Genotype-Dependent Characteristics of Behavior in Mice in Cognitive Tests. The Effects of Noopept

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Male C57BL/6J, BALB/c, and DBA/2J mice showed differences in their abilities to perform two cognitive tests. C57BL/6J mice had good learning ability and memory trace retention (at 10 days) in a simplified Morris maze, while BALB/c mice had low levels of memory trace retention and DBA/2J mice had low learning ability in this test. I.p. administration of the nootropic agent Noopept (GVS-111, N-phenylacetyl-L-prolylglycine ethyl ester) at a dose of 0.5 mg/kg 15 min before the start of the test induced significant improvements in long-term memory in this test in BALB/c mice but no further improvement in C57BL/6J mice, and had no effect in DBA/2J mice. On testing the ability to extrapolate the direction of movement of a stimulus, administration of Noopept increased the proportion of correct responses in C57BL/6J and BALB/c mice, but had no effect in DBA/2J mice.

KEY WORDS: cognitive tests, Morris test, extrapolation ability, behavioral genetics, mice, inbred strains, nootropic effects, Noopept.

Genetic differences in behavior [10–15, 23, 25, and others] and in the levels of development of cognitive abilities have been studied in humans in psychogenetic studies and in experiments with laboratory mice and rats of various strains. Studies in mice have demonstrated interstrain differences both in neurochemical measures [18, 26] and in cognitive abilities [3, 8, 9, 12–14, 22]. Many investigators now regard the category "cognitive abilities" or "cognitive behavior" as including not only the ability to form concepts, for example, spatial concepts [22, 29], and solve logical tasks [3, 8], but also the learning of various skills. The Morris water maze test [19], which allows assessment of the formation of concepts of space and spatial memory in animals, is used to evaluate the effects of factors causing deterioration or improvement in cognitive functions [13, 28], and in pharmacogenetic experiments [15, 29]. Use of the test based on extrapolation of the direction of movement of a stimulus disappearing from the field of vision has demonstrated that laboratory mice of most genotypes do not have this cognitive ability [22]. This excludes some groups, such as mice carrying Rb(8.17)1 Iem [22] or bred for increased brain weight [8]. It has been demonstrated that CBA/Lac/Sto mice, which initially cannot solve extrapolation tasks, showed significant levels of task solution when treated with the heptapeptide Selank [21]. Comparison of the abilities of mice of different genotypes to solve cognitive tests in normal conditions and after administration of substances with nootropic actions [24] may be of value in studying the physiological mechanisms of cognitive processes. Previously reported experiments have demonstrated that Noopept decreases anxiety in mice and intensifies their investigative activity, these effects being present to different extents in BALB/c, C57BL/6J, and DBA/2J mice [1]. We report here our analysis of the abilities of mice of three inbred strains – BALB/c, C57BL/6J, and DBA/2J – to solve two cognitive tests in control conditions and after administration of the nootropic agent Noopept [16, 27].

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METHODS

Experimental animals. Studies used male nice of the inbred strains C57BL/6J (henceforth C57BL, n = 42), BALB/c (n = 38), and DBA/2J (henceforth DBA, n = 39), obtained from Stolbovaya, Russian Academy of Medical Sciences. The animals weighed 20–23 g. Each experimental series used 18–21 mice of each strain. Animals were kept in plastic cages of size 30 × 70 × 40 cm in groups of 6–8 animals per cage with natural illumination; they were fed with Kombikorm from MEST (Russia) and water without restriction. Animal studies were performed in accord with the "Regulations for Studies using Experimental Animals" (Decree of the Ministry of Health of the USSR No. 755, August 12, 1977).

Noopept (GVS-111, N-phenylacetyl-L-prolylglycine ethyl ester), developed at the State Research Institute of Pharmacology, Russian Academy of Medical Sciences [16, 27], was dissolved in distilled water and given at a dose of 0.5 mg/kg i.p. (in 0.01 ml/g) 15 min before experiments started. Animals of the control group received equivalent volumes of physiological saline at the same times.

