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Effects of Activation and Blockade of Serotonin 5-HT$_{1A}$ Receptors on the Immune Response in Rats Selected for Different Levels of Aggressiveness

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Abstract

The present study examines the effects of serotonin (5-HT) 1A receptor ligands on humoral immune response in two rat lines selected for over 75 generations for the enhancement or elimination of aggression. Activation of presynaptic 5-HT$_{1A}$ receptors with a low dose of the selective 5-HT$_{1A}$ receptor agonist 8-OH-DPAT (0.1 mg/kg) or the blockade of postsynaptic 5-HT$_{1A}$ receptors with the antagonist WAY-100635 (1.0 mg/kg) did not affect the numbers of IgM-antibody forming cells (IgM-AFC) in the spleen of highly aggressive rats, which were characterized by higher immune responsiveness compared to nonaggressive line. On the other hand, the same doses of 8-OH-DPAT and WAY-100635, as well as a higher dose of 8-OH-DPAT (1.0 mg/kg), which is known to activate postsynaptic 5-HT$_{1A}$ receptors, produce immunostimulation in nonaggressive rats. However, only the highest dose of 8-OH-DPAT (5.0 mg/kg) was able to cause immunosuppression in nonaggressive rats that was mainly dependent on stimulation of postsynaptic 5-HT$_{1A}$ receptors. In contrast to nonaggressive rats, the dose of 1.0 mg/kg 8-OH-DPAT was sufficient to produce a decrease in the numbers of IgM-AFC in highly aggressive rats. Thus, pharmacological activation of pre- and postsynaptic 5-HT$_{1A}$ receptors, as well as the blockade of postsynaptic 5-HT$_{1A}$ receptors, produced different effects on the immune response in two lines of rats selected for high level of aggression or its absence. These data may have implications for more efficient treatments of a number of mental disorders associated with abnormal aggression.

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Keywords

Aggressive Behavior, Serotonin Pre- and Postsynaptic 5-HT$_{1A}$ Receptors, 8-OH-DPAT, WAY-100635, IgM-Immune Response

1. Introduction

Aggression is a complex problem with important implications for social life and health. Excessive aggression is a symptom in a variety of neuropsychiatric disorders, such as schizophrenia, depression, anxiety disorder, and substance abuse [1]-[4], which have long been known to be associated with immune dysfunctions [5]-[8]. Consistent with clinical observations, data obtained on the basis of several animal models (isolation housing, social interactions or genetic predisposition) have indicated that aggressive behavior is accompanied with altered immune reactivity [9]-[22].

Immune abnormalities under aggression may be related to changes in serotonin (5-HT) neurotransmission and functional activity of 5-HT$_{1A}$ receptors which have been implicated not only in mediating aggressive behaviors [1]-[4] [23]-[25], but also in neuroimmunomodulation both in normal and psychoemotional stress conditions [12] [26]-[31].

There is growing evidence that genetic factors along with exposure to chronic stressful events have a significant influence on immunity both in humans and animals differing in psychoemotional states. Breeding for a selected behavioral phenotype provides a valuable research model to examine neurochemical correlates, genetic mechanisms of high and abnormal forms of aggression and their link to other systems of the organism, including functioning of the immune system.

It has been recently found that two lines of rats selectively bred for over 75 generations at the Institute of Cytology and Genetics (Novosibirsk, Russia) for the enhancement or elimination of aggressiveness towards humans differing in their ability to respond to a T-dependent antigen [17] [32]. Compared to nonaggressive line, highly aggressive rats showed an increased humoral immune response to sheep red blood cells (SRBC). There are also data that these rat lines differ in the activity of the 5-HTergic system and 5-HT$_{1A}$ receptors [23] [25] [33]-[38].

The present study, therefore, focuses on the role of pre- and postsynaptic 5-HT$_{1A}$ receptors in the immune response modulation in two lines of rats with different genetic predisposition to aggression. For this purpose, we analyzed the effects of a full pre- and postsynaptic 5-HT$_{1A}$ receptor agonist 8-OH-DPAT and selective 5-HT$_{1A}$ receptor antagonist WAY-100635 on IgM-antibody formation in highly aggressive and nonaggressive rats.

