CHANGES IN THE SEROTONIN CONCENTRATION IN THE LIMBIC STRUCTURES OF THE BRAIN DURING IMMUNIZATION

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Experiments on rabbits showed that immunization with typhoid Vi-antigen is accompanied by a decrease in the serotonin concentration in the structures of the hypothalamus and also, in most animals, of the hippocampus. The possible mechanism of the participation of serotoninergic structures in the regulation of immunogenesis is discussed.

The cortical and subcortical parts of the limbic system of the brain participate in the regulation of immunological reactions. This has been shown with respect to the hippocampus and amygdaloid complex [6, 10] and the hypothalamus [3, 4, 11, 15] and has been confirmed by clinical studies [5]. Not only the functional and structural integrity of the various limbic regions, but also preservation of their connections with each other [6] are essential for the adequate control of immunological processes. Hence it is clear that the reactions of immunity are regulated not by single structures of the CNS, as was hitherto considered, but by a complex system of interconnected zones.

The limbic system is richest in serotoninergic and serotonin-reactive structures [14]. Antigenic stimulation is evidently reflected in the state of these structures, for the serotonin concentration in the brain tissues changes in response to injection of an antigen [9]. It has been postulated that the reaction to an antigen may be mediated through the serotoninergic structures of the hypothalamus [1].

Changes in the serotonin concentration in the hypothalamus and hippocampus were studied during immunization with typhoid Vi-antigen. A change in the concentration of this amine in a certain part of the limbic system is evidence of the involvement of its serotoninergic structures in the complex chain of reactions to the antigenic stimulus.

EXPERIMENTAL METHODS

The serotonin concentration was determined in the hypothalamus and the dorsal portion of the hippocampus in rabbits weighing 2.9-3.2 kg on the 1st and 6th days after intravenous injection of 140 μg of standard typhoid Vi-antigen. The blood antibody titer was estimated by the agglutination test with erythrocytic Vi diagnostic serum in a microtitrator of the Takachi system. As a first step the immunologic reactivity of the animals was determined by specific (Vi-agglutinins) and nonspecific (complement and lysozyme activity of the blood) tests. The animals were decapitated and the parts of the brain for testing, weighing 150-500 mg, were kept for 24 h in liquid nitrogen. Serotonin was determined by a spectrofluorimetric method [12] and expressed in μg/mg wet weight of tissue. Physiological saline in the equivalent volume was injected into a vein of the ear of the control animals.

EXPERIMENTAL RESULTS AND DISCUSSION

In most animals the serotonin concentration in the hypothalamus and hippocampus was altered during the first day after injection of the antigen, i.e., long before the appearance of specific antibodies in the

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TABLE 1. Changes in Serotonin Concentration (in μg/g wet weight of tissue) in Hypothalamus after Immunization with Typhoid Vi-Antigen

Group of animals	Serotonin concentration (M ± m)	Range of serotonin concentrations			
		0,290—0,320	0,400—0,520	0,530—0,770	0,800—0,990
		No. of animals			
Unimmunized (control)	0,660±0,038	—	1	12	3
Immunized:					
1 day after immunization	0,526±0,044	2	3	6	—
P	<0,05				
6 days after immunization	0,519±0,050	1	4	5	—
P	<0,05				

TABLE 2. Changes in Serotonin Concentration (in μg/g wet weight of tissue) in Hippocampus after Immunization with Typhoid Vi-Antigen

Group of animals	Serotonin concentration (M ± m)	Range of serotonin concentrations				
		0,052—0,085	0,090—0,112	0,120—0,150	0,154—0,190	0,240—0,280
		No. of animals				
Unimmunized (control)	0,155±0,006	—	—	7	8	—
Immunized:						
1 day after immunization	0,149±0,025	3	3	1	—	3
P	0,1<P>0,05					
6 days after immunization	0,120±0,018	5	1	2	1	1
P	0,1<P>0,05					

blood. The serotonin level in the hypothalamus of the immunized animals was considerably lowered, and although it still remained within normal limits, it was nearer the lower limit (Table 1). The serotonin concentration in the hippocampus remained within normal limits in only one of the 10 rabbits. In six animals it was significantly below normal, while in three rabbits it was slightly above the upper limit of normal (Table 2). Comparison of the changes in the serotonin concentration in the hypothalamus and hippocampus of individual rabbits showed that in four animals it was lowered in both parts of the brain and in two rabbits it was lowered in the hippocampus only, remaining at the lower limit of normal in the hypothalamus. In three animals the serotonin concentration was significantly raised in the hippocampus and almost unchanged in the hypothalamus. On statistical analysis of the data by the method of mean values a significant decrease in the serotonin level in the hypothalamus and a tendency toward a decrease, although not significant, in the hippocampus were discovered.

In the productive phase of immunogenesis the serotonin concentration in the hypothalamus was lowered by 20%. The serotonin concentration in the hippocampus was significantly below normal in six of 10 rabbits, within normal limits in three, and significantly higher than normal in one.

The results show that serotoninergic structures of those parts of the limbic system that are concerned with the regulation of immunogenesis take part in the response of the body to an antigenic stimulus. Presumably a change in the concentration of a neurotropic amine with such high biological activity as serotonin is bound to be reflected in the state of the serotoninergic structures and of the systems under their control. The serotonin concentration in the limbic structures is known to determine the functional state of the pituitary-adrenal system. An experimental increase in the serotonin level in the dorsal portion of the hippocampus or in the hypothalamus leads to a corresponding decrease or increase in the secretion of corticosteroids [7]. The hippocampus has a delaying effect on the secretory activity of the hypothalamic-pituitary-adrenal system, whereas the hypothalamus stimulates the secretory function of the subordinate system [13]. The decrease in the serotonin level in the hippocampus observed in the early phases of immunogenesis conceivably leads to weakening of the ordinary delaying effects of this

part of the limbic system on the hypothalamus and the hormonal system under its control. This evidently brings about the characteristic hypothalamic stimulation of the system under its control, and this could lead to an increase in the secretion of adrenocortical hormones concerned with the regulation of the state of the immunocompetent organs [2]. Increased secretion of corticosteroids up to a certain level is evidently a factor controlling the immunological process in its early stages, for after injection of an antigen their blood concentration rises rapidly [8]. Lowering of the serotonin concentration in the hippocampus was characteristic of most of the immunized animals. In the inductive phase of immunogenesis, however, the serotonin concentration in the hippocampal structures of one-third of the animals was significantly above the upper limit of normal. In this connection it is interesting to note that in about one-third of the immunized animals low immunologic reactivity was found. The highest titer of antibodies recorded on the 6th-8th day after immunization in one-third of the animals did not exceed 1:5-1:20, whereas in most of the experimental animals it reached 1:80-1:320.

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