Effects of Type 1A Serotonin Receptor Agonist 8-OH-DPAT on Immune Response

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The selective agonist of type 1 A serotonin receptors 8-hydroxy-2-(di-n-propyl-amino)tetralin (8-OH-DPAT) suppressed the immune response. Intraperitoneal administration of 1 mg/kg 8-OH-DPAT to Wistar rats over 2 days after immunization decreased the count of plaque- and rosette-forming cells on day 5. Our results indicate that type 1A serotonin receptors are involved in the realization of the immunosuppressive effects of the serotoninergic system.

Key Words: *8-OH-DPAT; type 1A serotonin receptors; immune response*

Serotonin is involved in neuroimmunomodulation and various agents modulating activity of serotoninergic structures affect the immune response [2,3,6,9]. Serotonin uptake blockers sertraline and CGP-6085A, serotonin, and its precursor 5-hydroxytryptophan cause immunosuppression [2,6]. The 5-HT_{2A} receptor antagonist cyproheptadine inhibiting the serotoninergic system stimulates immune reactions, which confirms the involvement of these receptors in immunomodulation [3].

Previous *in vitro* studies showed that the 5-HT_{1A} receptor agonist 8-OH-DPAT affects various immunological parameters [7,8]. *In vivo* experiments revealed that LSD (lysergic acid diethylamide) in low doses stimulates 5-HT_{1A} autoreceptors, suppresses the serotoninergic system, and enhances the immune response. In high doses this agent stimulates postsynaptic 5-HT_{1A} receptors, activates the serotoninergic system, and suppresses the immune response [2]. Since nonselective 5-HT_{1A} receptor agonist LSD possesses high affinity to 5-HT_{2A} receptors, it is impossible to evaluate its contribution into immunomodulation of 5-HT_{1A} receptors. Here we studied *in vivo* effects of the selective and total agonist of 5-HT_{1A} receptors 8-OH-DPAT.

MATERIALS AND METHODS

Experiments were performed on 65 male C57Bl/6J mice aging 2.0-2.5 months, weighing 21-23 g, and obtained from the nursery of the Laboratory of Experimental Biological Modeling (Tomsk). Wistar rats (n=20) weighing 180-200 g were obtained from the nursery of the Novosibirsk State Medical Academy. Each series included at least 7 animals. The rats were kept under standard vivarium conditions. For immunization sheep erythrocytes (5×10^8 cells) were injected into the caudal vein (mice) or intraperitoneally (rats). 8-OH-DPAT (Serva) was injected intraperitoneally in a single dose of 1 mg/kg 30 min before immunization. Some animals received the second injection of this preparation on the next day after immunization. 8-OH-DPAT was dissolved in 0.2 ml distilled water. Control mice received an equivalent volume of distilled water.

On day 5 after immunization (peak of immune response) the mice were killed by cervical dislocation; the rats were decapitated. The spleens were weighted. The immune response was studied by the number of plaque-forming (PFC, IgM-producing cells) [5] and rosette-forming cells (RFC) that constitute a hetero-

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TABLE 1. Parameters of the Immune Response in C57Bl/6J Mice Treated with 8-OH-DPAT on Day 5 after Immunization (*M*±*m*)

Parameter	Control (*n*=14)	8-OH-DPAT, 1 mg/kg	
		single (*n*=7)	2 times (*n*=12)
RFC count per 10^3 cells	22.29	21.86	10.79*
PFC count			
per 10^6 cells	266.08±19.36	239.11±13.70	191.08±15.96**
per spleen	31,379.26±15,128.55	26,766.63±1674.07	17,002.25±1967.83**
Weight of the spleen, mg	114.36±7.48	111.86±2.06	88.17±5.79*

Note. Here and in Table 2: *p<0.001 and **p<0.01 compared to the control.

TABLE 2. Parameters of the Immune Response in Rats Receiving 8-OH-DPAT on Day 5 after Immunization (*M*±*m*)

Parameter	Control	8-OH-DPAT, 2 times
RFC count per 10^3 cells	21.39±2.0	11.00±1.8*
PFC count		
per 10^6 cells	324.54±15.30	197.52±18.90*
per spleen	467,383.2±39,676.5	266,837.8±47,556.7**
Weight of the spleen, mg	1441.8±111.6	1312.8±135.0***

Note. *p<0.05 compared to the control.

geneous population of immunocompetent cells involved in immune reactions. [6]. RFC were counted by phase-contrast microscopy in a mobile system using a floating coverslips (no less than 1000 cells in each sample were examined).

The results were analyzed by one-way ANOVA and pairwise Student's *t* test.

RESULTS

8-OH-DPAT produced an immunosuppressive effect, which depended on the treatment schedule. Single administration of 8-OH-DPAT to mice 30 min before immunization did not modulate the immune response (the number of RFC and PFC did not differ from the control, Table 1). Repeated treatment with this preparation for 2 days decreased the count of RFC by 2 times ($F(1.40)=145.5$, $p<0.001$, Table 1). We revealed a decrease in the count of PFC per 10^6 cells ($F(1.24)=4.43$, $p<0.05$) and per spleen ($F(1.24)=9.19$, $p<0.005$). The weight of the spleen also decreased ($F(1.24)=7.28$, $p<0.01$, Table 1). In rats, repeated treatment with 8-OH-DPAT for 2 days decreased the count of RFC ($F(1.14)=16.64$, $p<0.001$) and PFC per 10^6 cells ($F(1.18)=27.39$, $p<0.001$) and per spleen ($F(1.8)=10.48$, $p<0.01$, Table 2).

Thus, the activation of 5-HT_{1A} receptors by 8-OH-DPAT suppresses immune reactions in mice and rats, which confirmed the involvement of these receptors in the inhibition of immunogenesis by the serotoninergic system.

Administration of the 5-HT_{2A} receptor agonist cyproheptadine to mice with transected hypophyseal stalk showed that central 5-HT_{2A} receptors are involved in the suppressive effect of serotonin on the immune response [3]. The effects of serotonin on the immune system are mediated by central mechanisms, which suggests that brain 5-HT_{1A} receptors play a role in immunomodulation [2]. Our previous experiments showed that destruction of the midbrain raphe nuclei enriched with serotoninergic neurons potentiates the immune response. By contrast, activation of the serotoninergic system with serotonin, its precursor 5-hydroxytryptophan, and serotonin uptake blockers sertraline and CGP6058A was followed by suppression of immunogenesis [2,6]. The central effects of these preparations are realized through the hypothalamic-pituitary complex [2]. The antigen-induced changes in the contents of serotonin and its metabolite 5-hydroxyindole acetic acid in various brain structures indicate that the central serotoninergic system is involved in neuroimmunomodulation [2,9]. Analysis of expression of cloned genes of various serotonin receptors revealed no 5-HT_{1A} receptors on immunocompetent cells [10]. Moreover, *in vivo* treatment with 8-OH-DPAT increases the concentration of ACTH [4], which mediates the inhibitory effect of serotoninergic structures on the immune response [1].

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