.7
	(28–128)	(22–92)	(18–89)	(44–110)	(21–134)	(34–112)
24 h	79.6	60.1	71.4	67.0	67.5	68.9
	(27–166)	(23–113)	(28–87)	(25–98)	(30–106)	(41–119)
Average time spent near the partition						
30 min	5.9	4.7	5.0	6.4	6.4	6.8
	(3–11)	(2–11)	(1.5–8)	(4–9)	(3–17)	(4–13)
24 h	7.1	6.2	6.9	6.6	7.4	6.8
	(3–14)	(3–12)	(2–12)	(4–9)	(6–9)	(4.0–11)

Data are presented as means with ranges. *U*-test
*$p < 0.05$, differs from saline treated males, $n = 10–12$.

of the brain dopaminergic systems through the formation of DOPAC in brain areas (14). The different effects of naltrexone on the aggressive behavior of males with the experience of different outcomes of aggression have been demonstrated (17). Naltrexone at high dose reduced the total attacking time and enhanced aggressive grooming in mice without prior aggression experience. In contrast, the total attack duration was increased in the naltrexone-treated experienced winners, who had been victorious through 20 days, aggressive grooming being unaffected. The aim of this work was to study the effects of haloperidol on aggressive behavior in male mice with different experience of aggressive confrontations. Haloperidol effects on communicative behavior, measured as the behavioral reactivity to the conspecific in the partition test (12), have also been examined.

METHOD

Animals

Adult male mice of C57BL/6J strain maintained at the Institute were used. The animals were housed under standard vivarium conditions and a natural light regime; food and water were available ad lib. One-month males were weaned and housed in 1-litter groups of 8–10 in plastic 36 × 23 × 12-cm cages. Experimental mice were 10–12 weeks of age.

TABLE 2

AGGRESSIVE BEHAVIOR IN MALE MICE WITH DIFFERENT EXPERIENCE OF AGONISTIC CONFRONTATIONS

Behavioral Parameters	Recruits	Experienced Winners	*U*-Value	*p*
Latency of first attack, s	61.0 (5–105)	343.8 (115–600)	0.0	<0.001
Total attacking time, s	157.7 (47–260.5)	31.2 (0–85)	7.0	<0.01
Number of attacks	14.6 (8–28)	3.1 (0–10)	2.0	<0.001
Average time of one attack, s	12.5 (3.5–23)	7.6 (0–16)	28.0	n.s.
Total time of aggressive grooming, s	25.6 (0–108)	87.4 (7–162)	14.0	<0.05
Number of aggressive grooming	2.7 (0–7)	11.1 (1–24)	9.5	<0.01
Average time of one aggressive grooming, s	4.6 (0–18)	12.0 (2–28)	21.0	≤0.05
Total time of aggressive behavior, s	183.3 (52–262)	118.7 (46–246)	17.0	<0.05

Data are presented as medians with ranges, $n = 10$.

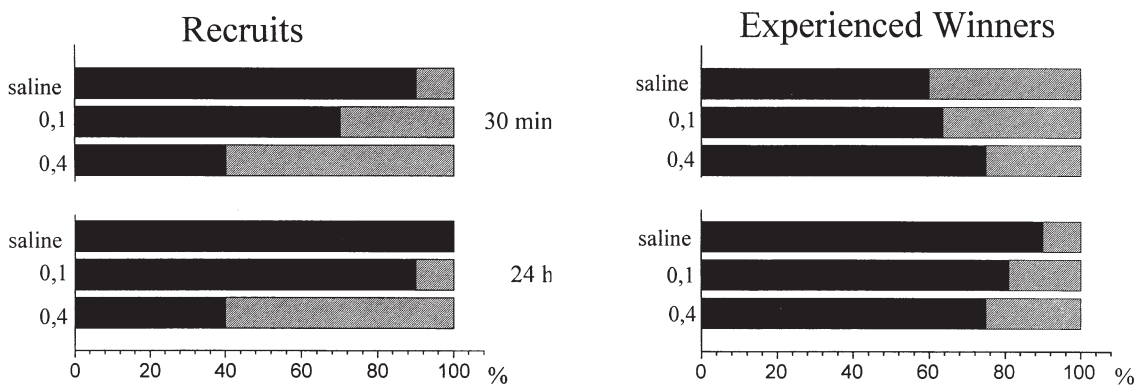


FIG. 1. Percents of winners that actively attacked (black bars) or/and performed aggressive grooming (black + gray bars) to the tester.