Behavioral Testing

Morris water maze. A modified Morris test [5] was used here, with a smaller basin (70 × 55 × 60 cm) than originally proposed by Morris [19]. The basin was filled with water at room temperature, colored white with milk. A platform of diameter 7 cm was placed in one corner and was submerged to a depth of 0.5 cm below the water level. The experimental procedure was also simplified. A mouse could find the platform and climb onto it to avoid remaining in the water. The animal was placed in the water in the basin corner opposite the platform and the time taken to find the platform was recorded. Each mouse performed the test five times, being launched from the same corner each time with intervals of 15 min. The animal's movement trajectory and platform finding time were recorded by hand. The test was repeated after 10 days (without prior administration of agents).

Test for ability to extrapolate the direction of movement of a stimulus. The ability to extrapolate was assessed by a previously described method [3, 9] using a chamber of size 35.5 × 23.5 × 11.5 cm, one of the walls projecting inwards by 4 cm and serving as a screen; a bowl of milk moved on the other side of the screen. Openings were located in the center and at the sides of the screen, though which the mouse could drink the milk; it could also use the central opening to follow the direction of movement of the bowl as it disappeared from the field of vision. Animals were deprived of food and water for 20 h prior to experiments. On testing, mice were placed in the experimental chamber and one of the bowls was placed in front of the central opening. A second milk-containing bowl, invisible to the animals was placed alongside, but on the other side of the screen. The mouse started to drink the milk, but after 1–2 sec the bowl was slowly moved towards one of the side openings, the second bowl being moved in the opposite direction (to equalize olfactory and sound stimuli). Solutions of the task were regarded as correct when the animals found the food in the side opening (i.e., moved to the side to which the food had disappeared). Six task presentations were made in each experiment, the direction of movement changing in random order. The ability of the mice to extrapolate was assessed in terms of the proportion of correct responses (as a percentage) of the total number of test presentations on both the first and repeated presentations.

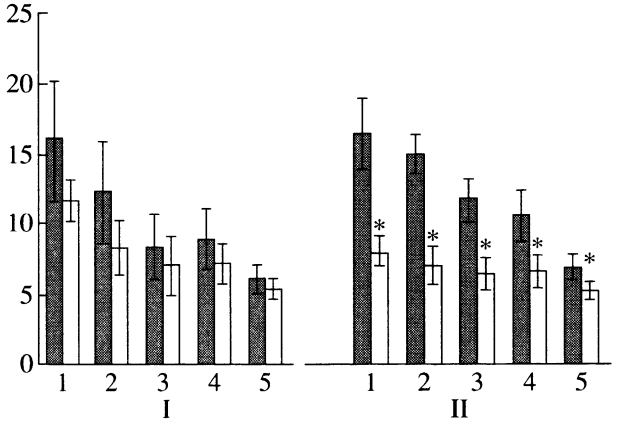

Fig. 1. Time taken to find the submerged platform (vertical axis, sec) by BALB/c mice in the simplified Morris maze test on training (I) and on testing for retention of the skill at 10 days (II). ■) Control group; □) i.p. Noopept, 0.5 mg/kg, 15 min before experiments. The horizontal axis shows test presentations on the experimental day. *Significant differences from control group, $p < 0.05$.

Statistical Analysis of Data.

The statistical significance of differences between groups of animals in the simplified Morris water maze were assessed by unifactorial dispersion analysis (ANOVA, run on standard program bundle Statistica).

The significance of differences in the abilities of mice to extrapolate was evaluated using the Fisher method (the φ method) for alternative proportions [4].

RESULTS

Simplified Morris water maze test. On first presentation of the test, the mean times taken by mice of all three strains to find the hidden (submerged beneath the water) platform were essentially identical (14.3 ± 4.5 sec for C57BL/6J, 16.1 ± 4.3 sec for BALB/c, and 19.5 ± 5.1 sec for DBA/2J). However, the control animals of the different strains showed interstrain differences as early as the first experiment. During five presentations of the test, C57BL and

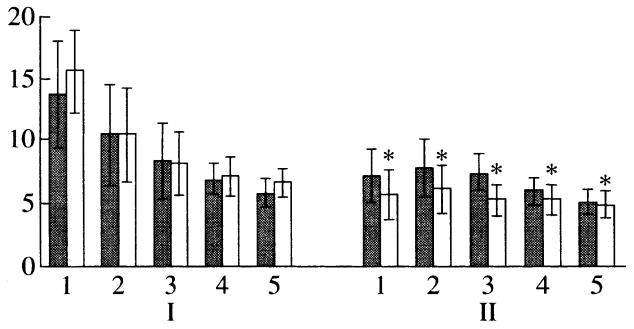

Fig. 2. Time taken to find the submerged platform (vertical axis, sec) by C57BL/6J mice in the simplified Morris maze test on training (I) and on testing for retention of the skill at 10 days (II). For further details see caption to Fig. 1.

