Interaction between Dopamine D_1 and D_2 Receptors in Modulation of the Immune Response

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The interaction between dopamine D_1 and D_2 receptors plays a role in immunomodulation. The results of thus interaction depends on the degree of receptor activation with selective agonists in different doses. Combined treatment with agonists of D_1 and D_2 receptors in high doses had a synergistic effect in the mechanisms of immunomodulation. Receptor agonists in low doses suppressed the immune response. Our results suggest that weak activation of one of these receptors is accompanied by inactivation of the other receptor type.

Key Words: *dopamine receptors; D_1 receptor agonist SKF 38393; D_2 receptor agonist quinpirole; immunomodulation*

Multiple functions of the dopaminergic system (*e.g.*., immunomodulatory activity) are provided by various types of dopamine (DA) receptors. Pharmacological study with selective agonists and antagonists of D_1 and D_2 receptors showed that these receptors play a role in immunostimulation [1-3,5]. Most researchers believe that a variety of effects of dopaminergic modulation are related not only to the involvement, but also to the interaction between D_1 and D_2 receptors [7,9,11-13]. Synergism between D_1 and D_2 receptors in the nucleus accumbens manifested in locomotor activity. The relationship of these receptors in the globus pallidus provides opposite behavioral changes probably related to the location of receptors on neurons with different neurochemical properties [6]. We found no published data on reciprocal influence of D_1 and D_2 receptors during immunostimulation.

The data on the existence and type of interaction between D_1 and D_2 receptors during DA-dependent stimulation of the immune response will elucidate the mechanisms of DA-dependent immunomodulation.

MATERIALS AND METHODS

Experiments were performed on 270 male CBA mice aging 2-2.5 months and weighing 18-23 g. The animals were obtained from nursery of the Siberian Division of the Russian Academy of Medical Sciences (Tomsk). Each group consisted of at least 10 animals. The mice were maintained in a vivarium (Institute of Physiology) under natural light/dark regimen and received standard ration.

Pharmacological study was performed with selective agonists of D_1 and D_2 receptors (SKF 38393 and quinpirole, respectively). (±)-SKF 38393 HCl (1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride, ICN Biomedicals Inc.) was administered in single doses affecting postsynaptic receptors (1 and 5 mg/kg). Quinpirole ((-)-quinpirole hydrochloride, Ly-171 555, Sigma) is a selective agonist of DA receptors that activates primarily postsynaptic D_2 receptors. Quinpirole was administered in a single dose of 0.5 or 1.0 mg/kg. SKF 38393 was dissolved in distilled water. Quinpirole was dissolved in physiological saline and

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injected intraperitoneally (0.2 ml) 30 min before immunization. During combined treatment the test preparations were administered separately on both sides of the abdominal cavity 30 min before immunization. Control animals intraperitoneally received an equivalent volume of the solvent.

During immunization, sheep erythrocytes (5×10^6 cells) were dissolved in 0.5 ml physiological saline and administered into the caudal vein. The immune response was estimated by the number of rosette-forming cells (RFC) in the spleen on day 5 after immunization [4].

The results were analyzed by Student's *t* test. Statistical treatment involved Statistica software.

RESULTS

Immunization of CBA mice after activation of D_1 and D_2 receptors with SKF 38393 (5 mg/kg) and quinpirole (1 mg/kg), respectively, increased the number of RFC (38.87±2.23 and 50.63±6.41, respectively, *vs*. 26.70±0.95 in the control, $p<0.001$, Fig. 1).

