MICROBIOLOGY AND IMMUNOLOGY

Effects of 5-HT$_{2A}$ Receptor Stimulation and Blocking on Immune Response

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 150, No. 8, pp. 184-186, August, 2010
Original article submitted July 9, 2009

Experiments on CBA mice showed that selective stimulation of 2A serotonin receptors with DOI agonist (1 mg/kg) led to suppression of the immune response and reduction of the spleen and peripheral blood CD8$^+$ T cell counts with the cytotoxic/suppressor function. Selective blockade of these receptors with ketanserin (1 mg/kg) had an opposite effect: immunostimulation with an increase in CD8$^+$ T cell count in the spleen. These data indicate the involvement of 2A serotonin receptors in immunosuppressive mechanisms of serotoninergic system.

Key Words: *serotonin receptors; serotoninergic system; CD8$^+$ T cells; immunomodulation; immune reaction*

The results of neurophysiological studies and pharmacological analysis with agents selectively modulating various aspects of serotonin (5-HT) synthesis, metabolism, and receptor mechanisms indicate that increase of 5-HT-ergic system activity leads to suppression of cellular and humoral immunity in different animal species [1-3,5,8,11]. Differentiated contribution of presynaptic (somatodendritic autoreceptors of the midbrain nuclei suture) and postsynaptic type 1A 5-HT receptors was revealed [1,3]. On the other hand, 5-HT$_{2A}$ receptors are also involved in 5-HT-ergic neurotransmission. Great interest to these receptors is explained by their important role in regulation of various functions in health, mental strain, and many mental diseases (schizophrenia, suicidal liability, depression, alcoholism) [6,10]. However, the role of 5-HT$_{2A}$ receptors in regulation of immune function remains unclear. There are published reports on the immunomodulating role of 2A receptors observed mainly *in vitro* experiments; just few studies were carried *in vivo* and only with 5-HT$_{2A}$ receptor antagonists [8,11].

We studied the involvement of 5-HT$_{2A}$ receptors in immunomodulation using highly selective agonists and blockers of these receptors.

MATERIALS AND METHODS

The study was carried out on 65 male CBA mice aged 2.0-2.5 months (18-23 g) from Breeding Center of Research Laboratory of Experimental Biomodeling of the Russian Academy of Medical Sciences.

Pharmacological analysis was carried out using selective 2A receptor agents: DOI (4-iodo-2,5-dimethoxyphenyl-isopropylamine) agonist (Sigma) with central action [7] and complete antagonist ketanserin (Sigma) easily passing through the blood-brain barrier and preventing the central effects of DOI [9].

The animals were divided into 3 groups. Group 1 mice were intraperitoneally injected with 1 mg/kg

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0007-4888/10/1502-0219

DOI in 0.2 ml saline 30 min before immunization and on the next day. Group 2 mice were intraperitoneally injected with 1 mg/kg ketanserin in 0.2 ml distilled water 30 min before immunization. Group 3 animals (control) were injected with the corresponding solvents. Each group consisted of at least 10 animals kept under standard vivarium conditions at natural light on standard diet. Experiments were carried out in accordance with the humanity philosophy, recorded in the Directions of the European Community (86/609/EC), and were approved by the Biomedical Ethics Committee of Institute of Physiology.

Mice were immunized with a single dose of sheep erythrocytes (5×10^8) injected into the caudal vein in 0.5 ml saline.

The immune response was tested at the peak of its development (day 4 after immunization) by the standard methods: estimation of the counts of IgM antibody producing (APC) and rosette forming (RFC) cells in the spleen [5].

The content of $CD8^+$ T cell subpopulations in the peripheral blood and spleens of mice were evaluated by laser flow cytometry on a FACS Calibur cytofluorometer (Becton Dickenson). Before estimations, the cells were treated with phycoerythrin-labeled monoclonal antibodies to surface lymphocytic antigens (Becton Dickenson).

The data were processed by one-way ANOVA/MANOVA with paired comparison by Student's *t* test.

RESULTS

Stimulation of 5-HT_{2A} receptors with DOI selective agonist led to a 2.5 times inhibition of the immune reaction at the peak of its development, tested by RFC count ($F(1.32)=4.30$; $p<0.05$; Fig. 1). In addition, the level of $CD8^+$ cytotoxic/suppressor T cells in the spleen reduced significantly under conditions of 5-HT_{2A} receptor stimulation ($F(1.20)=4.34$; $p<0.05$) and even more so in the peripheral blood ($F(1.29)=45.12$; $p<0.0001$)