A Technique for Generating Aggression-Type Behavior in Male Mice

Aggressive behavior in the male mice was provoked using the sensory contact model (11). To remove group effects, the mice were caged individually for 5 days. Animals of nearly the same weight were then placed by pairs in steel cages (28 × 14 × 10 cm) divided into halves by a perforated transparent partition that allowed them to see, hear, and sense the smell of the neighbor but not to contact physically. Test sessions commenced 2 days after adaptation of animals to these new housing conditions (sensory contact). Every afternoon (1400–1700 h, local time), the steel cover of the cage was replaced by a transparent one, and 5 min later (the period necessary for an individuals' activation and habituation to new lighting conditions) the partition was removed for 10 min to allow agonistic interaction. Undoubted superiority of one of the partners was evident within two to three tests in daily social encounters with the same opponent. One partner was seen to attack, bite, and chase the other, which only displayed defensive behavior (sideways, upright postures, "on the back," or "freezing") during the tests. As a rule, aggressive confrontations between males are discontinued by putting the partition down if the intensive attacks lasted more then 3 min. Every day after the test, each defeated member of one pair was paired with the winning member of another pair behind the partition in an unfamiliar cage. The aggressive males (winners) were left in their own compartments.

Three experimental groups were used in experiments: "experienced winners"—winners that have been repeatedly victorious in 20 daily aggressive confrontations; "recruits"—males housed individually for 5 days before testing; and testers—losers that have been repeatedly defeated in 20–22 daily agonistic confrontations. These males would never demonstrate aggression.

Aggressive Behavior

The measures of aggressiveness during a 10 min test were as follows: 1) % of fighting males; 2) % of males demonstrating attacks or/and aggressive grooming; 3) latency of the first attack (s); 4) total attacking time (s); 5) number of attacks; 6) average time of one attack (s): (total attacking time/number of attacks); 7) total time of aggressive grooming (s). Herein, the winner mounts itself onto the loser's back, holds it down (to the floor), and intensively nibbles and licks it for a long time, mainly at the loser's scruff area. The victim is wholly immobilized, often stretches out the neck and freezes under the aggressor; 8) number of events of aggressive grooming; 9) average time of aggressive grooming (total time of aggressive grooming/number of events of aggressive grooming) (s); and 10) total time of aggressive behavior (total attacking time + total time of aggressive grooming) (s).

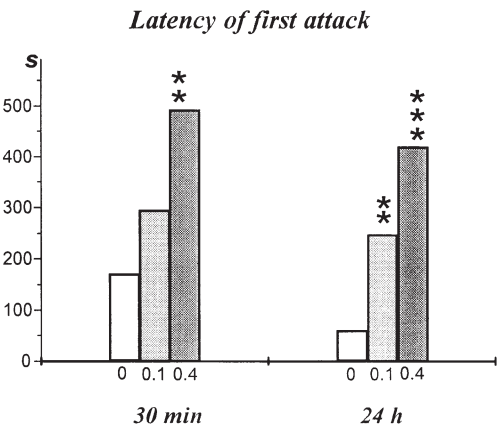
If an animal did not make an attack and only demonstrated aggressive grooming, the latency of the first attack was assumed as 600 s (test duration), and all the other attacking counts were assumed as zero.

Communicative Behavior

The level of communicative behavior was measured in the partition test (12). The steel cover of the experimental cage was replaced by a transparent one, and 5 min later (the period of activation and habituation to new lighting conditions) the measures of behavioral activity near the transparent perforated partition, as a reaction to the testers in neighboring compartment of common cage, were recorded. The following quantitative parameters were estimated in a 5 min test: 1) the number of approaches to the partition; 2) total time spent near the partition (s). Generally, this is the reaction to the mouse in the neighboring compartment. Mice move near the partition, smell and touch it with either forepaw or with both, clutch and hang on it, put their noses into the holes, or even gnaw there. Briefly, the total time spent when males touched the partition with foreparts (noses, paws) was recorded. The periods of time over which the males demonstrate sideways postures or "turning away" near the partition are not recorded; and 3) average time spent near the partitions (s) during one approach, i.e., the ratio of the total time spent near the partition to the number of approaches.

