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Role of 5-HT$_{2A}$ Receptors in Immunomodulation in Animal Models of Aggressive Behavior

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Abstract

Serotonin 5-HT$_{2A}$ receptors are playing an important role in the pathophysiology of aggressive behaviors and in the control of immune function. In the present study, we analyzed the effects of activation and blockade of 5-HT$_{2A}$ receptors with selective ligands on the immune response formation in animals with aggressive behaviors induced by genetic factors (rats selected for the increased aggressiveness toward human) or by chronic social stress (mice of the CBA/Lac strain engaged in 10 days of social confrontations). Activation of 5-HT$_{2A}$ receptors with DOI at 1.0 mg/kg reduced the immune response level both in aggressive rats and mice compared to the corresponding vehicle-treated groups, while DOI administration did not alter the immune reaction in nonaggressive animals. The blockade of 5-HT$_{2A}$ receptors with ketanserin at 1.0 mg/kg resulted in immunostimulation both in mice of the CBA strain not subjected to social stress (the controls) and in nonaggressive rats selected for elimination of aggressiveness. On the other hand, its administration to CBA mice demonstrating offensive aggression enhanced the immune reaction, while the same dose of ketanserin did not modify the immune response level in rats with genetic predisposition to the increased defensive aggression. Thus, our data suggest that the role of 5-HT$_{2A}$ receptors in immunomodulation depends on the specific type of aggression that may be taking into account in the treatment of some neuropsychiatric disorders with the antipsychotic drugs and antidepressants targeting 5-HT$_{2A}$ receptors.

Keywords

Aggressive Behavior, Serotonin 5-HT$_{2A}$ Receptors, DOI, Ketanserin, IgM-Immune Response

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1. Introduction

Most of the evidence to date provides support for a key role of the serotoninergic (5-HT) system and specific receptor subtypes in the regulation of aggressive forms of behavior [1]-[6]. Among several types of 5-HT receptors, 5-HT_{2A} receptors have long been implicated in the pathophysiology of aggressive behaviors [1]-[6]. Moreover, a number of atypical antipsychotic drugs and antidepressants, targeting 5-HT_{2A} receptors, have been successfully used in patients with various neuropsychiatric disorders [4], which are known to be associated with abnormal aggression and altered immune function [7]-[9]. A number of studies have also demonstrated that 5-HT receptor subtypes are involved in the 5-HTergic mechanisms of immunomodulation [10]-[18].

An important role of pre- and postsynaptic 5-HT_{1A} receptors in the immune response control has been shown not only in normal, but also in mice and rats displaying either depressive-like behavior or increased aggressiveness [14] [16] [18]-[21]. It has also been reported that activation of 5-HT_{2A} receptors, localized only postsynaptically, with their preferential agonist DOI resulted in a decrease of the rosette-forming cell numbers and cytotoxic/suppressor $CD8^+$T lymphocytes in the spleen of mice [15], as well as in the proliferative activity of T lymphocytes in rats [13]. At the same time, the blockade of these receptors with cyproheptadine or ketanserin induced immunostimulation [12] [15] [22]. However, less attention has been paid to the impact of 5-HT_{2A} receptors in the modulation of immune reactions in animals differing in psychoemotional state. Taking into account that aggression is influenced by a broad range of genetic and environmental factors, it is essential to clarify the potential role of these receptors in the modulation of immune function using various models of aggression. The main aim of the present study, therefore, was to analyze the effects of activation and blockade of 5-HT_{2A} receptors on the immune response in rats selected for the increased aggressiveness toward human (defensive aggression) or its absence, and in aggressive mice of the CBA/Lac strain exposed to chronic stressful conditions (offensive aggression).

2. Materials and Methods

2.1. Animals

Rats. The experiments were performed in male Norway rats weighing 300 - 350 g (3 months of age) selected for over 75 - 78 generations for elimination (nonaggressive) or enhancement (aggressive) of aggressiveness towards humans at the Institute of Cytology and Genetics SB RAS (Novosibirsk, Russia). Point scales for defensive responses of both lines of rats from 2 to 3 months of age were based on the "glove test" [23]-[25].