2. Materials and Methods

2.1. Animals

The experiments were performed in male rats weighing 300 - 350 g, which were selected from one population of wild-caught rats (*Rattus norvegicus*) for over 70 - 75 generations for elimination (nonaggressive) or enhancement (aggressive) of aggressiveness towards humans at the Institute of Cytology and Genetics (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" [25] [33] [34] [37].

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 Research Institute of Physiology and Basic Medicine and Institute of Cytology and Genetics SB RAS.

2.2. Behavioral Experiments

Glove Test

The level of aggressiveness was measured in the "glove test" by confronting rats of both lines with an ap-

proaching human hand and attempting to handle them [25] [33] [34] [37]. 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.

2.3. Drug Administered

To affect the functional activity of 5-HT_{1A} receptors we used the 5-HT_{1A} receptor agonist (±)-8-hydroxy-2-(dipropylamino) tetralin (8-OH-DPAT) (Sigma, USA) at the doses, activating either presynaptic (0.1 mg/kg) or postsynaptic (1.0 and 5.0 mg/kg) 5-HT_{1A} receptors [27] [39]. 8-OH-DPAT was dissolved in distilled water and administered intraperitoneally (i.p.) in a volume of 0.2 ml/rat. Rats were injected with 5.0 and 0.1 mg/kg of 8-OH-DPAT once, 15 min before immunization and at a dose of 1.0 mg/kg—twice for 2 days with 1st injection 30 min before immunization and the 2nd one—on the following day. The blockade of 5-HT_{1A} receptors was performed by a selective 5-HT_{1A} receptor antagonist *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridyl) cyclohexanecarboxamide (WAY-100635) (Sigma, USA) that was administered in 0.2 ml of saline i.p. once at a dose of 1.0 mg/kg 30 min prior to immunization. The doses, timing and administration routes of drugs were based on the data of other authors [27] and on those used in our previous studies [29]. 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 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 plaque-forming cells (IgM-AFC) [40] in the spleen of 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 Pre- and Postsynaptic 5-HT_{1A} Receptors on IgM-Immune Response in Rats Selectively Bred for Different Levels of Aggressiveness

In agreement with previous data [17] [32], rats selected for the enhanced level of aggressiveness were found to have significantly higher spleen numbers of IgM-AFC in response to SRBC compared to low-aggressive line, (groups C1 and C2), $F_{1,52} = 12.41$, $p < 0.001$ (**Figure 1**). Activation of presynaptic 5-HT_{1A} receptors with a low dose of 8-OH-DPAT (0.1 mg/kg) markedly increased the numbers of AFC in nonaggressive rats compared to animals of this line not treated with the drug (vehicle-injected group C1), $F_{1,39} = 13.72$, $p < 0.001$ (**Figure 1**). In this rat line activation of postsynaptic 5-HT_{1A} receptors with 8-OH-DPA at a dose of 1.0 mg/kg produced a similar result. As seen in **Figure 1**, the numbers of AFC appeared to be significantly higher the control values (group C1) in rats with reduced aggressiveness receiving 1.0 mg/kg of 8-OH-DPAT ($F_{1,40} = 5.23$, $p < 0.05$). In contrast, treatment of nonaggressive rats with a higher dose of 8-OH-DPAT (5.0 mg/kg), which is also known to activate postsynaptic 5-HT_{1A} receptors, significantly decreased the AFC numbers compared to the control group C1