Drug Treatment

Animals within each group were injected intraperitoneally with either 0.1, 0.4 mg/kg (in volume of 0.01 ml/g) haloperidol (Sigma) or physiological saline (0.9% NaCl, Baxter, Co., USA). The drug was diluted in saline. Measurement of behaviors were taken 30 min and 24 h after injection (see Experimental Design). Haloperidol at the indicated doses has been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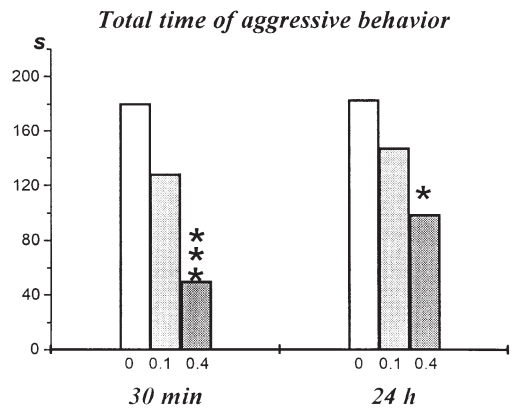
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30 min
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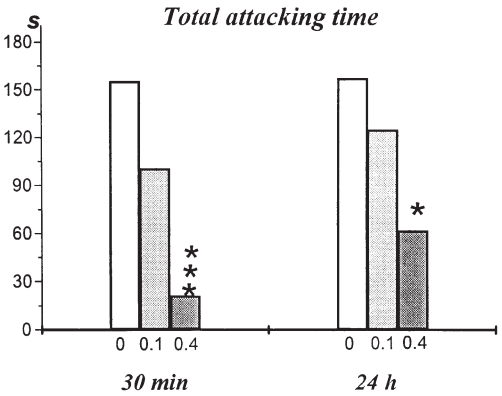
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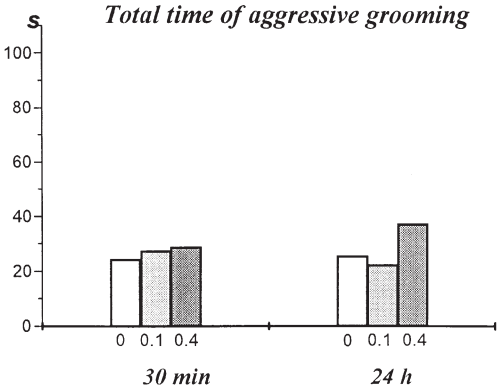
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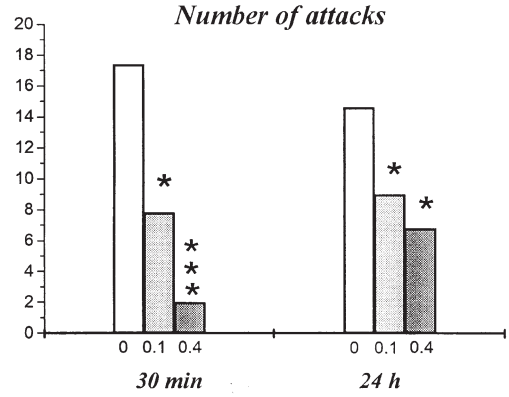
Number of attacks
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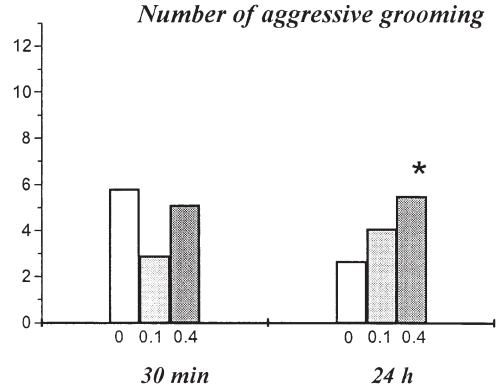
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30 min
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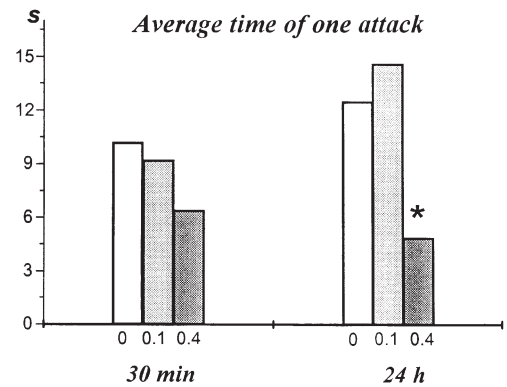
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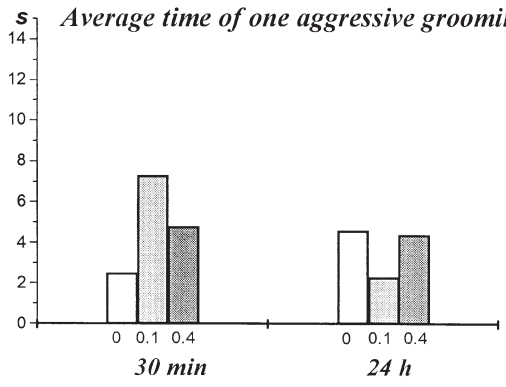
30 min
24 h


