IMMUNOSTIMULATING EFFECT OF QUINPIROLE, A D2 DOPAMINE RECEPTOR AGONIST

M. A. Cheido and E. L. Al'perina

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The study of the role of various neurotransmitter systems in modulation of the immune response has shown that the neurochemical basis of the immunostimulating effect is linked with activation or predominance of the dopaminergic system. The use of dopamine agonists enables the dopaminergic system to be activated by action directed toward its presynaptic [4] and postsynaptic [12] receptors. Biochemical investigations with radioligand binding have recently revealed at least two types of postsynaptic receptors, namely D1 and D2 [8, 9, 11]. The selective agonists of these receptors are known to differ in their activity on behavioral effects induced in intact rats [5, 13]. So far as immunogenesis is concerned, the immunostimulating action of apomorphine, a mixed agonist of D1 and D2 postsynaptic dopamine receptors, was discovered previously [1]. This paper describes data on the role of D2 receptors in the modulating action of the dopaminergic system on the immune response, using a specific agonist of D2 receptors — quinpirole.

EXPERIMENTAL METHOD

Experiments were carried out on 150 male CBA mice weighing 22 g on the 3rd and 5th days of development of the immune response. Altogether there were four series of mice in the experiment, two control and two experimental, each undertaken on at least ten animals. The experimental mice were given an intraperitoneal injection of quinpirole (Ly 171555, Eli Lilly Co., USA) in a dose of 1 mg/kg in 0.2 ml of distilled water 30 min before immunization with sheep's red blood cells (SRBC, $5 \cdot 10^8$). Control animals received 0.2 ml of distilled water in accordance with the same scheme. The effects of the drug on the immune response was assessed by the number of IgM-antibody-forming cells (IgM-AFC) [7] and IgM- and IgG-rosette-forming cells (IgM- and IgG-RFC) [3], in the spleen of each mouse. The results were subjected to statistical analysis by Student's t test. Differences were taken to be significant at $p \leq 0.05$.

EXPERIMENTAL RESULTS

Analysis of the results showed that under the influence of quinpirole, a specific agonist of D2 dopamine postsynaptic receptors [11], marked stimulation of the IgM-immune response took place with the peak of its development on the 5th day after immunization (Fig. 1, Table 1). On the 3rd day of the immune response the total number of RFC in mice receiving quinpirole was almost twice as many as in the control. In the control on the 3rd day an immune response was formed with stimulation of rosettes mainly of the IgM-type (Fig. 1). The results are in agreement with the view that the IgM response is an earlier form of response both phylogenetically and oncogenetically. After administration of quinpirole to the mice the immune process was characterized by an increase in the number mainly of IgM-RFC, and the ratio between the number of IgM- and IgG-RFC was unchanged: rosettes of IgM-type evidently play a decisive role in the formation of the immune response in this case just as previously.

Laboratory of Mechanisms of Neurochemical Modulation, Institute of Physiology, Siberian Branch, Academy of Medical Sciences of the USSR, Novosibirsk. (Presented by Academician of the Academy of Medical Sciences of the USSR Yu. P. Nikitin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 109, No. 4, pp. 374-376, April, 1990. Original article submitted June 23, 1989.

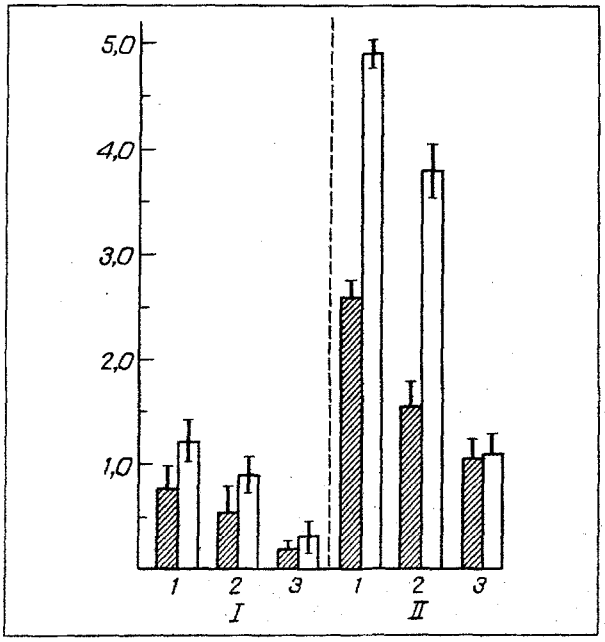

Fig. 1. Increase in number of IgM-rosette-forming cells in spleen of CBA mice receiving quinpirole, on 3rd and 5th days after immunization with SRBC ($5 \cdot 10^8$). Abscissa, intraperitoneal injection of quinpirole (unshaded columns); I) 3rd day after immunization, II) 5th day after immunization. 1) Total number of RFC, 2) of IgM-RFC, 3) if IgG-RFC. Shaded columns represent control (intraperitoneal injection of water). Ordinate, number of RFC among 1000 cells examined.

TABLE 1. Effect of Quinpirole on IgM-AFC in Spleen of CBA Mice on 3rd and 5th Days after Immunization (SRBC, $5 \cdot 10^8$; $M \pm m$)

Experimental group	Dose, mg/kg	IgM-AFC per 10^6 cells				IgM-AFC per spleen			
		3rd day	p	5th day	p	3rd day	p	5th day	p
Control		190,7±14,8		400,3±45,2		32,4280±2632,6		35583,7±5092,2	
Quinpirole (Ly 171555)	1	243,0±12,5	<0,01	633,7±52,7	<0,002	41673,0±3820,0	>0,05	52184,8±4530,1	<0,02

On the 5th day there was an increase in the total number of RFC in the control compared with the 3rd day due to rosettes of IgM- and IgG-types, but with accumulation mainly of IgM-RFC. If the 5th day of development of the immune response in mice receiving quinpirole is compared with the 3rd day, it will be clear that the total number of RFC, and also of IgM- and IgG-RFC was increased by many times, evidence of continuing stimulation of development of the immune response. Thus whereas the total number of RFC in the control increased from the 3rd through the 5th day threefold, in animals receiving quinpirole the increase was fourfold; the rate of growth in this case was determined mainly by a (fivefold) increase in the number of IgM-RFC, whereas in the control the increase was threefold. The increase in the number of IgG-RFC on the 5th day was the same both in the control mice and in those receiving quinpirole. Immunostimulation in this case was accompanied by an increase in the number of IgM-RFC only.

Analysis of the IgM-AFC demonstrated the presence of the same relationship as when IgM-RFC were determined. The number of cells forming IgM-antibodies in mice treated with quinpirole, on both the 3rd and, in particular, the 5th day of the development of the immune response, was increased compared with their number in the control animals (Table 1). Consequently, activation of the dopaminergic system by injection of quinpirole, a selective agonist of D2 dopamine receptors, induces stimulation of the immune response both in the early phase of its development and also later. Involvement of postsynaptic dopamine mechanisms in immunostimulation on account of the IgM-response also is confirmed by data obtained previously after injection of apomorphine into mice in a dose of 1 mg/kg or more [1].

Apomorphine is known to be a specific and effective agonist of dopaminergic receptors, whose action in systems in vivo [6] and in vitro [10] is manifested on both types of receptors: D1 and D2. These receptors may play opposite roles in the regulation of biochemical, behavioral, and electrophysiological effects. It can be concluded from the results that D1 and D2 postsynaptic dopamine receptors are functionally indistinguishable in their immunostimulating effect, and their activation leads to stimulation of the immune response.

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