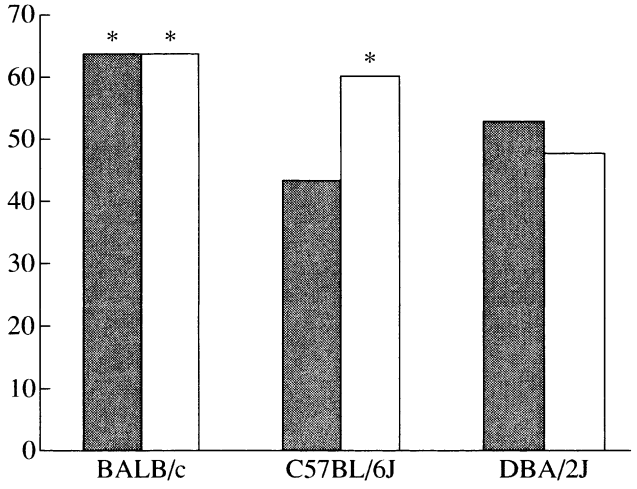

Fig. 3. Proportions of correct solutions (vertical axis, %) of the task consisting of extrapolating the direction of movement of a stimulus on first presentation. *Significant difference from that 50% random level, $p < 0.05$. For further details see caption to Fig. 1.

BALB/c mice showed significant decreases in the platform seeking times (to 5.7 ± 1.1 sec in C57BL and to 6.1 ± 1.2 sec in BALB/c, $p < 0.05$), i.e., these animals showed a learning process. In DBA mice, the seeking time decreased insignificantly (from 19.5 ± 5.1 to 13.5 ± 3.2 sec, $p > 0.05$).

On testing for skill retention at 10 days, control C57BL mice found the hidden platform significantly more quickly ($p < 0.05$) than on initial training. ANOVA data showed that administration of Noopept produced no significant changes in seeking time either during initial training or on testing for memory trace retention ($F_{2.37} = 0.85$; $p > 0.05$ and $F_{2.37} = 1.72$; $p > 0.05$, respectively, Fig. 1).

C57BL mice can be suggested (both in control conditions and after administration of Noopept) to have learned to locate the platform as quickly as possible and with the optimum trajectory, such that administration of the nootropic agent did not alter the course of their learning in this test.

Unlike C57BL mice, BALB/c mice of the control group tested at 10 days required only slightly less time to find the platform than in the baseline experiment. In the initial experiment, BALB/c mice given Noopept showed a marginal reduction in the platform-seeking time as compared with controls ($F_{2.40} = 2.7$; $p > 0.05$; see Fig. 2).

On testing at 10 days, control BALB/c mice spent as much time in seeking the platform on the first presentation as in the first experiment; from the first to the fifth presentations, this time, as in the initial experiment, decreased significantly ($p < 0.05$) (from 16.9 ± 3.3 to 5.8 ± 1.0 sec). In other words, judging from this measure, signs of learning the skill of finding the platform were not evident at 10 days in control BALB/c mice. Testing for retention of the skill in mice of the experimental group (administration of Noopept in the initial experiment) showed that these animals found the platform significantly more quickly than initially ($F_{2.40} = 6.37$; $p < 0.01$). In other words, administration of Noopept to BALB/c mice facilitated fixation of the memory related to the platform-finding skill.

The mean platform-finding time in control DBA mice was the greatest (21.7–15.2 sec); administration of Noopept had no effect either in the initial experiment or on testing at 10 days. Thus, DBA mice were unable to learn the water-avoidance skill, and the nootropic agent had no effect on the skill formation process.

Extrapolation ability test. The proportion of correct task solutions on extrapolation by BALB/c control mice on first presentation was 65% (which was significantly, $p < 0.05$, different from the 50% level characterizing random events). In C57BL and DBA mice, the proportions of correct solutions in this test on first presentation did not differ from the random level (Fig. 3).

