Characteristics of Antiamnestic Effects of Blockade and Activation of Dopamine D1 Receptors after Stress Stimulation in Mice

N. I. Dubrovina

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 152, No. 10, pp. 392-395, October, 2011
Original article submitted June 9, 2010

Changes in the effects of D1-receptor activation and blockade on the amnesia induced by delay in unsafe compartment in mice after forced swimming were studied using conditioned passive avoidance test. The most pronounced antiamnestic effects in mice with behavioral despair reaction were observed after administration of D1 receptor antagonist SCH23390, while D1 receptor antagonist SKF38393 was most effective in mice without preliminary stimulation.

Key Words: *memory; amnesia; depression; stress; mice; SKF38393; SCH23390*

Predisposition to amnesia and the possibility of preventing memory deficiency are in many respects determined by pre-exposures to stress and by variations in individual baseline state of the organism. For instance, in clinical practice depressive patients demonstrate higher susceptibility to amnestic agents [6]. We previously demonstrated resistance to "psychogenic" amnestic factor in aggressive mice, in mice with high predisposition to freezing reaction, but not in mice with behavioral despair reaction [2,4]. Bearing in mind the importance of dopamine (DA) system in the regulation of the responses to stress stimulation used for the modeling of depressive behavior [1,5,9] and in the development of various amnesias [11,13-15], it is interesting to study the role of D1- and D2-receptor functions in the control of the resistance to the amnestic agents. D1- and D2-receptors are known to play either complementary or opposite roles in antiamnestic effects of pharmacological DA-agents [3,12,14]. However, the effect of baseline functional state of the organism on the efficiency of DA-agents is poorly studied.

The objective of this study was to analyze the possibility of preventing amnesia in activation and blockade of D1-receptors in mice after stress stimulation leading to the development of behavioral despair.

Institute of Physiology, Siberian Division of the Russian Academy of Medical Sciences, Novosibirsk, Russia. ***Address for correspondence:*** dubrov@physiol.ru. N. I. Dubrovina

MATERIALS AND METHODS

Experiments were carried out on 3-3.5-month old male C57Bl/6J mice weighing 22-27 g obtained from Tomsk nursery. The mice were kept under standard vivarium conditions with free access to food and water. The experiments were carried out in compliance to humanity principles according to "Rules for Working with Experimental Animals" (Appendix to the Order of Ministry of Health USSR dated 12.08.1977, No. 755) and were approved by Ethical Committee of Institute of Physiology, Siberian Division of the Russian Academy of Medical Sciences.

Stress stimulation included forced swimming in a cylinder (20 cm diameter, 24 cm high, water temperature 21-22°C) for 5 minutes daily for 3 days. The procedure is used in experiments as a model of depressive-like state, behavioral despair [2,10]. One day before passive avoidance conditioning, single habituation to experimental apparatus (dark/light chamber with a hole) was performed to assess motor activity and anxiety behavior. The latency of the first transition to the dark compartment, time spent in the light

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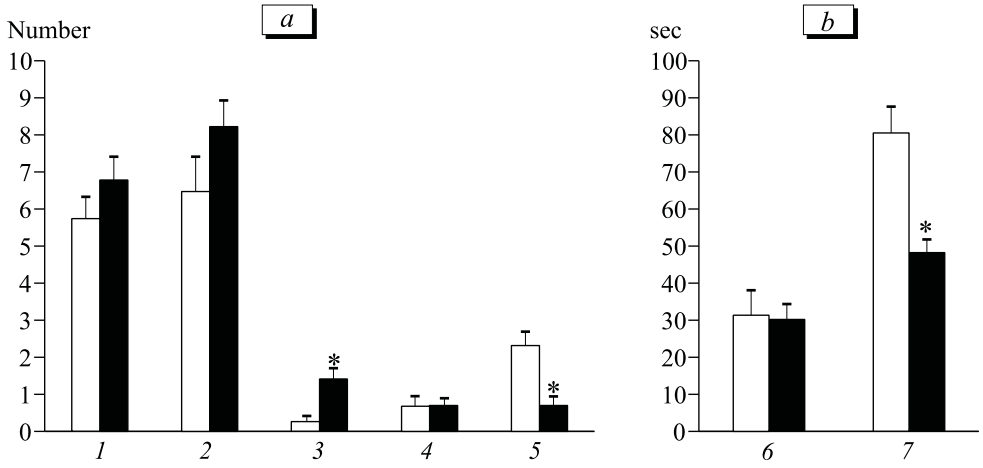