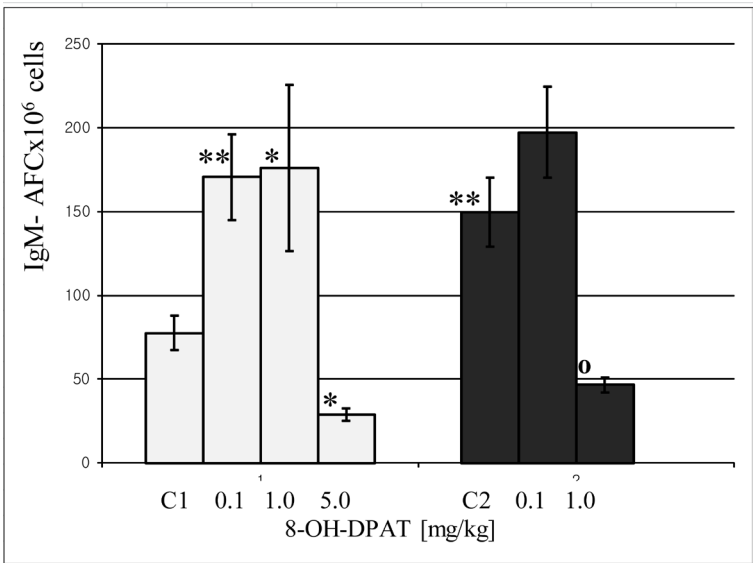

Figure 1. Effects of activation of pre- and postsynaptic 5-HT_{1A} receptors with 8-OH-DPAT on IgM-AFC numbers in nonaggressive (light columns) and highly aggressive (dark columns) rats on the 5th day after immunization with SRBC (5×10^8). Rats were injected with 0.1 and 5.0 mg/kg of 8-OH-DPAT i.p. once, 15 min before immunization and at a dose of 1.0 mg/kg—twice for 2 days (1st injection 30 min before immunization, the 2nd on the following day). Control groups (C1 and C2) received an equivalent volume of distilled water. Data are presented as means ± SEM. *$p < 0.05$, **$p < 0.001$ when compared with the group C1; $^0p < 0.05$ when compared with the group C2.

($F_{1,40} = 5.24$, $p < 0.05$) (**Figure 1**).

Unlike the nonaggressive line, there were no significant differences in the numbers of AFC between the highly aggressive rats receiving 8-OH-DPAT at 0.1 mg/kg and the vehicle-injected group C2 (**Figure 1**). However, 8-OH-DPAT injected at a dose of 1.0 mg/kg resulted in a decrease of the immune response level in rats with increased aggressiveness relative to aggressive rats receiving only vehicle (group C2), $F_{1,40} = 5.23$, $p < 0.05$ (**Figure 1**).

3.2. Effect of the Blockade of Postsynaptic 5-HT_{1A} Receptors with WAY-100635 on IgM-Immune Response in Rats Selectively Bred for Different Levels of Aggressiveness

Compared to nonaggressive line, aggressive rats showed significantly higher immune response ($F_{1,29} = 16.13$, $p < 0.001$) (**Figure 2**), consistent with that observed in the experiments with 8-OH-DPAT administration (section 3.1.) as well as earlier findings [17] [32].

The blockade of postsynaptic 5-HT_{1A} receptors with WAY-100635 (1.0 mg/kg) significantly increased the numbers of AFC in nonaggressive rats compared to the vehicle-injected control C1, $F_{1,42} = 24.84$, $p < 0.001$ (**Figure 2**). At the same time, the immune response of the highly aggressive rats treated with WAY-100635 (1.0 mg/kg) did not differ significantly from the response of aggressive rats receiving vehicle (the control group C2) (**Figure 2**).

4. Discussion

The results of the present study demonstrate that pharmacological activation of pre- and postsynaptic 5-HT_{1A} receptors, as well as the blockade of postsynaptic 5-HT_{1A} receptors, produced different effects on the immune response in two lines of rats selected for high level of aggression or its absence.

It is well established that the 5-HTergic system is involved in the regulation of aggressive forms of behavior [2]-[4] [23]-[25] [35] [41] [42]. Clinical and animal studies suggest that high and abnormal aggression is associated with altered function of the 5-HTergic system as well as sensitivity and density of 5-HT_{1A} receptors [2] [4] [23]-[25] [41] [42], which are known as a key mechanism modulating brain 5-HT neurotransmission [24] [39] [43].

