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EXPERIMENTAL PAPERS

Effect of TAAR1 Knockout on Behavior Characteristics of Mice in Tests Assessing Anxiety and Depressive-Like Behavior

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Abstract—The aim of this study was to investigate the functional role of the TAAR1 receptor, one of the representatives of trace amine-associated receptors (TAARs). The behavior of TAAR1-KO knockout mice and wild-type (WT) mice were studied in tests reflecting the anxiety and depressive-like conditions. In the Novelty-Suppressed Feeding test, it was shown that in TAAR1-KO mice the average time to approach the bait was significantly shorter than in WT mice. No statistically significant differences were found for all other parameters of feeding behavior (latency before the start of eating, duration of food consumption, number of approaches with sniffing the bait, number of meals). In the tail suspension test and the Porsolt forced swimming test, the LP of the first immobilization was significantly higher in TAAR1-KO mice. In the Porsolt test, TAAR1-KO mice showed a lower duration of immobilization compared to WT mice.

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INTRODUCTION

Much attention is currently being paid to elucidating the role of the trace amine system in the vertebrate central nervous system [1, 2]. Trace amine-associated receptors (TAARs) belong to the class of G-protein-coupled receptors identified in humans and other vertebrates and invertebrates. Of the family of TAARs, the TAAR1 receptor is the best studied.

In the mammalian brain, the TAAR1 receptor is expressed in the cortical and striatal projections of dopaminergic neurons and in the corticolimbic projection sites of 5-HT neurons; the TAAR1 receptor is found in many limbic and mesolimbic structures: Hippocampus, hypothalamus, amygdala, bed nucleus of the striatum terminalis, ventral tegmental area, dorsal raphe nucleus and medial prefrontal cortex [3]. TAAR1 is known to play an important role in the regulation of dopaminergic, serotoninergic and glutamatergic transmission and is therefore widely implicated in many brain functions [1, 4]. Trace amines are structurally similar to classical monoamines, and disorders in this system are associated with a wide range of pathologies including depression, schizophrenia, neurodegenerative diseases and attention deficit hyperactivity disorder [2, 3, 5].

The data accumulated to date indicate that the TAAR1 receptor is a promising target for pharmacological action in the treatment of a number of diseases. This has generated considerable interest in the functional role of the TAAR1 receptor and stimulated the search for selective agonists of the TAAR1 receptor for the therapy of psychiatric disorders [6, 7, 8].

A number of drugs that act through the TAAR1 system are in clinical trials for the treatment of schizophrenia spectrum disorders and negative symptoms of schizophrenia [9, 10]. The TAAR1 agonist RO 5263397 has been shown to alleviate dyskinesia induced by the choline acetyltransferase inhibitor α-NETA [11]. It is thought that TAAR1 deficiency or impairment may enhance dopamine-dependent behaviors and functions, whereas TAAR1 agonists attenuate them [12]. Systemic administration of TAAR1 receptor agonists reduces the duration of immobilization in the forced swim test in rats and has anxiolytic effects in models of stress-induced hyperthermia in mice [7, 13, 14].

Data on the effect of TAAR1 receptor knockout on animal behavior are unclear and sometimes contradictory. Studies in recent years have increasingly shown similar behavioral signs in TAAR1-KO animals with some manifestations of depressive and anxiety states: increased locomotor activity, decreased grooming and increased aggression against a background of no changes in testosterone levels, pronounced dominant behavior in the resident-intruder test in males [15, 16]. TAAR1-KO females show an absence of the early component of the behavioral response to acute immobilization stress in contrast to wild-type animals [17]. Studies of anxiety levels in the elevated-plus maze test showed no significant differences in motor and exploratory behavior and anxiety levels between TAAR1-KO and WT males [15, 18]. In the elevated-zero maze test, anxiety levels were higher in TAAR1-KO females compared to WT females and motor levels were lower [17]. A change in anxiety levels was also found in TAAR1-KO mice with aging [19]. In addition, TAAR1-KO mice showed reduced response in the prepulse inhibition test [15] and reduced sensory gating [20], which may indicate abnormalities in sensorimotor filtering mechanisms characteristic of patients with schizophrenia and a number of other brain disorders.

As the data on the behavioral characteristics of TAAR1-KO mice are rather scarce and ambiguous, it was decided to study the behavior of TAAR1-KO and WT males in tests in which they had not previously been studied: the Novelty-Suppressed Feeding test and the Tail suspension test. The Porsolt test was also used as a comparative test for depressive-like behavior.

