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STIMULATION OF THE IMMUNE RESPONSE IN CYPROHEPTADINE-INDUCED BLOCKADE OF SEROTONIN RECEPTORS

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KEY WORDS: serotonin receptors; immune response; thymus; pituitary; cyproheptadine.

The existence of several different types of serotonin receptors, involved in the realization of behavioral reactions, temperature regulation, and other functions of the body, is now known [8, 9, 11, 14].

When drugs affecting serotonin turnover and deposition are used, the serotoninergic system has an inhibitory effect on immunogenesis [5, 10]. There is no information in the literature about which receptors are responsible for this effect.

The aim of this investigation was to study the possible role of C_2-receptors in the modulating action of serotonin on immunogenesis and to study the mechanism of this action.

EXPERIMENTAL METHOD

Experiments were carried out on 178 male CBA mice weighing 20-25 g. The immune response was tested on the 5th day after immunization with sheep red blood cells (SRBC) in doses of $5 \cdot 10^6$ or $5 \cdot 10^8$ by counting the number of rosette-forming cells (RFC) [6]. Cyproheptadine (Cyp; from Serva, West Germany) was injected intraperitoneally in doses of 10, 20, and 30 mg/kg in distilled water once 30 min before immunization. 5-Hydroxytryptophan (5-HTP; Serva) in a dose of 300 mg/kg and haloperidol (from Gedeon Richter, Hungary) in a dose of 1 mg/kg were injected intraperitoneally in physiological saline twice a day for 2 days, the first injection being given 30 min before immunization. In the case of combined administration of 5-HTP and Cyp, and also Cyp and haloperidol, the interval between injections of the drugs was 5-10 min.

To study the role of the pituitary and thymus in the modulating action of Cyp on the immune response, the drug was injected into mice with a divided pituitary stalk or into thymectomized mice. Intact and thymectomized mice, and also mice with a divided pituitary stalk, receiving the same volume of physiological saline, served as the controls.

The pituitary stalk was divided in the mice under pentobarbital anesthesia through a transauricular route, and thymectomy was performed through a midline incision in the region of the sternum, by aspiration with a vacuum pump. The accuracy of destruction of the pituitary stalk and of removal of the thymus was estimated visually after decapitation of the animals.

The numerical results were subjected to statistical analysis by Student's t test.

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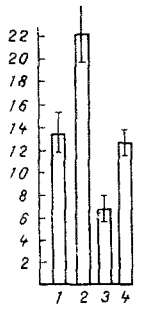

Fig. 1

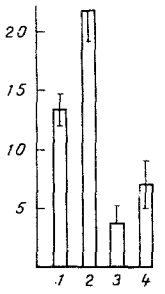

Fig. 2

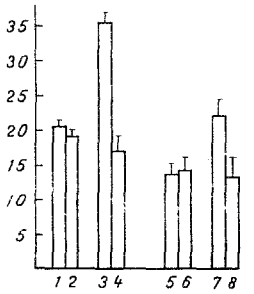

Fig. 3

Fig. 1. Prevention of inhibitory action of 5-HTP on immune response by Cyp in CBA mice immunized with SRBC ($5 \cdot 10^6$). 1) Control; 2) Cyp (30 mg/kg, intraperitioneally, 30 min before immunization); 3) 5-HTP (300 mg/kg, intraperitoneally, twice a day for 2 days, first injection 30 min before immunization); 4) Combined administration of 5-HTP and Cyp in the above doses with an interval of 5-10 min between injections. Here and in Figs. 2 and 3, ordinate: number of RFC per 10^3 cells.

Fig. 2. Abolition of stimulating action of Cyp on the immune response by haloperidol. 1) Control (immunization of CBA mice with SRBC in a dose of $5 \cdot 10^6$); 2) Cyp (30 mg/kg, intraperitoneally, single injection 30 min before immunization); 3) Haloperidol (1 mg/kg, twice in the course of 2 days, first injection 30 min before immunization); 4) Cyp + haloperidol (combined administration of drugs in above-mentioned doses with interval of 5-10 min before injections).