After administration of Noopept, the proportion of correct solutions of this test on first presentation in C57BL mice (unlike BALB/c and DBA) was significantly ($p < 0.05$) greater than that in animals of the control group (data not presented) and significantly exceeded the random level (Fig. 3). In BALB/c mice (with high levels of correct solutions on first presentation in controls), administration of Noopept produced no significant changes in this measure. In DBA mice (Fig. 3), there was some increase in the proportion of correct solutions after administration of Noopept (tendency, $p = 0.0587$).

The results in terms of solutions of the extrapolation task on repeated presentation provided additional information on the behavior of the animals in this test. In control C57BL and DBA mice, the proportion of correct solutions to the extrapolation task, using data from six presentations, was no greater than the 50% level (Fig. 4). In BALB/c control mice, the proportion of correct solutions of this task, using data from six presentations, as on the first presentation, was significantly greater than 50% ($p < 0.05$). After

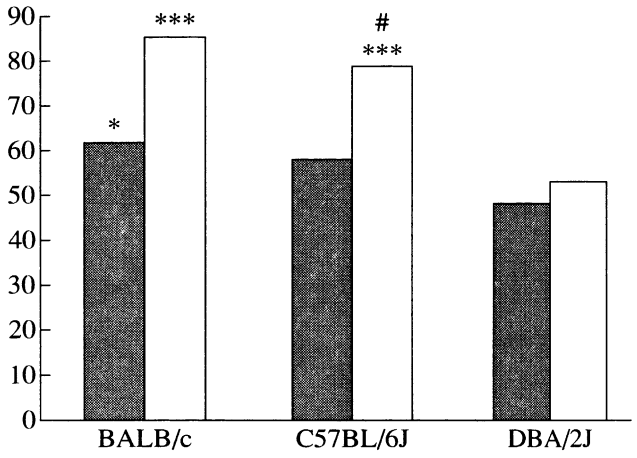

Fig. 4. Proportions of correct solutions (vertical axis, %) of the task consisting of extrapolating the direction of movement of a stimulus for six task presentations. *,***Significant difference from that 50% random level, $p < 0.05$ and $p < 0.001$; #significant difference from control strain ($p < 0.05$). For further details see caption to Fig. 1.

administration of Noopept, the proportion of correct solutions of the extrapolation test in mice of this line, on repeated presentation, was even greater, and was very significantly greater than the random level ($p < 0.001$) and the proportion of correct solutions in controls ($p < 0.05$).

In C57BL mice, administration of Noopept led to an increase in the proportion of correct solutions ($p < 0.001$ compared with the random level; $p < 0.05$ compared with the control level).

In DBA mice, the proportion of correct solutions of the extrapolation test after administration of Noopept, as in controls, was not significantly greater than the 50% random level.

DISCUSSION

The version of the Morris test used in the present studies was significantly less complex than that initially proposed [5, 19]. This simplified version decreases the need to form an intrinsically "spatial" concept. In our experiments, the animal was always launched into the water from the same point on the basin perimeter, which allowed it to use "route calculation," i.e., the simplest strategy which is used by the animal for orientation in space and which is independent of the receipt of information from outside [20]. The extent to which external orienting features are used and a "spatial map" is formed, i.e., a strategy characteristic of the orientation of rats and mice in the "large" Morris test basin, could not be determined in the present experiments.

On first presentation of this test, all mice in the control groups spent no more than 15 sec seeking the platform, C57BL/6 mice finding the platform the most quickly. We suggest that the 5–6 sec taken by the animals to find the platform by the fifth test presentation is the time required to achieve the aim via the shortest trajectory. The seeking time decreased with increasing test presentations in control C57BL and BALB/c mice (Figs. 1 and 2), i.e., learning of the water-avoidance skill occurred; this did not take place in DBA mice (data not presented).

Retention of the skill at 10 days also depended on genotype. In C57BL mice, the platform seeking time was 6.9 ± 1.8 sec as early as the first presentation. This was significantly ($p < 0.05$) faster than in the initial experiment (14.3 ± 4.5 sec). In DBA mice, the time taken to find the platform was 19–20 sec. In control BALB/c mice, the platform finding time was the same as that in the initial experiment. However, as in the initial experiment, the time taken to find the safe platform decreased in these animals from the first to the fifth presentation. Thus, interstrain differences were seen in control animals both in initial learning of the platform-finding skill and in retention of the skill at 10 days.