MATERIALS AND METHODS

Study object. The study was carried out in male TAAR1-KO mice (n = 20), with wild-type (WT) males (n = 15) used as controls. The WT and TAAR1-KO strains were based on 129S1/Sv and C57BL/6 mice. Animals were obtained from the Resource Centre of the Vivarium of the Science Park of St. Petersburg State University at the age of 3.5 months. The mean weight of the animals was 26.7 ± 0.3 g for TAAR1-KO and 27.2 ± 0.5 g for WT mice. All animals were housed under standard conditions with ad libitum access to food and water and a 12-hour light/dark cycle indoors. Animals were housed in individual transparent plastic boxes with perforated walls (30×15×17 cm). Animals were kept in the laboratory for 14 days prior to the start of the work and were subjected to a handling procedure to prevent the occurrence of a stressor response to being held by hand during the experiment.

Apparatus and methods. Novelty-Suppressed Feeding test (NST) (novelty-induced hypophagia or hyponeophagia). This test assesses the suppression of food intake under the influence of a potentially noxious novel environment [21]. Anxiolytics and antidepressants (when used chronically) are known to reduce hyponeophagia in this test [22, 23], so it is assumed that the results of the NST test reflect the level of anxiety. There are two ways of performing this test. Animals are either deprived of food for 8–16 h prior to the test [24], or they are pre-treated with a new palatable food [25], which is then offered during the test in an unfamiliar environment. The palatable food option prevents a possible pre-test stress response in mice due to food deprivation and was therefore chosen for this study. Three days before the test, the animals were given dried mealworm larvae (*Tenebrio molitor*) in their home cage for 2 consecutive days to introduce them to new food. The time to eat the larvae in the home cage on day 2 was less than 60 s for all mice, with no statistically significant differences between the TAAR1-KO and WT mouse groups. On the day of the experiment, TAAR1-KO and WT mice were individually placed in an unfamiliar setup (30 × 20 × 5 cm) with dried mealworm larvae on a plastic plate in the middle for 5 min. The animals were familiar with both the plate and the larvae, but not with the NST test set-up. The latent period (LP) of approach to the

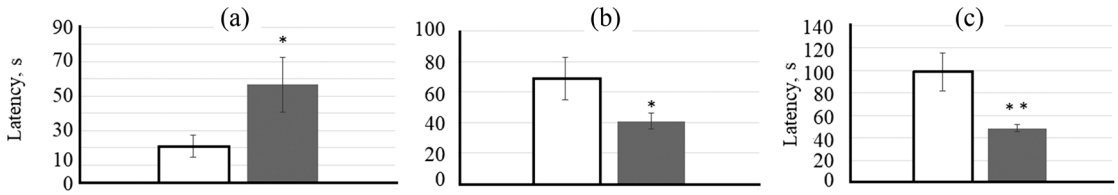

Fig. 1. The latency of reaction. (a) The latency of the approach to food in Novelty-Suppressed feeding test, (b) the latency of the first immobilization in the tail suspension test, (c) the latency of the first immobilization in the Porsolt test. *Horizontally*: groups of animals, *vertically*: the latency in seconds (s). The white mouse bars are TAAR1-KO, the black ones are WT. * $p < 0.05$, ** $p < 0.01$.

bait was considered to be the approach to the larvae with a sniffing response, as this response was considered to be an important component of feeding behavior. Two independent observers analyzed the following behavioral components from the video recordings: the LP of approach to the larva and the number of times the mouse sniffed the bait, the LP of food initiation and the duration of food intake. If the mouse did not approach or eat the bait for 300 s, the test was terminated and the LP for 300 s was counted.

The tail suspension test was performed in a setup with walls of red organic glass, the size of the setup being 20 × 40 × 60 cm. The mouse was placed at a distance of 150 mm from the walls of the chamber. Each mouse was suspended by its tail at a height of 60 cm above the floor of the chamber using adhesive tape placed less than 1 cm from the tip of the tail. The duration of the test was 5 min. A 2.5 cm plastic cylinder was placed on the tail to prevent attempts to climb out using the tail. The behavior of the mice was analyzed by two independent observers using video recording to determine the following parameters: number of immobilization episodes, total immobilization time, LP of first immobilization.

Porsolt test. The forced swim test was used as a model of depression-like behavior in accordance with existing protocols [26, 27]. The apparatus consisted of a glass cylinder with a diameter of 20 cm and a height of 45 cm. The cylinder was filled with water (temperature 23–25°C) to a height of 20 cm so that the animal placed in the cylinder would swim without being able to get out of the cylinder. The duration of the test was 6 minutes. The total time the animal was immobilized, the number of immobilizations and the LP of the first immobilization were recorded. Each behavioral test was performed on all animals on one day between 13:00 and 17:00 h. The behaviors studied in all experiments were recorded by a video camera. All tests were performed sequentially on the same animals with a one-day interval. After completion of the handling procedure, behavioral tests were performed in the following order: NST, tail suspension test, Porsolt test.