Average time of one aggressive grooming
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0 0.1 0.4
30 min
24 h

employed by many researchers in behavioral experimentation with mice (24,31). Even 0.4 mg/kg was an appropriate dose for the experimental purposes, because its effect on aggressive behavior was evident, while its depressing action on motor activity was moderate (27).

Experimental Design

The testers were placed into the free compartments of experimental cages for sensory contact, with "recruits" or "experienced winners" behind the partition, 1 day before testing. The effects of haloperidol on behavior were examined 30 min after injections. The saline-treated males of the respective experimental groups were used as control. The cage cover was replaced by a transparent one, and 5 min later the animals were studied in the partition test. The partition was then removed to let agonistic confrontations begin. The testing was repeated 24 h after injection.

All procedures are in compliance with European Communities Council Directive of 24 November 1986 (86/609/EEC).

Statistical Analysis

For each behavioral category differences between saline- and drug-treated animals in every experimental group were examined by two-tailed Mann–Whitney *U*-tests.

RESULTS

Communicative Behavior

In the "recruits" and "experienced winners," the measures of partition behavior, including the number of approaches, and total and average time spent near the partition as a reaction to the tester in the neighboring compartment were similar (Table 1). Thirty minutes after injection with haloperidol at either dose (0.1 or 0.4 mg/kg), the "recruits" spent in total significantly less time near the partition than after exposure to saline ($U = 26$ for 0.1 mg/kg and $U = 25$ for 0.4 mg/kg, accordingly, $p < 0.05$), the number of approaches and average partition time being unaffected. Twenty-four hours later behavioral activity near the partition was restored. No partition behavior measure was changed in the "experienced winners" 30 min or 24 h after injection with the drug at either dose.

Aggressive Behavior

Repeated experience of daily aggressive confrontations changed the parameters of aggressive behavior in male mice (Table 2). The total time of aggressive behavior, including the attack and aggressive grooming duration, was significantly lesser in the "experienced winners" than in the "recruits." Number of attacks and total attacking time became significantly less, and the number, total, and average time of aggressive grooming became significantly higher under the influence of repeated experience of victories. The average time of attacks did not differ significantly in both experimental groups. The latency of the first attack was five times more in the "experienced winners" than in the "recruits" (Table 2).

Aggressive behavior (attacks or/and aggressive grooming) was demonstrated by 100% of the saline- and drug-treated animals in both experimental groups. Ninety percent of the "recruits" and 60% of the "experienced winners" demonstrated attacking behaviors 30 min after saline injection (Fig. 1). One hundred percent of the "recruits" and 90% of the "experienced winners" actively attacked the testers 24 h after injection. Thirty minutes after injection with haloperidol, the number of actively attacking "recruits" decreased in a dose-dependent manner. Only 40% of "recruits" exposed to 0.4 mg/kg dose of haloperidol demonstrated intensive fighting 24 h after drug administration (Fig. 1).