Fig. 1. Parameters of mouse behavior during habituation to experimental light/dark chamber for CPA training. Light bars: mice without stress stimulation (normal); dark bars: mice exposed to forced swimming for 3 days. *1*) transitions from one compartment to another; *2*) rearings; *3*) defecation level; *4*) peepings into the dark compartment; *5*) peepings out of the dark compartment; *6*) latency for the first entering to the dark compartment; *7*) time in light compartment. **p*<0.05 in comparison with normal animals.

compartment, number of transitions between compartments, number of rearings, number of peepings in the dark compartment, number of peepings out of the dark compartment, and defecation boluses were registered.

Training in conditioned passive avoidance task (CPA) was carried out according to conventional single trail procedure. On the training day, the mouse was placed into the light compartment with its tail toward the hole; after transition into the dark compartment with four paws, the mouse received painful electrical stimulus (0.5 mA, 2 sec duration). Amnesia-inducing procedure consisted in forced restraining of the animal in the dark compartment for 5 min immediately after painful stimulus. CPA was tested in subsequent testing (day 1-4 after learning) in the apparatus with registration of the latency of transition to the dark compartment. Maximum time of testing prescribed by the experimental procedure was 180 sec.

Under conditions of amnesia, effects of D1-receptor agonist SKF38393 in a dose of 5 mg/kg and antagonist SCH23390 in a dose of 1 mg/kg were evaluated. Six groups of mice were used. SKF38393 and SCH23390 were administered intraperitoneally under normal conditions (without preliminary stressing; n=10 and n=9, respectively) and after 3 day exposure to forced swimming (mice with reaction of behavioral despair; n=13 and n=14, respectively) 30 min before training and amnesia-inducing procedure. Control groups (n=8 and n=10) received physiological saline.

The data were processed using one-way and two-way (first factor is the group and second factor is the testing time) ANOVA for repeated observations with subsequent post-hoc Newman–Keuls test and LSD comparisons.

RESULTS

Behavioral analysis before CPA training in the dark/light chamber revealed similar motor and exploratory activities in mice with normal functional state and in mice with behavioral despair (Fig. 1). No significant differences in the latency of the first entrance into the dark compartment, number of transitions between the compartments, rearings, and peepings into the dark compartment were detected (p>0.05). At the same time, less time spent in the light compartment ($F_{1,62}$=20.37; p<0.0001), reduced number of peepings out the dark compartment ($F_{1,62}$=13.90; p=0.0005), and increased defecation rate ($F_{1,62}$=19.40; p=0.0001) attested to anxious behavior in mice after stress stimulation.

Peculiarities of D1-receptor involvement during amnesia in mice after test stimulation were investigated in CPA testing. Notably, preliminary stress did not affect amnesia development in response to detention in the unsafe compartment. Analysis of entrance latency

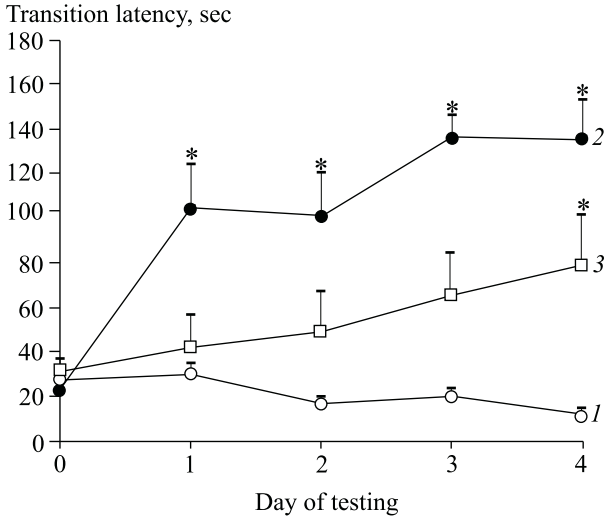

Fig. 2. Effects of activation and blockade of D1-receptors on memory trace retrieval after amnesia in mice without stress stimulation. Here and in Fig. 3: *1*) amnesia control; *2*) D1-agonist SKF38393 (5 mg/kg intraperitoneally 30 min before the training); *3*) D1-antagonist SCH23390 (1 mg/kg). 0: day of training); **p*<0.05 in comparison with the control.

for all the groups revealed significance for group factor ($F_{5,58}$=10.37; p<0.0001), day of testing ($F_{4,232}$=25.94; p<0.001), and their interaction ($F_{20,232}$=6.12; p<0.001).