Mice. Male mice of the CBA/Lac (CBA) strain weighing 22 - 24 g (2 - 3 months of age) were maintained at the Scientific Research Institute of Physiology and Basic Medicine (Novosibirsk, Russia).

All animals were kept under standard laboratory conditions under natural light-dark cycle corresponding to the outside conditions with free access to food and water. Experiments were carried out in the light phase of day from 9.00 to 15.00, local time.

All procedures were performed in compliance with principles of the Declaration of Helsinki and approved by local Ethical Committees of the Scientific Research Institute of Physiology and Basic Medicine and Institute of Cytology and Genetics SB RAS.

2.2. Behavioral Experiments

2.2.1. Glove Test

The level of aggressiveness was measured in the "glove test" by confronting rats of both lines with an approaching human hand and attempting to handle them [23]-[25].

The intensity of response to handling was evaluated according to the following five-score system: 0—rat permits to handle and does not make any attempts of avoiding; 1—permits to handle and makes evasive movements in the hand; 2—moves away from the hand and while being picked up tries to break loose; 3—actively escapes handling and while being picked up, rat can emit loud screaming noises, opens mouth or bites; 4—rat does not permit to handle, attacks the hand and emits loud screaming noises. In our experiments we have used rats, which were characterized by either extremely high aggression (4 points according to the scale) or by a complete lack of aggressiveness (0 points according to the scale). The immune response assay was performed within 2 - 3 weeks after behavioral testing.

2.2.2. Production of Aggressive Behavior in Male Mice in the Social Conflict Model

To produce aggressive behavior in CBA mice, the model of sensory contact was used [26]. Males were weighed and individually caged for 5 days to abolish group-living effects. Pairs of animals of nearly the same weight were placed in a steel 28 × 14 × 10-cm cage divided in half by a transparent partition with holes. This permitted animals to see and smell each other but prevented physical contact. After 2 days of adaptation to the housing conditions and sensory contact a test started. Every morning (11:00 a.m., local time), a steel cover of cage was replaced by a transparent one and, 5 min later (a period of individual activation), the partition was removed for 10 min, allowing an agonistic interaction between mice. Agonistic interactions were observed in an overwhelming majority of cages (90% - 100%). A daily test of social confrontations continued for 10 days; if animals did not fight, they were excluded from the experiment. Clear superiority of one partner was evident within two or three tests in daily social encounters in the same cage. One partner demonstrated aggression, attacking, biting and chasing the other one which displayed defense behaviors (sideways, upright postures, and "on the back" or "freezing") during the tests. The control for wounding during the aggressive encounters did not show severe injuries in the animals that could alter the immune parameters. Group-housed males, after 5 days of individual housing, were used as a control group (nonaggressive mice), since in this case there was no experience of aggressive encounters.

2.3. Drug Administered

To examine the role of 5-HT_{2A} receptors we used a selective 5-$HT_{2A/2C}$ receptor agonist DOI (4-indo-2, 5-dimethoxyphenylisopropilamine) (Sigma, USA), and the 5-HT_{2A} receptor antagonist ketanserin (Sigma, USA). Both drugs were injected at the dose of 1.0 mg/kg intraperitoneally (i.p.) in 0.2 ml of vehicle. DOI was dissolved in saline and administered twice for 2 days with 1st injection 30 min before immunization and the 2nd one—on the following day. Ketanserin was dissolved in distilled water and injected once 30 min before antigen administration. The doses, timing and administration routes of drugs were based on our previous data [15]. Control groups of rats received an equivalent volume of corresponding vehicle for the same period of time.

2.4. Immunization

All experimental groups of animals were immunized with sheep red blood cells (SRBC), which were suspended in saline and were injected i.p. at 5×10^8 per 0.5 ml.

2.5. Immune Response Measurement

The immune response was assessed by measuring the numbers of IgM-antibody-forming cells (IgM-AFC) [27] in the spleen of mice on the 4th and rats on the 5th day after immunization.