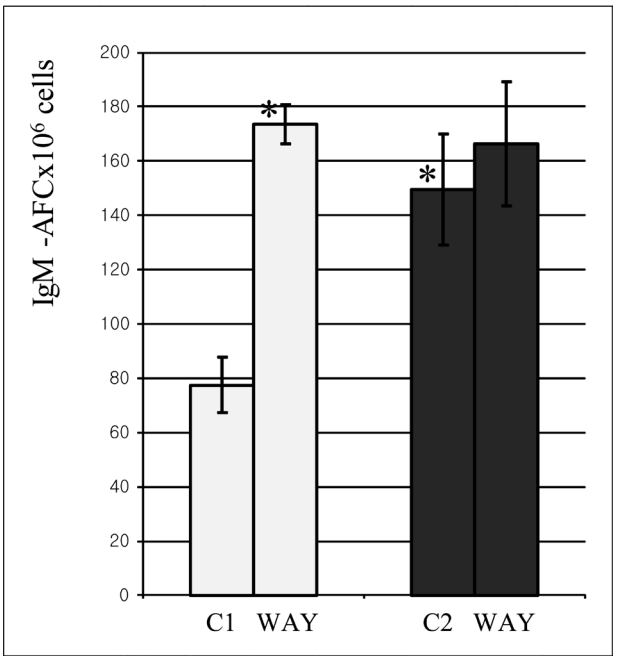

Figure 2. Effects of the blockade of 5-HT_{1A} receptors with WAY-100635 (1.0 mg/kg) on IgM-AFC numbers in nonaggressive (light columns) and highly aggressive (dark columns) rats on the 5th day after immunization with SRBC (5 × 10^8). WAY-100635 was injected i.p. once 30 min prior to immunization. Control groups (C1 and C2) received an equivalent volume of saline. Data are presented as means ± SEM. *$p < 0.001$ when compared with the group C1.

There is also much evidence that the 5-HTergic system is involved in the mechanisms of immunosuppression [12] [27]-[31] [44], mediated by separate types of 5-HT receptors, including pre- and postsynaptic 5-HT_{1A} receptors [28]-[31] [45]. As shown previously, activation of presynaptic 5-HT_{1A} receptors (8-OH-DPAT, 0.1 mg/kg) induced an increase in immunoreactivity in normal animals (mice of different strains and Wistar rats), which was prevented by the blockade of these receptors with WAY-100635 at 0.1 mg/kg or destruction of the nuclei raphe [30] [31], where high densities of 5-HT somatodendritic autoreceptors are presented. On the other hand, activation of postsynaptic 5-HT_{1A} receptors (8-OH-DPAT, 1.0 mg/kg) caused the immune response suppression, completely antagonized by high doses of WAY-100635 [28]-[30].

In our experiments, 8-OH-DPAT administered in a dosage (0.1 mg/kg), stimulating mainly presynaptic 5-HT_{1A} receptors [30] [31] [39], also induced significant elevation of the immune reaction in nonaggressive rats compared to nonaggressive controls.

The immunoinhibitory 5-HTergic system is closely linked to other neurotransmitter systems including the dopamine (DA) ergic system [43] [46], which has been found to exert the stimulating influence on immunity [12] [30] [44] [47]-[49]. Moreover, a number of studies indicate that activation of presynaptic 5-HT_{1A} receptors having the effect of inhibitory regulation on the release of 5-HT, may stimulate the release of DA in several corticolimbic areas [4] [46]. These brain structures are also considered to play a role in immunostimulation [12] [30] [47]-[49]. It is likely that an imbalance between the 5-HT and DAergic systems, accompanied with prevailing DAergic activity, may provide the neurochemical basis for the immune response increase found in nonaggressive rats, receiving 0.1 mg/kg of 8-OH-DPAT.

Interestingly, that the blockade of postsynaptic 5-HT_{1A} receptors with WAY-100635 (1.0 mg/kg), leading to a decrease in activity of the 5-HTergic system, produced similar immunostimulating effect in nonaggressive rats that may also be related to growing activity of the DAergic system. This suggestion is in agreement with our earlier findings that the reduction of 5-HT levels in the brain of normal rats and mice by electrolytic lesion of the midbrain nuclei raphe, by the 5-HT synthesis inhibitor p-chlorophenylalanine or the blockade of 5-HT_{2A} receptors with cyproheptadine was associated with the immune response elevation, which was abolished by the DA D2 antagonist haloperidol [12] [50].

Activation of the DAergic system may also underlie a more intense immune response found in highly aggressive rats when compared to rats of nonaggressive line. These results confirm previous findings obtained in rats of these rat lines [17] [32], as well as other data showing the increased immune reactivity in animals subjected to aggressive encounters [9]-[12] [14] [15] [21]. Most of the evidence to date provides support that aggressive behavior in animals and humans is accompanied by an increased level of DA and its metabolites in various brain structures [2]-[4] [12] [33] [51] [52]. There were also significant line differences in the activity of the DAergic system between highly aggressive and nonaggressive rats used in our experiments. Compared to nonaggressive rats, rats with the enhanced aggressiveness showed higher level of DA in the striatum and mesolimbic system [33] that may contribute to differences in immune function between these rat lines.