The effect of Noopept administration on learning in this test was much more marked in BALB mice. In other words, administration of the agent to BALB/c mice was followed by the finding that the platform-finding skill was retained. Given that platform-finding was very rapid in control C57BL mice, the effects of the nootropic agents on memory could not be detected. Interstrain differences in the success of assimilating the skill of finding the submerged platform in the Morris test have also been seen by other authors [14, 29, 30] and, as in our experiments, C57BL mice were the most successful and DBA the least.

In the vast majority of laboratory mice of different strains and genotypes, the proportion of correct solutions of the extrapolation task was no different from the 50% random level [22]. A significant difference between this proportion and the random level was seen only in mice of some genetic groups, particularly some inbred lines and carriers of chromosomal mutations [8, 22]. A similar pattern was also seen in the present study: BALB/c mice showed a high level of correct solutions of this test. The level was no greater than the 50% random in control mice of the other two strains.

On administration of Noopept, the proportion of correct solutions of the task in C57BL/6 mice was significantly above the random level ($p < 0.05$). Administration of Noopept to BALB/c mice had no effect on the proportion of correct task solutions on first presentation, but increased the proportion of correct solutions in six (repeated) presentations of the test (Figs. 3, 4). In DBA mice, administration of Noopept had no effect on performance of this test.

The inbred strains used in the present studies differed from each other in terms of a very large number of neurochemical parameters, including those associated with the functions of the main neurotransmitter systems of the brain [17]. Evidently, some of these differences may be causally related to the differences in the level of success in perform-

ing cognitive tests seen in the present studies. However, our data do not give an exact answer as to the factors with which these differences in behavior are associated. At the same time, the different nature of the effects of Noopept on performance of the tests by mice of different strains may bring us somewhat closer to an understanding of these differences.

In BALB/c mice, the effect of the nootropic agent was seen on performance of both tests, which points to the need for more detailed analysis of the reported characteristics of the behavior of mice of this strain [30]. The review of Ingram and Corfman [17] showed that BALB/c mice are characterized by lower acetylcholine concentrations in the neocortex, hippocampus, and caudate nucleus than C57BL mice. The failure of control BALB/c mice to retain the platform-finding skill on testing at 10 days may be associated with this feature. However, these animals did show retention after administration of Noopept. This effect should logically be compared with the previously observed "acetylcholine-positive" effect of this agent [7]. On the other hand, Noopept is known to be characterized by a combination of nootropic and anxiolytic actions [2, 6]. This property of Noopept may make some contribution to the increase in the efficiency of performing both tests by BALB/c mice noted above, as it is known that they are highly sensitive to stress-inducing factors [10, 11]. The decrease in the level of anxiety probably facilitates the appearance of the intrinsic "cognitive abilities" of these animals. The increased stress response to novel situations may also determine their behavioral characteristics in the "stressful" elevated plus maze and slippery funnel tests, as we have demonstrated previously [1].

DBA mice were the least sensitive to the effects of Noopept. As demonstrated previously, Noopept affects hippocampal and cerebral cortical functions [6], and also modulates the functions of cholinergic neurons. It can be suggested that the organization of the structures of the hippocampal formation inherent to DBA mice [12, 18, 21, 25] and the demonstrated cholinergic system deficit [28] prevent the action of Noopept.

Thus, the data obtained here not only support the existence of interstrain differences in the abilities of mice to solve cognitive tests, but also demonstrate the genotype-dependent nootropic properties of Noopept.

CONCLUSIONS

1. Intact C57BL/6J, BALB/c, and DBA/2J mice were found to show differences in the performance of tests addressing the animals' cognitive abilities (the simplified Morris maze and the extrapolation ability test). Good initial learning ability and memory were demonstrated in C57BL/6J, along with low levels of both measures in DBA/2J mice and a deficit in long-term memory in BALB/c mice.

2. Noopept (GVS-111) has a genotype-dependent nootropic effect in the simplified Morris test, which was clearly marked in BALB/c mice and virtually absent in DBA mice.

3. Noopept increased the ability of C57BL/6J and BALB/c mice to solve an elementary logical task consisting of extrapolating the direction of movement of a stimulus but had no effect on measures of the solution of this test in DBA/2J mice.

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