Fig. 3. Prevention of immunostimulating action of Cyp in mice by thymectomy and division of the pituitary stalk. 1, 5) Control (immunization of CBA mice with SRBC in a dose of $5 \cdot 10^6$); 2) Thymectomy; 3,7) Cyp (30 mg/kg, intraperitoneally, single injection 30 min before injection of antigen); 4) Thymectomy + Cyp; 6) Hypophysectomy; 8) Hypophysectomy + Cyp.

EXPERIMENTAL RESULTS

Injection of Cyp in doses of 10, 20, and 30 mg/kg caused dose-dependent stimulation of the immune response. With an increase in the dose the number of RFC increased from 15 ± 0.57 to 22.2 ± 1.32 compared with 13.5 ± 0.8 in the control. Enhancement of the immune response after injection of Cyp was observed in mice immunized with SRBC in a dose of $5 \cdot 10^6$ regardless of the season of the year when the experiment was done, for the level of immune response varied with the season. On increasing the immunizing dose of antigen to $5 \cdot 10^8$, administration of Cyp also led to stimulation of the immune response (37.2 ± 1.4 compared with 24.7 ± 0.6 in the control).

Cyp is known to block type C_2 serotonin receptors [11, 14]. However, investigations have shown that the action of Cyp on the various functions and reactions of the body may be connected with its effect on GABA-ergic [8] and cholinergic systems [15].

As Fig. 1 shows, when Cyp was given after the serotonin precursor, 5-HTP, its action on immune responses was determined by blockade of the serotonin receptors. Injection of 5-HTP caused a marked decrease in the number of RFC, but injection of Cyp prevented the inhibitory action of 5-HTP on the immune response: the magnitude of the immune response of these animals was the same as that in the control animals.

To discover whether stimulation of the immune response by Cyp is due to the fact that serotonin receptors are blocked and do not participate in the immunomodulating inhibitory action, or their blockade leads to activation of another (dopaminergic) system, which stimulates the immune response [4] and has reciprocal relations with the serotoninergic system [5, 13], experiments were carried out with haloperidol, a specific blocker of dopamine receptors. Haloperidol, when given against the background of serotonin receptor blockade abolished the stimulating action of Cyp (Fig. 2). Injection of haloperidol alone caused a decrease in the number of RFC, as was found previously [4]. Also, as will be clear from Fig. 3, stimulation obtained by injection of Cyp was not found after removal of the thymus, which is the peripheral stage in the action of the dopaminergic system on immunogenesis [1]. It can be concluded from the

results that stimulation of the immune response after blockade of the serotonin receptors is dopamine-dependent and takes place through the participation of the thymus [2, 6].

It has been shown that the modulating action of serotonin is effected by central mechanisms with the participation of the hypothalamo-hypophyseal complex [2, 5, 10]. Meanwhile some investigations have shown that serotonin can be bound directly with lymphocytes [3] and that serotonin can inhibit the immune response in experiments in vitro [12]. The workers cited accordingly concluded that serotonin has a peripheral action on immunogenesis. Our own investigations, in which serotonin receptors were blocked in animals with a divided pituitary stalk, showed that in the absence of connections between hypothalamus and pituitary, Cyp does not exhibit its effect. The number of RFC in these animals was the same as in the control (Fig. 3).

It can accordingly be postulated that the C_2 receptors of the brain itself participate in the mechanism of the inhibitory action of serotonin on immunogenesis.

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IMMUNOCHEMICAL STUDY OF HETEROGENEITY OF TROPHOBLASTIC β_1-GLYCOPROTEIN

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The blood serum of pregnant women has been shown to contain a trophoblastic β_1-glycoprotein (TBG) [4], which has been widely used for the diagnosis of pregnancy and of trophoblastic tumors [6].

It has been shown that TBG forms complexes with mucopolysaccharides [2, 7], but the reactions of its components with these polysaccharides have not been studied. TBG also exists in the plasma of pregnant women in several forms, which differ in their affinity for monospecific

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