2.6. Statistical Analysis

Statistical analyses were performed by using Statistica for Windows (version 10.0). Values were expressed as the mean ± standard error of the mean (S.E.M.) and are considered significant when corresponding p values are ≤ 0.05. All data were analyzed by one-way analysis of variance (ANOVA). When there were statistically significant F values, Tukey HSD post hoc tests were conducted comparing drug treatments with the corresponding vehicle group.

3. Results

3.1. Effects of Activation of 5-HT_{2A} Receptors on the Immune Response in Rats with Genetic Predisposition to Different Levels of Aggressiveness

Compared to nonaggressive line, rats selected for the enhanced aggressiveness toward humans showed significantly higher IgM-immune response to SRBC (**Figure 1**), that is characteristic of this genetic line [18] [28] [29]. Activation of 5-HT_{2A} receptors with DOI (1.0 mg/kg) in nonaggressive rats did not affect the numbers of IgM-AFC ($p > 0.05$) compared to animals of this line not treated with the drug (vehicle-injected group). However, rats of the aggressive line, receiving the same dose of DOI, were found to have an eight-fold reduction of the immune response level compared to vehicle-injected aggressive animals ($p < 0.001$).

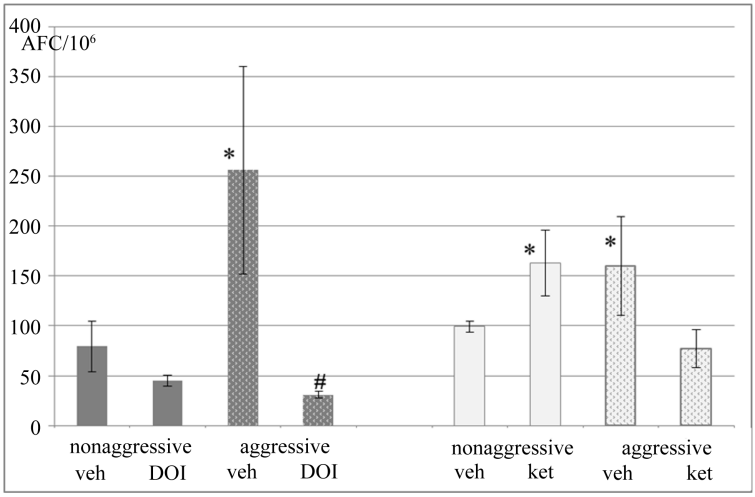

Figure 1. Effects of activation of 5-HT_{2A} receptors with DOI and their blockade with ketanserin (ket) on IgM-AFC numbers in nonaggressive and highly aggressive rats on the 5th day after immunization with SRBC (5 × 10^8). Both drugs were injected at the dose of 1.0 mg/kg, i.p.; DOI—twice for 2 days (1st injection 30 min before immunization, the 2nd—on the following day), ket—once 30 min before antigen administration. Saline was used as a vehicle (veh) for DOI, distilled water—for ket. Data are presented as means ± SEM. $^*p < 0.001$ when compared with the corresponding group of nonaggressive rats; $^\#p < 0.001$ when compared with the aggressive group, receiving veh.

3.2. Effect of the Blockade of 5-HT_{2A} Receptors on the Immune Response in Rats with Genetic Predisposition to Different Levels of Aggressiveness

The blockade of 5-HT_{2A} receptors with ketanserin (1.0 mg/kg) in nonaggressive rats produced an increase of IgM-AFC numbers when compared to rats of this line receiving only vehicle (**Figure 1**) ($p < 0.001$). In contrast, ketanserin administration to highly aggressive rats did not significantly change the immune response relative to the control group of aggressive animals.

3.3. Effect of Activation of 5-HT_{2A} Receptors on the Immune Response in Mice of the CBA Strain

Activation of 5-HT_{2A} receptors with DOI at 1.0 mg/kg significantly decreased IgM-immune response in CBA mice displaying aggression during 10 days of social confrontations relative to aggressive mice not treated with the drug ($p < 0.01$), while DOI did not alter the immune response in mice without experience of social encounters (**Figure 2**).