The non-parametric Mann–Whitney test for independent samples was used for statistical analysis and to assess the reliability of the differences. This criterion was chosen because of the small size of the groups compared and the impossibility of assessing the nature of the distribution. The critical significance level was set at $p < 0.05$. Results are presented as mean and standard error of the mean ($M \pm SEM$).

RESULTS

Assessment of anxiety levels in TAAR1-KO mice in a NST showed statistically significant differences in the LP duration of the first approach to the food. In TAAR1-KO mice, the mean approach time to the food was 21.0 ± 6.6 s, which was significantly different from the LP duration in WT mice, which was 56.7 ± 15.8 s ($p = 0.035$) (Fig. 1a).

Although TAAR1-KO mice approached the bait relatively quickly, they did not start eating immediately but continued to move around actively in the new environment. No statistically significant differences were found between animals in the two groups for all other parameters of eating behavior (LP before initiation of eating, duration of eating, number of sniffing approaches to the bait, number of food intake) (Table 1).

The tail suspension test showed statistically significant differences in the latency of the first immobilization response. In TAAR1-KO mice, the first immobilization response was observed significantly later (68.8 ± 13.7 s) compared to WT mice (40.8 ± 5.3 s) (Fig. 1b). The total duration of immobilization tended to increase in WT mice compared to TAAR1

Table 1. Behavior profile of TAAR1–KO and WT mice in the Novelty-Suppressed Feeding test

	TAAR1-KO ($n = 20$)	WT ($n = 15$)
Latency to approach food (s)	21.0 ± 6.6	56.7 ± 15.8, $p = 0.035$
Latency to eat (s)	189.0 ± 19.3	208.0 ± 22.5
Number of approaches to food (sniffing food)	5.6 ± 0.8	4.0 ± 0.9
Duration of food intake (s)	13.0 ± 3.5	17.8 ± 8.7
Number of food intake	1.5 ± 0.3	1.1 ± 0.3

Data are presented as mean ± *SEM* (Mann–Whitney *U*-test).

Table 2. Behavior profile of TAAR1–KO and WT mice in the tail suspension test

	TAAR1- KO ($n = 20$)	WT ($n = 15$)
Latency to immobility (s)	68.8 ± 13.7	40.8 ± 5.3, $p = 0.049$
Total time spent immobile (s)	124.7 ± 11.2	137.6 ± 12.6
Number of immobilized acts	15.0 ± 1.2	15.4 ± 1.5
Number of fecal boluses	0.7 ± 0.2	1.2 ± 0.4

Data are presented as mean ± *SEM* (Mann–Whitney *U*-test).

Table 3. Behavior profile of TAAR1–KO and WT mice in Porsolt test

	TAAR1-KO ($n = 20$)	WT ($n = 14$)
Latency to immobility (s)	99.0 ± 17.0	39.0 ± 4.5, $p = 0.001$
Total time spent immobile (s)	85.5 ± 10.7	123.0 ± 11.9, $p < 0.05$
Number of immobilized acts	19.1 ± 1.5	18.0 ± 2.2
Number of fecal boluses	2.4 ± 0.3	2.6 ± 0.4

Data are presented as mean ± *SEM* (Mann–Whitney *U*-test).

KO group animals, but did not reach the level of statistical significance. The number of immobilized acts during the entire experimental period did not differ between animals in the two groups (Table 2).

Porsolt test. TAAR1-KO mice had a significantly longer latency for the first immobilization response (99.0 ± 17.0 s) compared to WT mice (39.0 ± 4.5 s) (Fig. 1c). In addition, TAAR1-KO mice had a shorter duration of immobilization over the entire test period (85.5 ± 10.7 s) compared to WT group mice (123.0 ± 11.9 s) (Table 3). The number of immobilizations was similar in both groups.

DISCUSSION

Behavior in a NST revealed that TAAR1-KO mice had a significantly shorter mean approach time to the food compared to WT mice. All other components of feeding behavior, including LP of food initiation, were not different in them compared to wild-type animals. The shorter LP of food onset in this test is usually interpreted as evidence of lower levels of anxiety [22, 28]. The latency to start eating was not significantly different between groups. This indicates the same suppression of eating behavior in the novel environment, and this fact can be interpreted as the absence of differences in anxiety levels between TAAR1-KO and WT mice. On the other hand, mice from the knockout group start exploring the new environment much earlier, approach the food more quickly, but do not start eating immediately, but continue to move around and explore the

environment for some time. Thus, the observed differences in the behavior of the knockouts may be related to a change in orienting and exploratory behavior and/or an increase in the general level of motor activity. In the elevated plus maze (EPM) test, increased orienting and exploratory behavior (as measured by the number of rears) has already been observed in female TAAR1-KO mice compared to wild-type mice [17].