Combined treatment with D_1 and D_2 receptor agonists in these doses was accompanied by a further increase in the number of RFC (66.70±3.52) compared to animals receiving only 5 mg/kg SKF 38393 (38.87±2.23, $p<0.001$) or 1 mg/kg quinpirole (50.63±6.41, $p<0.05$). These data show that during combined administration of SKF 38393 and quinpirole in maximum doses, D_1 and D_2 receptors operate in a synergistic manner. Under these conditions the immune response increases more significantly compared to experiments with individual administration of agonists. Combined treatment with SKF 38393 in low dose not affecting the number of RFC (1 mg/kg) and quinpirole in high dose (1 mg/kg) increased the number of RFC (40.53± 3.25) compared to controls (26.70±0.95, $p<0.001$) and animals receiving 1 mg/kg SKF 38393 alone (30.90±2.38, $p<0.05$, Fig. 1). D_1 and D_2 receptor agonists in these doses did not increase, but maintained the immune response at the level observed in animals receiving 1 mg/kg quinpirole. During combined treatment with D_2 and D_1 receptor agonists in the effective and ineffective doses, respectively, the degree of immunostimulation depends on activity of D_2 receptors. Combined administration of quinpirole in high dose (1 mg/kg) and D_1 receptor agonist in low dose (1 mg/kg) slightly suppresed the immune response. Similar results were obtained after combined treatment with 5 mg/kg SKF 38393 and 0.5 mg/kg quinpirole. The immune response in these animals exceeded the control (42.70±2.85 and 26.70±0.95, respectively, $p<0.001$),

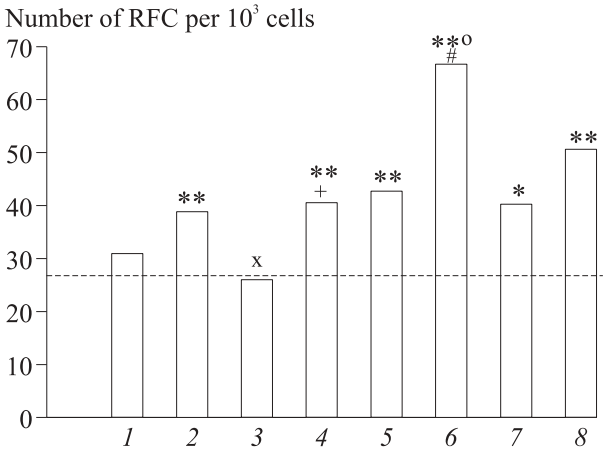

Fig. 1. Number of rosette-forming cells (RFC) in the spleen of mice on day 5 after immunization with sheep erythrocytes and combined treatment with D_1 and D_2 receptor agonists. Dotted line, control; QP, quinpirole. *1*) 1.0 mg/kg SKF 38393 (SKF1); *2*) 5.0 mg/kg SKF 38393 (SKF5); *3*) SKF1+0.5 mg/kg QP; *4*) SKF1+1.0 mg/kg QP; *5*) SKF5+0.5 mg/kg QP; *6*) SKF5+1.0 mg/kg QP; *7*) 0.5 mg/kg QP; *8*) 1.0 mg/kg QP. $^*p<0.01$ and $^{**}p<0.001$ compared to the control; $^xp<0.01$ compared to *7*; $^+p<0.05$ compared to *1*; $^op<0.01$ compared to *2*; $^\#p<0.05$ compared to *8*.

but did not differ from that in rats receiving 5 mg/kg SKF 38393 alone or 0.5 mg/kg quinpirole alone. No summation of the effects was observed under these conditions.

Combined treatment of mice with 1 mg/kg SKF 38393 and 0.5 mg/kg quinpirole did not increase the immune response, but even decreased the number of RFC compared to animals of the quinpirole group (26.00±1.72 and 40.23±3.62, respectively, $p<0.01$). Combined administration of D_2 receptor agonist quinpirole in a dose increasing the number of RFC (1 mg/kg) and SKF 38393 in a dose not modulating the immune response (1 mg/kg) tended to suppress the immune response. The immune response did not increase after administration of quinpirole in a dose of 0.5 mg/kg. Under these conditions the number of RFC did not differ from the control.

Our results suggest that the interaction between D_1 and D_2 receptors plays a role in immunomodulation. Published data show that activation of receptors depends on the dose of agonists [7,12]. The existence and consequence of interaction between D_1 and D_2 receptors can be evaluated by the degree of activation of various receptors, which depends on the dose of DA receptor agonist.

We conclude that treatment with D_1 and D_2 receptor agonists in high doses producing the immunostimulating effect is followed by more pronounced increase in the immune response. These data illustrate synergism between D_1 and D_2 receptors. Minimal activation of one of these receptors does not increase, but even decreases activity of

another receptor. Functional coupling exists between D_1 and D_2 receptors in the regulation of the immune response.

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