Most of the measures of aggressive behavior of male mice in the first agonistic confrontation changed in a dose-dependent manner after drug injections (Fig. 2). The 0.1 mg/kg dose of haloperidol significantly decreased the number of attacks 30 min ($U = 18.5$, $p < 0.05$) and 24 h ($U = 20$, $p < 0.05$) after injection. The 0.4 mg/kg dose was the most effective, and decreased the total attacking time ($U = 3$, $p < 0.001$), number of attacks ($U = 0.5$, $p < 0.001$), total time of aggressive behavior ($U = 2$, $p < 0.001$), and increased the latency of the first attack ($U = 9$, $p < 0.01$) in "recruits." However, haloperidol did not affect the measures of aggressive grooming: the number of grooming events, average, and total time of grooming. Twenty-four hours after acute injection, an inhibiting effect of 0.4 mg/kg dose of drug on aggression remained similar to those displayed 30 min after; the total time of aggressive behavior ($U = 18$, $p < 0.05$), total attacking time ($U = 18$, $p < 0.05$), number of attacks ($U = 23$, $p < 0.05$), and, additionally, average time of one attack ($U = 19$, $p < 0.05$) were still significantly reduced, and the latency of first attack was significantly increased ($U = 2$, $p < 0.001$) in the drug-treated "recruits" than in the saline-treated animals over the respective periods of time. Stimulating effects of 0.4 mg/kg haloperidol on the number of aggressive grooming ($U = 21.5$, $p < 0.05$) and inhibiting effects on the average time of one attack ($U = 19$, $p < 0.05$) 24 h after injection have also been demonstrated.

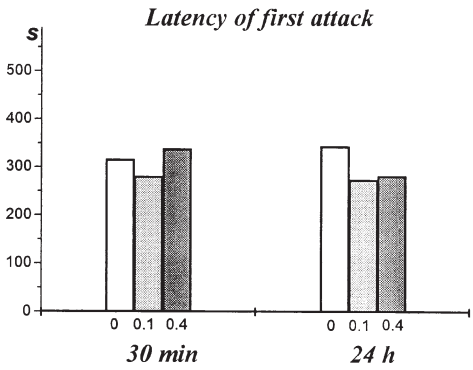
No significant effects of either dose of haloperidol have been observed on any measure of aggressive behavior 30 min or 24 h after injection in "experienced winners" (Fig. 3).

DISCUSSION

The sensory contact technique significantly enhances aggressive behavior in the male mice of different strains. It has been shown that 90–100% of C57BL/6J males are strongly aggressive for 120–180 s in the first confrontation in a 10-min test (11). In such widely used models as social isolation or a resident–intruder paradigm only 16–60% of males of this strain demonstrated attacks, for no longer than 30–50 s (2,3,9,16,32). Our experiment provides support to our previous data that 90–100% of males actively attacks and bites the losers (about 150 s) or at least demonstrates aggressive grooming. However, an acute injection reduces this figure to 60% in "experienced winners."

Repeated experience of victories changes aggressive behavior in male mice. After 20 days of agonistic confrontations, such measures as number of attacks, total attacking time, and total duration of aggressive behavior were decreased, while the latency of the first attack, number, total, and average time of aggressive grooming were increased in