The EPM and elevated zero maze (EZM) tests are also currently used to study the neurobiological basis of anxiety and to screen anxiolytic drugs. It has previously been shown that no significant behavioral differences were found between male TAAR1-KO and WT mice in the EPM test [15, 18], and the same results were obtained when comparing female TAAR1-KO and WT mice [17]. At the same time, in the EZM test, which is widely used together with the EPM, the anxiety level of female TAAR1-KO mice was higher compared to WT mice in a number of parameters (distance travelled in open arms, duration of stay in open arms, number of entries into open arms, number of head dips) [17]. It can be speculated that, in addition to sex differences, this may be due to differences in the sensitivity of the tests. In particular, the EZM test has been shown to be more sensitive than the EPM in assessing the effects of benzodiazepines in mice [29, 30].

Overall, our finding of no differences in anxiety levels, initially obtained by comparing the behavior of TAAR1-KO and WT mice in a Novelty-Suppressed Feeding test, is consistent with most findings on TAAR1-KO anxiety levels using other tests.

The tail suspension test and the Porsolt test are widely used animal models for testing potential antidepressants. The state of immobilization that occurs during the performance of these tests is considered to be the development of a depression-like state with a refusal to fight, known as “despair behavior” [31, 32]. The use of antidepressants in mice leads to a reduction in the duration and an increase in the LP of immobilization [33–35], and after stressors in rodents, a reduction in the LP of the first immobilization and an increase in the duration of immobilization are observed [36–40].

In this study, it was shown for the first time that in the tail suspension test, the LP of the first immobilization response was significantly longer in TAAR1-KO mice compared to WT mice, while other parameters (total duration and number of immobilizations) did not differ between the two groups.

The data obtained in these tests are similar in many respects to those obtained in the NST. The main index of depression-like behavior, the duration of immobilization, did not differ, while the LPs of the first immobilization response were significantly longer in the knockouts, which can also be explained by an increase in the general level of motor activity rather than a greater tendency to develop a depressive state.

In the Porsolt test, male TAAR1-KO mice not only had a longer initial immobilization LP, but also a shorter total immobilization duration over the entire test period. It should be noted that it was previously shown that TAAR1-KO females also had a longer LP of first immobilization compared to WT females, while the duration of total immobilization was not significantly different between them [17].

There are two possibilities to explain the differences in the manifestation of immobilization in the Porsolt test. One interpretation of these changes is the development of a depressive-like state with refusal to fight—“despair behavior” [31, 32]. However, the transition to passive behavior may reflect an adaptive strategy of coping with stress to conserve energy rather than a refusal to try to find a way out of the situation [41, 42].

For example, comparing the behavior of male TAAR1-KO and WT mice in tests that assess the level of anxiety and depressive-like behavior shows that baseline indicators of anxiety levels and the development of depressive-like states remain unchanged after TAAR1 receptor knockout. The main differences between TAAR1-KO and WT mice are observed in the early stages of the tests and are manifested by increased motor activity in TAAR1-KO mice when exposed to a stressful situation. The observed changes in motor activity in knockouts can be explained by the close interaction of TAAR1 receptors with the dopaminergic system in the brain [3, 43], which plays an important role in the regulation of motor activity.

CONCLUSIONS

It was found that in all three tests performed, the main parameters reflecting the level of anxiety and depression-like behavior in TAAR1-KO mice did

not differ from those in wild-type mice. At the same time, for the first time, very well expressed behavioral traits of TAAR1-KO mice were detected, associated with increased motor activity of the animals when exposed to a stressful situation. In the Porsolt and tail suspension tests, a pronounced increase in motor activity in the initial phase leads to a significant increase in the LP of the first immobilization. In the Novelty-Suppressed Feeding test, the increased motor activity is manifested in a shortening of the LP of approach to the food, TAAR1-KO mice start to explore the environment faster, show a kind of motor restlessness, move around the chamber actively all the time, but abstain from eating.

For the first time, we obtained comparative data on the behavior of TAAR1-KO and WT mice in the novelty-suppressed feeding test and the tail suspension test.

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AUTHORS' CONTRIBUTION

Idea of the paper and development of the research design (E.P.V., A.A.A.), data collection (E.P.V., A.V.K., D.V.B, D.N.O.), data analysis and interpretation (E.P.V., A.A.A.), statistical processing of the data set (A.V.K.), manuscript writing and editing (E.P.V., A.A.A.).

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed were in accordance with the ethical standards approved by the legal acts of the Russian Federation, the principles of the Basel Declaration, international standards for the conduct of biomedical research using animals [44], and the recommendations of the Ethics Committee of the Biology Department of St Petersburg State University (Protocol no. 131-03-2, dated March 13, 2024).

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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