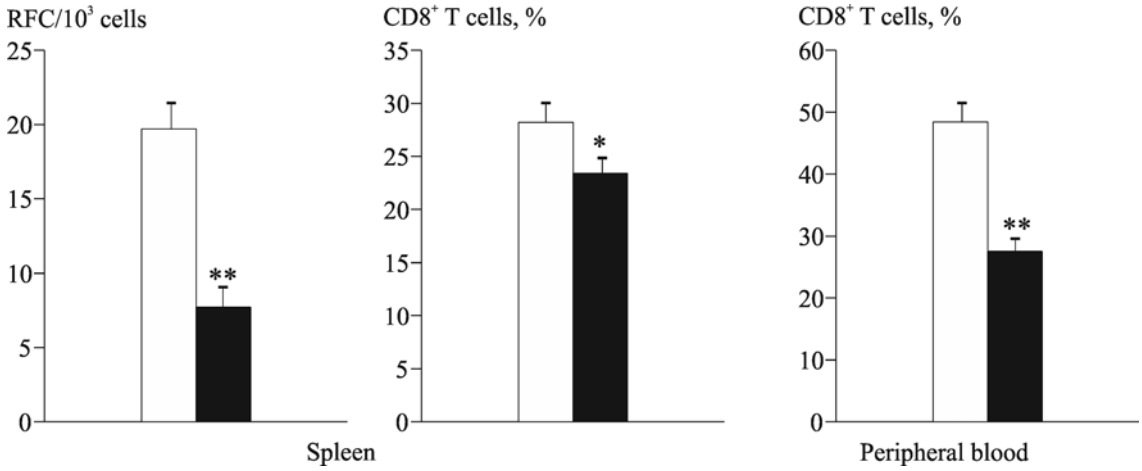

Fig. 1. Immune response reduction in CBA mice after DOI stimulation of 5-HT_{2A} receptors. Light bars: control; dark bars: DOI. *$p<0.05$, **$p<0.001$ compared to the control.

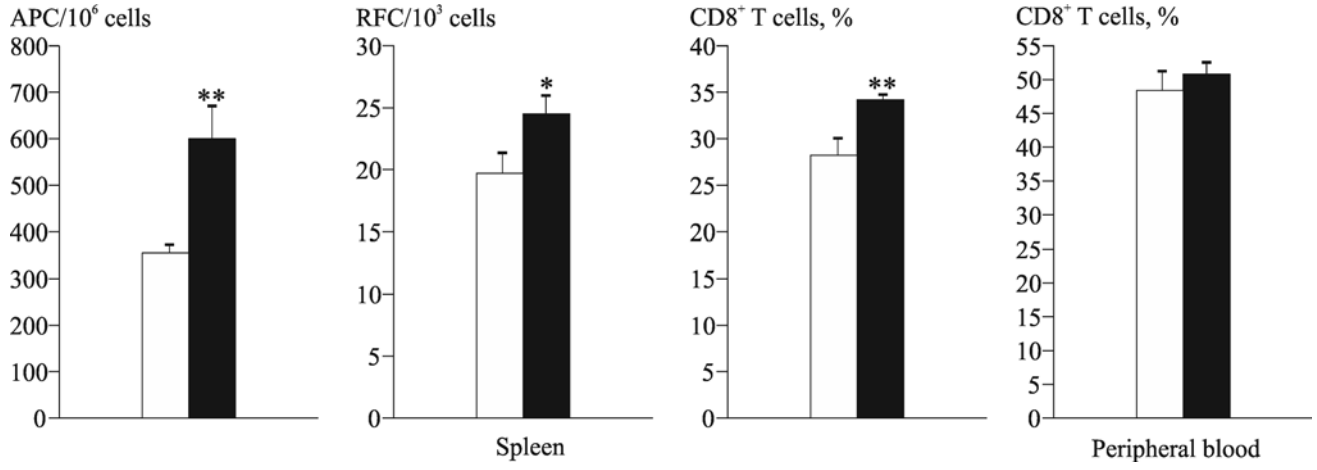

Fig. 2. Immunostimulation in CBA mice under conditions of ketanserin blocking of 5-HT_{2A} receptors. Light bars: control; dark bars: ketanserin. *$p<0.01$, **$p<0.001$ compared to the control.

(Fig. 1). Similar data on suppression of another immunological value, T-cell proliferation, were obtained in experiments with DOI injection to rats 2 h before isolation of lymphocytes [8].

A quite opposite effect of DOI stimulation of 5-HT_{2A} receptors was obtained in group 2 mice: the counts of APC ($F(1.31)=24.11$; $p<0.0001$), RFC ($F)1.35)=5.10$; $p<0.05$), and cytotoxic/suppressor $CD8^+$ T cells ($F(1.20)=7.81$; $p<0.01$) in the spleen increased, while the peripheral blood count of $CD8^+$ T cells was unchanged (Fig. 2).

On the other hand, central or systemic injection of ketanserin in a higher dose (5 mg/kg) 2 h before the organ removal did not modify the proliferation of T cells [8].

The immunostimulatory effect was observed previously in mice and rats injected with cyproheptadine – not a highly selective 5-HT_{2A} receptor antagonist, modulating the receptors of other neuromediator systems [11]. However, the fact that cyproheptadine canceled the immune reaction inhibition in response to 5-hydroxytryptophane (5-HT precursor) indicates its 5-HT dependence.

It is known that 5-HT_{2A} receptors are present in many brain structures, but in contrast to 1A receptors, they were detected only on postsynaptic membranes [4]. Similarity of changes in immune response, detected in stimulation and blocking of postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors, is worthy of note [3]. This fact seems to be due to universal changes in activity of the 5-HT-ergic system involved in immunity regulation under conditions of modulation of postsynaptic receptors of both types.

Hence, our data on reduction of immunological values in stimulation of 5-HT_{2A} receptors and increase of the immune function under conditions of their blocking confirms the involvement of this receptor type in immunomodulation.

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