FIG. 2. Effects of haloperidol (0.1 and 0.4 mg/kg) 30 min and 24 h after acute injection on the parameters of aggressive behavior in "recruits." Data are presented as mean values. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ vs. saline-treated males on two-tailed Mann–Whitney *U* test, n = 10.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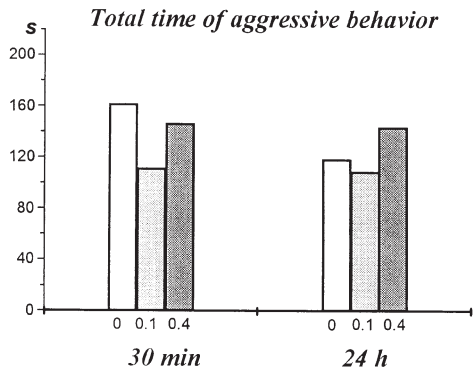
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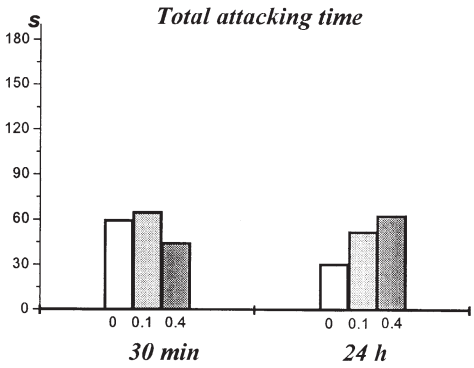
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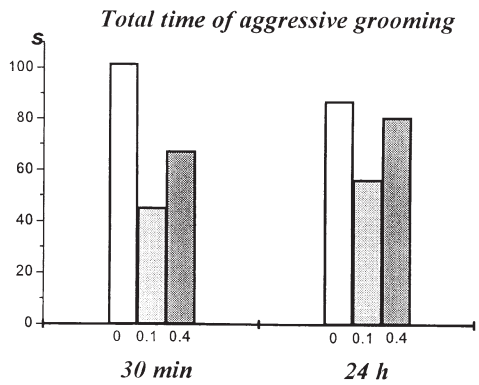
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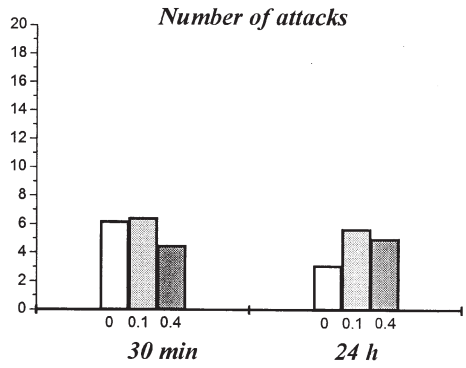
Number of attacks
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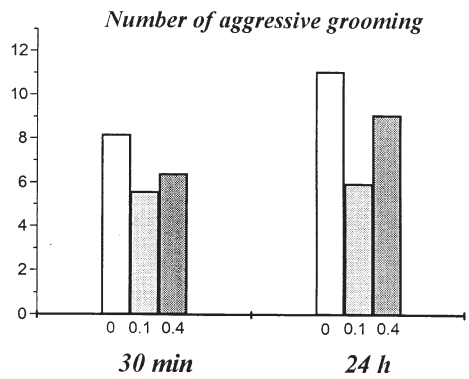
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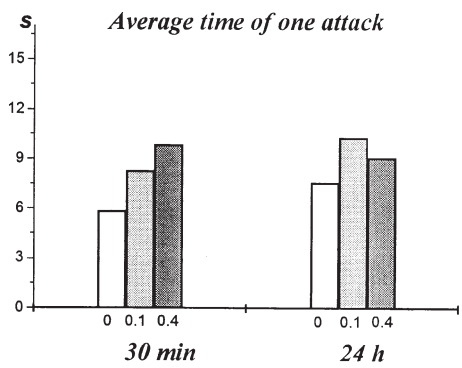
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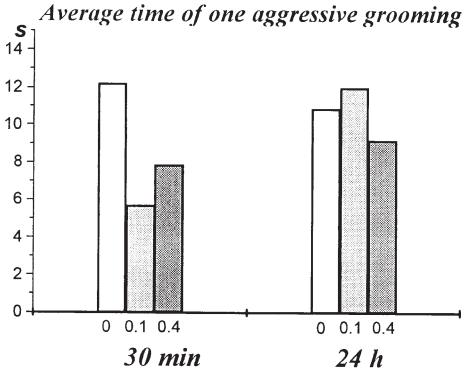
Average time of one aggressive grooming
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30 min
24 h

"experienced winners." Similar data were shown earlier (17). It was proposed (13,17) that the demonstration of expressed aggression by "recruits" is substituted by its ritual manifestation under the influence of repeated positive fighting experience, i.e., by aggressive grooming, that does not require as much physical effort as aggressive attacks do. With the acquisition of aggressive (i.e., victorious) experience, males are learning a better behavioral strategy. It has been suggested that elements of learned aggression in male mice must develop due to repeatedly experienced victories (17). Noteworthy, the average time of one attack did not change significantly in this or other experimental situations (15).

