Immune Response during Activation of Pre- and Postsynaptic Serotonin 5-HT_{1A} Receptors in C57Bl/6J Mice at Various Stages of a Depression-Like State

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The development of a depression-like state in C57Bl/6J mice with repeated defeat experience (10 and 20 days) was accompanied by inhibition of the immune response (evaluated from the number of IgM antibody-producing cells). Activation of postsynaptic 5-HT_{1A} receptors with a selective agonist 8-OH-DPAT (1.0 mg/kg) in these animals had no effect on the immune reaction. In mice without the experience of confrontations, stimulation of postsynaptic receptors caused a decrease in the number of IgM antibody-producing cells at the peak of the immune response induced by sheep erythrocytes (5×10^8 cells). However, the count of these cells remained unchanged in mice with a depression-like state (irrespective of the stage of disorder). Activation of presynaptic 5-HT_{1A} receptors with 8-OH-DPAT (0.1 mg/kg) in control animals and mice with 10-day defeat experience was followed by immune stimulation. These changes were not observed in mice with a depression-like state caused by 20-day social stress.

Key Words: *depression-like state; serotoninergic system; pre- and postsynaptic serotonin 5-HT_{1A} receptors; immune response*

Depressive disorders constitute a group of common mental diseases that are accompanied by immune dysfunction [4,6,8,11]. Experiments on the model of social conflict with an aggressive partner showed that submissive C57Bl/6J mice are characterized by depressive behavior [7]. Depending on the duration of defeat experience, this state is divided into the following stages: development of depression (10 days); and severe depression (20 days) [1]. They are characterized by specific changes in functional activity of the brain serotoninergic (5-HT) system [4,7] and decrease in the immune response [2,4]. 5-HT_{1A} receptors play an important role in the pathogenesis of depression [4,10,12] and regulate immune functions under normal conditions and during the formation of aggressive or submissive behavior [3-5].

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It is interesting to evaluate changes in the immune response during activation of 5-HT_{1A} receptors in animals with depressive behavior of different severity (due to social stress of various durations). The IgM immune response in C57Bl/6J mice with depression-like state (social confrontations for 10 or 20 days) was studied after activation of pre- or postsynaptic 5-HT_{1A} receptors with selective agonist 8-OH-DPAT in doses of 0.1 and 1.0 mg/kg, respectively.

MATERIALS AND METHODS

Experiments were performed on 125 male C57Bl/6J mice (age 2.0-2.5 months and body weight 18-23 g). Each group consisted of least 10 animals. The mice were maintained in a vivarium under standard conditions, natural light/dark cycle, and standard diet. The study was conducted according to the requirements of the European Community Directive (86/609/EC) and Biomedical Ethics Committee (Institute of Physiology).

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Depression-like state was induced on the model of distant sensory contact [7]. The study was performed during two stages of depression-like state, "development of depression" and "severe depression". They differ in some criteria that are extensively used to evaluate the degree of depressive behavior in animals [1]. This behavior was formed in submissive animals after repeated defeat experience (10 and 20 days) in social confrontations with an aggressive partner.

8-OH-DPAT (8-hydroxy-(di-n-propylamino) tetralin, Sigma) served as the selective agonist of 5-HT_{1A} receptors. Taking into account specific distribution of 5-HT_{1A} receptors and different sensitivity of pre- and postsynaptic 5-HT_{1A} receptors to agonists [9], the agent was administered in low (0.1 mg/kg) and high doses (1.0 mg/kg). 8-OH-DPAT in these doses has a modulatory effect on somatodendritic autoreceptors and postsynaptic receptors, respectively [3,5]. 8-OH-DPAT was dissolved in 0.2 ml distilled water and injected intraperitoneally. The animals received an injection of 8-OH-DPAT in a single dose of 0.1 mg/kg 15 min before immunization. 8-OH-DPAT in a dose of 1 mg/kg was injected twice in the following periods: day 0 (antigen treatment), 30 min before immunization; and on the next day (+1 day).

The immune response was evaluated in the following three series: series I, mice without experience of confrontations; and series II and III, mice with a depression-like state (defeat experience for 10 and 20 days, respectively). Each series was conducted with the following groups of animals: solvent (distilled water); 8-OH-DPAT, 0.1 mg/kg; and 8-OH-DPAT, 1.0 mg/kg. The mice without confrontation experience were kept in individual cages for 5 days before immunization (to withdraw the effect of group maintenance).

During immunization, the mice received a single injection of sheep erythrocytes (SE, 5×10^8 cells in 0.5 ml physiological saline) into the caudal vein. The peak of the immune response was evaluated from the number of IgM antibody-producing cells (APC) on day 4 after administration of SE [13].

The results were analyzed by one-way analysis of variance (ANOVA/MANOVA) with Statistica 5.0 software. The significance of differences between the mean values (at the normal distribution of experimental data) was evaluated by paired Student's *t* test.