3.4. Effect of the Blockade of 5-HT_{2A} Receptors on the Immune Response in Mice of the CBA Strain

The blockade of the 5-HT_{2A} receptors with ketanserin (1.0 mg/kg) produced a pronounced increase in the numbers of AFC in CBA mice that did not experience social contact compared to the vehicle-injected group ($p < 0.001$) (**Figure 2**). Similarly, CBA mice with repeated experience of aggression receiving1.0 mg/kg of ketanserin showed significantly higher immune response than aggressive mice not treated with the drug ($p < 0.001$) (**Figure 2**).

4. Discussion

The present study has demonstrated that changes in activity of 5-HT_{2A} receptors by their activation with a preferential 5-HT_{2A} agonist DOI or blockade with a selective 5-HT_{2A} antagonist ketanserin significantly affect the immune response formation in animals with aggressive behaviors induced by genetic factors or by chronic social

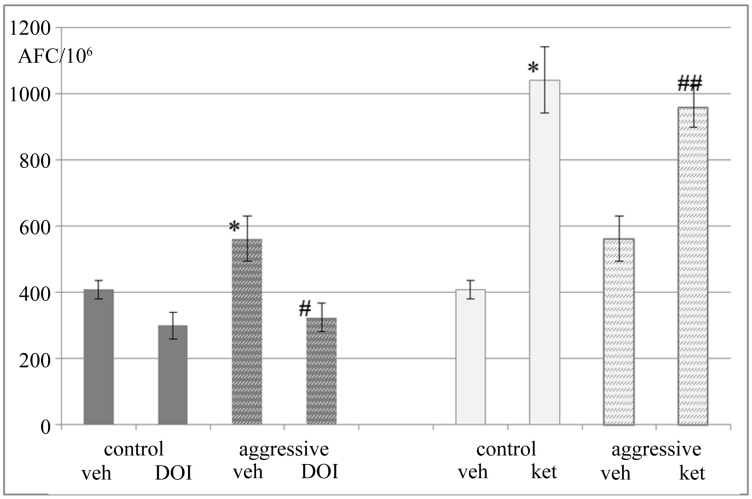

Figure 2. Effects of activation of 5-HT_{2A} receptors with DOI and their blockade with ketanserin (ket) on IgM-AFC numbers in aggressive mice of the CBA strain on the 4th day after immunization with SRBC (5×10^8). Both drugs were injected at the dose of 1.0 mg/kg, i.p.; DOI—twice for 2 days (1st injection 30 min before immunization, the 2nd—on the following day), ket—once 30 min before antigen administration. Saline was used as a vehicle (veh) for DOI, distilled water—for ket. Data are presented as means ± SEM. $^{*}p < 0.001$ when compared with the corresponding control groups not subjected to stress conditions; $^{\#}p < 0.01$, $^{\#\#}p < 0.001$ when compared with aggressive mice, receiving veh.

stress. Activation of 5-HT_{2A} receptors with DOI at 1.0 mg/kg reduced the immune response level both in rats selected for a high level of aggressiveness and in aggressive mice engaged in social confrontations for 10 days compared to the corresponding vehicle-treated groups. However, DOI administration did not alter the immune response in nonaggressive animals.

There is much evidence that 5-HT_{2A} receptors are involved in the regulation of aggressive behaviors [1]-[6]. Some data suggest the increased responsiveness of 5-HT_{2A} receptors to their agonists and antagonists in aggressive animals. For example, it has been shown that activation of 5-HT_{2A} receptors with DOI may enhance the aggressive behavior in isolated rats and mice [30] [31]. There is also data that microinjections of a 5-$HT_{2A/2C}$ agonist into the medial hypothalamus and into the periaqueductal gray matter increased defensive aggression in cats [32]. In addition, unlike agonists, the 5-HT_{2A} receptor antagonist ritanserin significantly inhibited the aggressive behavior of isolated mice without having any effect on nonaggressive behavior [30] [31].

