PRODUCTION OF HUMORAL ANTIBODIES IN RABBITS AFTER DESTRUCTION OF THE NUCLEUS OF THE MIDBRAIN RAPHE

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Electrolytic destruction of the nucleus of the midbrain raphe in rabbits immunized with bovine serum albumin led to stimulation of antibody formation and increased the intensity of the primary immunological response. The character and intensity of the secondary immune response were unchanged.

An increase in the free serotonin concentration after administration of the amine itself or its precursor 5-hydroxytryptophan, by disturbance of oxidative deamination through blocking of monoamine oxidase, or the same effect produced by blocking transport of the monoamine into storage granules all lead to inhibition of synthesis of humoral antibodies, to hypersensitivity of delayed type, and to a decrease in the activity of lymph gland cells; the hypothalamo-hypophyseal system takes part in the mechanism of this inhibitory effect [1-5]. The decrease in the serotonin concentration in these structures should presumably have the opposite effect. The decrease in the serotonin content in the hypothalamus is particularly interesting, for its structures play a direct role in the regulation of immune responses [6, 7, 15].

It has been shown [9, 11] that the zone of preferential localization of serotoninergic neurons in the brain lies in the nuclei of the midbrain raphe. After destruction of this region there is a marked decrease (by 60%) in the serotonin concentration in the forebrain structures including the hypothalamus [12, 14]. The synthesis of monoamine also is disturbed under these circumstances [16].

The object of this investigation was to study the production of humoral antibodies in rabbits after electrolytic destruction of the nucleus of the midbrain raphe.

EXPERIMENTAL METHOD

Experiments were carried out on 20 male chinchilla rabbits weighing 3-3.5 kg. Electrolytic destruction of the nucleus of the midbrain raphe was carried out in a stereotaxic apparatus under pentobarbital anesthesia by a current of 2 mA passed for 30 sec. The electrodes were inserted in accordance with the coordinates of the atlas of the rabbit brain.

To determine the localization of the electrodes at the end of the experiment sections were cut through the brain stem on a freezing microtome. Only those results obtained in animals in which the zone of destruction was limited to the region of the nucleus of the midbrain raphe, namely AP+9, L−0, H −6, were considered in the analysis.

One week after the operation the rabbits were immunized with crystalline bovine serum albumin (Difco) in a dose of 5 mg/kg. Reimmunization was carried out on the 40th day with the same dose of antigen. Blood was taken before immunization, on the 4th, 7th, 10th, 14th, 21st, 28th, and 40th days after primary immunization, and on the 2nd, 4th, 7th, and 10th days after secondary immunization. Antibodies were determined by the passive hemagglutination test [11] with appropriate controls: inhibition of the reaction by antigen, the presence of nonspecific agglutination of tanninized red cells, sensitized red cells, and antigens.

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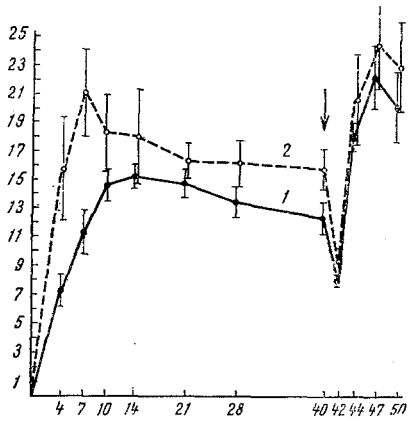

Fig. 1. Effect of destruction of nucleus of midbrain raphe on primary and secondary immune response in rabbits: 1) control rabbits; 2) rabbits undergoing operation. Arrow indicates secondary antigenic stimulation. Ordinate, titer of antibodies ($\log_2$); abscissa, days after immunization.

EXPERIMENTAL RESULTS

Destruction of the nucleus of the midbrain raphe caused significant changes both in the dynamics and in the intensity of the primary immune response in the rabbits so treated. The most marked changes in antibody formation in the animals after destruction of the nucleus of the midbrain raphe occurred in the initial period of the productive phase of the immune response, i.e., on the 4th and 7th days of observation when the mean antibody titer in the animals undergoing the operation was almost twice as high as the mean antibody titer in the control rabbits. At the maximum of the primary immunological response the intensity of antibody formation in the animals after destruction of the nucleus of the midbrain raphe also was much higher than in the control group (Fig. 1).

Significant differences also were found in the dynamics of the primary response. In the control group maximal antibody production was observed on the 14th day. In the animals in which the nucleus of the midbrain raphe had been destroyed the immunological response reached its maximum on the 7th day, after which the antibody titer fell.

With respect to the secondary immune response no statistically significant differences could be found between the groups, although before secondary immunization the antibody concentration in the serum was much higher in the animals undergoing the operation than in the control rabbits. However, analysis of the character and intensity of the secondary immune response for each animal individually revealed a very slight increase in antibody production during the secondary response in animals showing well-marked stimulation after the primary antigenic stimulus. A similar phenomenon, in which additional injections of antigen evoke only a very slight increase in antibody titers, arises during hyperimmunization, when repeated large doses of antigen are given [13].

The more intensive immune response with a rapid rise of the antibody titers to a maximum observed in the present experiments after destruction of the nucleus of the midbrain raphe can be attributed to a decrease in the serotonin level in the structures of the anterior portions of the brain, including the hypothalamus. This conclusion is in agreement with the writers' observations showing stimulation of the immune response during selective inhibition of serotonin synthesis by the pharmacological route (administration of p-chlorophenylalanine, blocking the activity of tryptophan hydroxylase and disturbing the synthesis of the serotonin precursor), and also during inhibition of the immune response associated with elevation of the active serotonin level through interference with its biosynthesis and storage [2, 5].

One possible cause of the more rapid development of the immune response could be facilitated antigen uptake by the cells of the reticuloendothelial system, or its absorption and retention by the germinal centers of the lymphoid tissue, for the converse situation, i.e., suppression of the immune response after destruction of the nuclei of the posterior hypothalamus, is accompanied by retention of antigen in the blood with consequent weakening of the plasma-cell response in the lymph glands [6-8].

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