RESULTS

C57Bl/6J mice with depressive behavior were characterized by a decrease in the immune response, which did not depend on the stage of this reaction (confrontation for 10 or 20 days). The number of IgM-APC at the peak of the immune response in these animals was lower than in mice receiving the solvent and not participating in confrontations [F(1,32)=10,9; $p<0.01$] (Fig. 1, *4*, *1*) and [F(1,1)=9,75; $p<0.01$] (Fig. 1, *7*, *1*). These data are consistent with the results of previous studies [2,4].

The brain 5-HTergic system has a suppressive effect on the immune functions [3-5]. We showed that activation of presynaptic 5-HT_{1A} receptors in animals without the experience of confrontations after administration of 8-OH-DPAT (0.1 mg/kg) causes an increase in the number of IgM-APC as compared to non-confronting mice of the solvent group [F(1,27)=9.9; $p<0.01$] (Fig. 1, *2*, *1*). However, stimulation of postsynaptic 5-HT_{1A} receptors with 8-OH-DPAT (1.0 mg/kg) and activation of the 5-HTergic system were followed by a decrease in the number of IgM-APC [F(1,33)= 15.9; $p<0.001$] (Fig. 1, *3*, *1*).

At the same time, activation of postsynaptic 5-HT_{1A} receptors after administration of 8-OH-DPAT (1.0 mg/kg) to animals with depressive behavior (10-day defeat experience) had no effect on the number of IgM-APC (as compared to depressive mice not receiving this agonist; [F(1,19)=0.92; $p>0.05$] (Fig. 1, *6*, *4*).

8-OH-DPAT-induced (0.1 mg/kg) stimulation of presynaptic 5-HT_{1A} receptors during the development of a depression-like state (10-day social stress) was followed by an increase in the number of IgM-APC as compared to animals not receiving this agonist [F(1,23)=9.0; $p<0.01$] (similarly to mice with no defeat experience; Fig. 1, *5*, *4*).

During the development of a severe depression-like state after 20-day social defeats (as compared to the solvent group) activation of presynaptic and

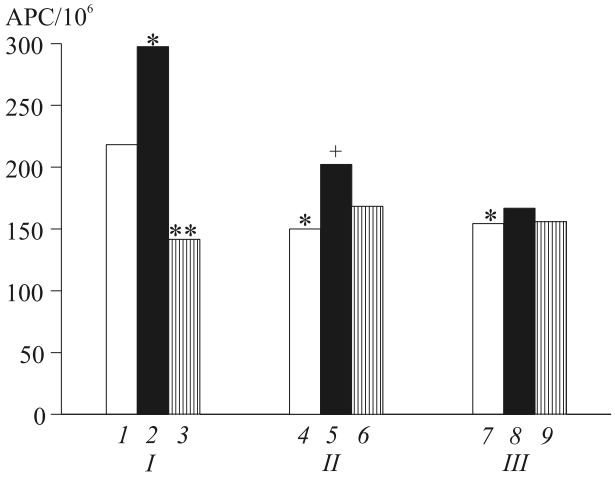

Fig 1. Effect of activation of pre- and postsynaptic 5-HT_{1A} receptors on the number of IgM-APC in animals with a depression-like state. Mice without the experience of confrontations (I); mice with a depression-like state due to 10-day defeat experience (II); mice with a depression-like state due to 20-day defeat experience (III). Solvent (*1*, *4*, *7*); 8-OH-DPAT, 0.1 mg/kg (*2*, *5*, *8*); 8-OH-DPAT, 1.0 mg/kg (*3*, *6*, *9*). $^*p<0.01$ and $^{**}p<0.001$ compared to *1*; $^+p<0.01$ compared to *4*.

postsynaptic 5-HT_{1A} receptors with 8-OH-DPAT in doses of 0.1 mg/kg [F(1.33)=0.26; p>0.05] (Fig. 1, *8*, *7*) and 1.0 mg/kg [F(1.27)=0.01; p>0.05] (Fig. 1, *9*, *7*), respectively, had no effect on the number of IgM-APC.

Our results indicate that activation of postsynaptic 5-HT_{1A} receptors in mice with depression-like state of different severity (defeat experience for 10 and 20 days; as differentiated from control animals with no defeat experience) does not modulate the immune response. Stimulation of presynaptic 5-HT_{1A} receptors has various effects on the immune response, which depends on the stage of depression-like state. Activation of presynaptic 5-HT_{1A} receptors is followed by an increase in the number of IgM-APC in mice with 10-day defeat experience, but not in animals subjected to 20-day social stress.

Our previous studies showed that animals with depression-like state are characterized by high activity of the 5-HTergic system (ratio of the major metabolite of 5-HT, 5-hydroxyindoleacetic acid, to the neurotransmitter; 5-HIAA/5-HT) in subcortical structures of the brain, which play a role in neuroimmunomodulation [4]. Moreover, mice with depressive behavior (10-day defeat experience) are characterized by desensitization of postsynaptic 5-HT_1 receptors and decrease in the number of these receptors in the frontal cortex and amygdala [1]. These data suggest that changes in functional activity of postsynaptic 5-HT_1 receptors do not depend on the stage of a depression-like state. After desensitization, these receptors become insensitive to the subsequent activating effect of the agonist. Apart from changes in activity of the 5-HTergic system [4], the observed variations play an important role in the development of IgM-immune dysfunction under these conditions.

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