It should be noted that in our experiments DOI at 1.0 mg/kg did not affect the immune response level in nonaggressive rats compared to the aggressive rat line. These findings suggest that the sensitivity of 5-HT_{2A} receptors in aggressive rats is higher than in nonaggressive animals. However, the analysis of the functional activity of 5-HT_{2A} receptors (measured by the number of head twitches) and the expression of the genes encoding these receptors in such brain structures as the midbrain, frontal cortex, and hippocampus failed to find any differences in the sensitivity of 5-HT_{2A} receptors or the levels of 5-HT_{2A} receptor gene expression between the aggressive and nonaggressive rat lines [5]. Moreover, we found that the blockade of 5-HT_{2A} receptors with ketanserin increased the numbers of IgM-AFC only in rats selected for the elimination of aggressiveness. It is of interest that other studies have reported that activation of the immune system by systemic bacterial endotoxin challenge (lipopolysaccharide) may increase the functional response of the 5-HT_{2A} receptor to DOI [33].

Our data indicate that the blockade of 5-HT_{2A} receptors with ketanserin (1.0 mg/kg) resulted in immunostimulation both in mice of the CBA strain not subjected to social stress (the controls) and, as it was noted above, in nonaggressive rats. On the other hand, ketanserin produced diverse effects on immune reactivity in aggressive animals, which were dependent on the type of aggression and animal species. Its administration to CBA mice demonstrating offensive aggression enhances the immune reaction, while the same dose of ketanserin did not modify the immune response level in rats with genetic predisposition to the increased defensive aggression.

Therefore, it can be assumed that the sensitivity of 5-HT_{2A} receptors to their ligands, and particularly to the antagonists, depends on different contribution of this receptor subtype to aggressive behaviors, and may explain dissimilar effects of ketanserin on immunity in aggressive rats and mice, observed in our experiments. It should also be considered that application of both agonists and antagonists of 5-HT_{2A} receptors in patients with various neuropsychiatric disorders and in several animal species is associated with the side effects of these compounds, such as the cognitive deficits, sedation or hypolocomotion [4] [5] [34], that, in turn, may differently affect immune reactivity in animals.

Recent evidence suggests not only the co-expression of postsynaptic 5-HT_{2A} and D_2 receptors in the same cells, but also the formation of 5-HT_{2A}-D_2 heteroreceptor complexes in the prefrontal cortex and DAergic structures such as substantia nigra and nucleus accumbens [35] [36], which are involved in neuroimmunomodulation [14] [37]-[39]. These complexes are considered as special targets for the drugs that changing the activity of 5-HT_{2A} receptors can modify their expression and as a result the formation of 5-HT_{2A}-D_2 complexes [36] [40] [41]. Moreover, it has been found previously that the immune response stimulation induced by the blockade of 5-HT_{2A} receptors in normal mice and rats is provided by increasing activity of the DAergic system with the involvement of D_2 receptors [14] [22] [42]. Thus, it is possible that the functional interaction between 5-HT_{2A} receptors and dopamine receptors, which are playing roles not only in mediating the aggressive behaviors [2] [43] but also in neuroimmunomodulation [10] [14] [16] [38] [39], may vary depending on aggressive behavior pattern.

5. Conclusion

The present study has shown the differential contribution of 5-HT_{2A} receptors in immunomodulation in animals demonstrating defensive or offensive types of aggressive behavior. Activation of 5-HT_{2A} receptors with their preferential agonist DOI produced immunosuppression both in rats selected for a high level of aggressiveness and in aggressive mice engaged in social confrontations for 10 days while its administration did not alter the immune response in nonaggressive animals. The blockade of 5-HT_{2A} receptors with a selective antagonist ketanserin caused the immune response stimulation in nonaggressive animals and in mice displaying stress-induced aggression, but did not affect the immune reaction in highly aggressive rats. Our data suggest that the role of 5-HT_{2A} receptors in immunomodulation depends on the specific type of aggression that may be taking into account in the treatment of some psychiatric disorders with the antipsychotic drugs or antidepressants targeting 5-HT_{2A} receptor.

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