According to literature data, haloperidol did not significantly affect social investigation in mice (38,39). However, behavioral reactivity to the conspecific in the partition test, assumed to be analogous to social investigation described by Martinez et al. (20), was decreased in "recruits" by both doses of haloperidol 30 min after injection. Reduced communicative behavior (total time) could be attributed to the anxiogenic effect of haloperidol. However, the absence of effects (36) of D_1 and D_2 receptors antagonists haloperidol whatsoever, or rather the presence of the anxiolytic effect of a D_2 receptor antagonist, sulpiride (37), has been revealed in the plus-maze test, which is sensitive to anxiolytic and anxiogenic drugs (18). Reduction in aggressive motivation under influence of haloperidol can be proposed as another interpretation of decrease of communicative behavior in the partition test. It has been shown earlier that the total time spent near the partition before confrontation positively correlated with total attacking time in the agonistic interaction that followed (10). In "experienced winners," haloperidol did not affect behavioral reactivity to the losers, estimated by total and average time spent near the partition. It might be because of a lower pharmacological sensitivity of the dopamine receptors produced by repeated aggressive confrontations. The motor activity measured as the number of approaches to the partition was not changed in "recruits" or "experienced winners" exposed to either dose of haloperidol. It may be concluded that haloperidol effects are apparently specific for communicative behavior in "recruits."

As in other studies (7,23,24,31), 30 min after injection haloperidol decreased in a dose-dependent manner the number of attacks, total attacking time, and total time of aggressive behavior, and increased the latency of the first attack in male mice in the first agonistic confrontations. This aggression-inhibiting effect remained much the same 24 h after injection. A similar effect was observed on aggressive animals after social isolation for 1 month (28), which was explained by the effect of the neuroleptic remaining in the tissues at substantial concentrations long after administration had stopped (5,28). This reduction of aggression by haloperidol also confirms the idea that aggressive motivation is decreased, as has been demonstrated here by the partition test. However, 24 h after injection total time spent near the partition returned to the initial level, and the inhibiting effect of the drug on aggression was still obvious. Thus, haloperidol administration reveals a more complicated association between the mechanisms of communicative and aggressive behavior than was believed.

Because no inhibiting effects on aggression were observed in "experienced winners" either 30 min or 24 h after haloperidol injection, it may be supposed, that repeated aggression experience decreases the pharmacological sensitivity of the dopamine receptors due to a chronically high dopaminergic activity; as has been shown, the repeated victory experience in daily aggressive confrontations causes total activation of the brain dopaminergic systems, as was confirmed by elevated DOPAC level in olfactory bulbs, amygdala, hippocampus, n. accumbens' midbrain, and striatum (14). Other studies on resident mice that attack and threaten an intruder also illustrate how execution of aggressive and defensive behavior results in increases of DA turnover in the n. accumbens (8,22). In current in vivo microdialysis studies on aggressive rats, large and long-lasting increases in DA are measured in the n. accumbens immediately before, during, and after episodes of threat and attack toward an intruding opponent (21). It may also be suggested that tolerance to haloperidol must be due to a change in the activity of the opioid systems involved, together with dopaminergic systems, into the reinforcing processes of aggressive behavior and into the formation of the aggressive type of behavior in male mice as a result of repeated victory experience. The change in the opioid activity in the "experienced winners" is confirmed by our latest data (17) revealing different effects of naltrexone (naltrexone hydrochloride, NIDA, 0.25 mg/kg and 1.0 mg/kg) on the communicative and aggressive behavior of "recruits" and "experienced winners." As well as haloperidol, naltrexone—at the doses employed—reduced communicative behavior in "recruits" but not in "experienced winners." Naltrexone (1.0 mg/kg) decreased the total attacking time and increased the duration of aggressive grooming in "recruits." Naltrexone (0.25 mg/kg) was ineffective. In contrast, naltrexone increased in a dose-dependent manner the total attacking time in "experienced winners," and did not significantly affect aggressive grooming. Our conclusion then was that repeated victory experience in daily aggressive confrontations changes the sensitivity of the opiate receptors, and that μ-receptors are involved in the neural mechanisms of formation of the aggressive type of behavior in male mice.

In human society, situations may demand a persistent demonstration of aggressiveness. The psychologists define this type of aggression as premeditated; possible examples are war, professional sporting activity (football, box etc.), security services, etc. This type of aggression is supposed to have been learned (social learning), but also is, in part, a function of the instincts laid down by our evolutionary heritage (1). The sensory contact model, under which the aggressive type of behavior is formed in male mice, is a promising method for studying the mechanisms of learned aggression and for a search of adequate methods for pharmacological correction of expressed aggressiveness in individuals.

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FIG. 3. Effects of haloperidol (0.1 and 0.4 mg/kg) 30 min and 24 h after acute injection on parameters of aggressive behavior in "experienced winners." Data are presented as mean values. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ vs. saline-treated males on two-tailed Mann–Whitney U-test, $n = 10$–12.

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