In these circumstances, we found that 8-OH-DPAT at the dose activating presynaptic5-HT_{1A} receptors did not change the immune response level in highly aggressive rats when compared to rats of the same line receiving only vehicle, suggesting the desensitization of presynaptic 5-HT_{1A} receptors in animals with genetic predisposition to aggressive behavior.

The results of previous studies have indicated significant differences in the functional state and expression of 5-HT_{1A} receptors between highly aggressive and nonaggressive rats [23] [25] [35]. For example, rats of the aggressive line showed a reduced functional activity of the brain 5-HT_{1A} receptors and lower expression of the 5-HT_{1A} receptor gene in the midbrain [23] [25] [35].

On the other hand, nonaggressive rats seem to have a lower sensitivity of postsynaptic 5-HT_{1A} receptors, since their activation with a higher dose of 8-OH-DPAT (1.0 mg/kg) led to immunostimulation, as it was found following presynaptic 5-HT_{1A} receptor activation. As noted above, the 5-HTergic system provides an inhibitory mechanism of immunomodulation, which is mediated via 5-HT receptors including the 5-HT_{1A} type [12] [29] [30] [44]. In our experiments, only the highest dose of 8-OH-DPAT (5.0 mg/kg) was able to cause immunosuppression that is mainly dependent on stimulation of postsynaptic 5-HT_{1A} receptors.

In contrast to nonaggressive rats, the dose of 1.0 mg/kg 8-OH-DPAT was sufficient to produce a decrease in the numbers of IgM-AFC in highly aggressive rats suggesting that the sensitivity of postsynaptic 5-HT_{1A} receptors is the aggressive rat line is significantly higher than in nonaggressive rats. Other authors have also demonstrated that genetic differences in aggressive behavior in mice and rats are associated with differences in 5-HT_{1A} receptor properties with higher sensitivity of postsynaptic 5-HT_{1A} receptors (as shown by a lower 8-OH-DPAT-induced hypothermia) in aggressive and impulsive individuals [24] [41] [51] [53]. Additionally, the experiments performed in mice, selectively bred for high or low levels of aggression, showed an up-regulation of postsynaptic 5-HT_{1A} receptors, both in receptor binding and in mRNA levels, in the aggressive line [41]. Likewise, activation of the 5-HTergic system, induced by the stimulation of postsynaptic 5-HT_{1A} receptor with 8-OH-DPAT (1.0 mg/kg), resulted in the immune response reduction in mice with aggressive status, acquired during social confrontations [28] [30], as seen in the analyzed aggressive rats treated with the same dose of 5-HT_{1A} agonist.

At the same time, a decrease in activity of the 5-HTergic system by the blockade of postsynaptic 5-HT_{1A} receptors with WAY-100635 (1.0 mg/kg), as well as by the activation of presynaptic 5-HT_{1A} receptors with a low dose of 8-OH-DPAT (0.1 mg/kg), did not affect the immune response level in highly aggressive rats.

It remains unclear whether the latter finding is related to changes in the sensitivity and/or density of 5-HT_{1A} receptors in rats of highly aggressive line or is provided by other mechanisms. As described earlier, different forms of aggressive behavior including genetic predisposition to hyper-aggression in rats used in our experiments are accompanied by increased activity of the DAergic system [2]-[4] [12] [33] [43] [51] [52], responsible for immunostimulation [12] [30] [44] [47]-[49]. Therefore, it seems likely that in aggressive rats with pre-activated DAergic system, a further increase in DAergic activity could not be achieved under the blockade of 5-HT_{1A} receptors that prevents the immune response elevation in this rat line.

5. Conclusion

In conclusion, the present data indicate that different genetic predisposition to aggression in Norway rats is associated with changes in the functional activity of pre- and postsynaptic 5-HT_{1A} receptors which determine differential effects of the activation and blockade of this receptor subtype on the immune response. The analysis of relationships between behavioral characteristics, activity of neuromediator receptors and immune function might be a useful approach for better understanding of the neurobiology of psychoemotional disorders and development of novel therapy and prevention.

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