In mice not exposed to forced swimming, the effect of D1-receptor activation after SKF38393 administration in a dose of 5 mg/kg 30 min before the training with amnestic stimulation consisted of substantial increase in transition latency in comparison with the control at all terms (Fig. 2). D1-receptor blockade with SCH23390 in a dose of 1 mg/kg gradually improved memory trace retrieval in those mice, but significant differences from the control were observed only on day 4 of testing (p<0.05). In mice exposed to forced swimming, D1-agonist SKF38393 increased the transition latency on days 3-4 of testing and antagonist SCH23390 starting from day 1 (Fig. 3).

Analysis of D1-receptor activation and blockade revealed certain peculiarities in amnesia prevention in mice exposed to stress stimulation with the development of behavior despair reaction [2,10] in comparison with normal animals. First, the antiamnestic SKF38393 effect in stressed mice appeared later: transition latency in these mice significantly increased only on day 3 of the testing, while in normal mice this effect was observed 24 h after training and restraining in unsafe compartment. Second, the antiamnestic effect of SCH23390 in mice with behavioral despair was more pronounced than in mice with unchanged baseline condition, since it was observed on day 1 of the testing and transition latencies during CPA testing were longer (134±14 sec in stressed mice and 78±22 sec in normal mice. Similar direction of antiamnestic effects of D1-receptor activation and blockade agree with published data [3,12,14,15].

Significant redistribution of D1-receptors in nucleus adjacent, amygdala complex, frontal complex [1,9], and therefore modification of their activity, are known to appear after stress resulting in the development of depressive-like state. The resistance to amnestic stimulation under conditions of either D1-receptor activation in non-stressed mice or D1-receptor blockade in stressed animals is formed due to optimal functioning of primarily mesolimbocortical DA system, which was different in the tested mice. It can not be excluded, that SKF38393 produced antiamnestic effect in normal mice via a mechanism of fear reaction potentiation and increasing attention to the context of experimental chamber [7,8]. Gradual manifestation of D1-antagonist antiamnestic effects of in normal mice and D1-agonist in mice with behavioral despair is worthy of note. One must admit that these effects are not stipulated by spontaneous memory trace recovery, since memory impairment persisted in control mice.

Thus, our findings suggest that the possibility for prevention of the amnesia under conditions of activation and blockade of D1-receptors depends on the baseline functional state of mice modified by stress stimulation.

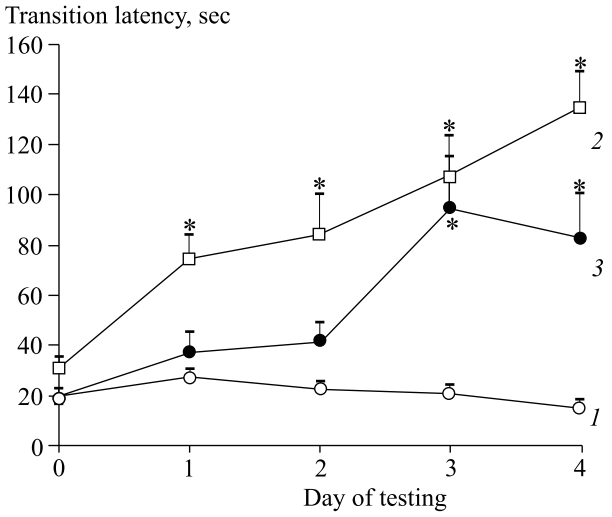

Fig. 3. Effects of activation and blockade of D1-receptors on memory trace retrieval after amnesia in mice exposed to forced swimming for 3 days.

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