CHANGES IN MONOAMINE CONTENT AND MONOAMINE OXIDASE ACTIVITY IN BRAIN STRUCTURES IN EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS

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The concentration of serotonin (ST), noradrenalin, and adrenalin in the blood, cerebrospinal fluid, and certain brain structures and the monoamine oxidase (MAO) activity were investigated in the course of experimental allergic encephalomyelitis in dogs. In the preparalytic period a tendency was observed for the ST concentration to fall and the catecholamine concentration to rise. The stage of clinical manifestations of encephalomyelitis was accompanied by lowering of the ST level in the white matter of the hemispheres and by generalized inhibition of adrenergic structures. No significant change in MAO activity was found, so that a disturbance of the biosynthesis of monoamines as a result of immune aggression could be the possible cause of inhibition of the monoaminergic system.

KEY WORDS: catecholamines and serotonin in the brain and blood; neuroallergy; monoamine oxidase.

Recent investigations have demonstrated the importance of tryptophan in the molecule of the basic protein of myelin or the corresponding polypeptide for the manifestation of encephalitogenic properties [7, 10, 12, 13, 19]. On the other hand, the tryptophan-containing site can be regarded as the possible receptor of serotonin (ST) in the CNS [7]. The development of immune responses in the brain during experimental allergic encephalomyelitis (EAE) can lead, it is suggested, to the disturbance of the mediator activity of ST [7, 14]. The functional connection of the serotoninergic structures with adrenergic formations [2, 15] suggests the possibility of changes within the monoaminergic system of the brain as a whole in neuroallergy.

The dynamics of the concentration of ST, adrenalin, and noradrenalin and monamine oxidase (MAO) activity in certain brain structures, the blood, and the cerebrospinal fluid (CSF) was investigated in various stages of formation of EAE.

EXPERIMENTAL METHOD

Altogether 104 sexually mature mongrel female dogs weighing 9-15 kg were used in the experiments. EAE was produced by immunization with a single dose of a mixture of emulsion of the white matter of homologous brain with Freund's complete adjuvant (0.2 ml mixture/kg body weight). The clinical picture of EAE (paralysis, paresis, tremor, nystagmus) developed on the 9th-14th day after immunization, most frequently on the 9th day. Material was taken in the preparalytic period (on the 7th day of sensitization), at the stage of clinical manifestations, and also on the 20th-24th day in the absence of neurological disturbances.

The concentration of monoamines was determined fluoremetrically: ST by the method of Udenfriend [5], catecholamines by Men'shikov's method [4], and MAO activity by the intensity of the color formed after incubation of tissue homogenates with paranitrophenylethylamine as the substrate for 1 h at 37°C [1].

EXPERIMENTAL RESULTS

Noradrenalin, adrenalin, and ST were detected in the cortex and white matter of the frontal lobes of

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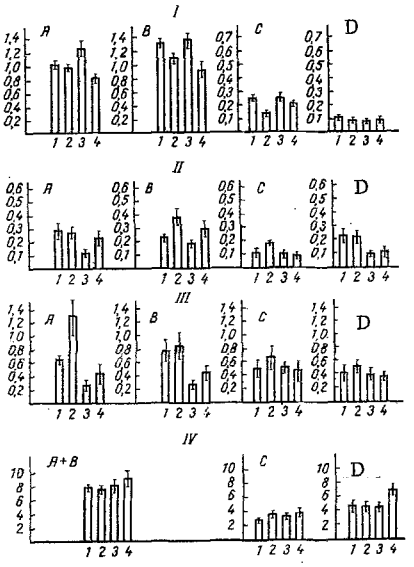

Fig. 1

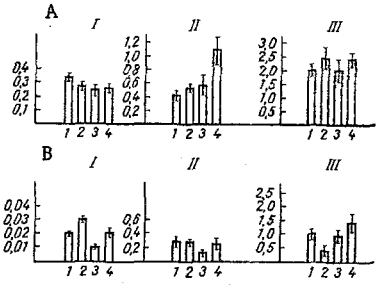

Fig. 2

Fig. 1. Concentration of biogenic monoamines (in μg/g wet weight of tissue) and MAO activity (in conventional units) in the course of experimental allergic encephalomyelitis in dogs: I) concentration of ST; II) of adrenalin; III) of noradrenalin; IV) MAO activity; 1) healthy dogs; 2) preparalytic period; 3) stage of clinical manifestations of EAE; 4) dogs without clinical manifestations; A) anterior hypothalamus; B) posterior hypothalamus; C) cerebral cortex; D) white matter of cerebral hemispheres.

Fig. 2. Concentration of biogenic monoamines in blood (A) and CSF (B) in dogs during development of EAE: I) ST concentration (in μg/ml); II) concentration of adrenalin (in μg/1000 ml); III) concentration of noradrenalin (in μg/1000 ml). Remainder of legend as in Fig. 1.

the cerebral hemispheres, the anterior and posterior zones of the hypothalamus, the CSF, and blood of healthy dogs. The highest concentration of the monoamines was found in the hypothalamus, which corresponded to the distribution of MAO activity. The monoamine concentration in the blood was higher than in the CSF: the blood/CSF ratio was 1.97 for noradrenalin and 17 for ST; the concentration of the latter amine in the CSF was thus very low (0.02 ± 0.002 μg/ml). The results for the distribution of monoamines and MAO activity in the healthy dogs agree with those given by other workers [9, 11, 18].

Changes in the monoamine content were detected even before the development of neurological disturbances. In the preparalytic period, for instance, a definite tendency for the ST concentration to fall and for the concentration of the catecholamines, especially noradrenalin, to rise was observed in the hypothalamus, cortex, and white matter of the cerebral hemispheres (Fig. 1) and also in the blood (Fig. 2). The changes in the CSF were in the opposite direction (Fig. 2).

At the stage of clinical manifestations of EAE there was a tendency for the ST level to be restored in the hypothalamus and cerebral cortex. The concentration of this amine was low in the white matter, blood, and CSF, just as it was in the preparalytic period. The catecholamine level in the brain structures studied also was low, in both the white matter and the cortex, and in the hypothalamic structures. Whereas inhibition of serotoninergic formations during the development of the clinical picture of EAE was observed mainly in the "target" of the inflammatory-demyelinizing process (the white matter), disturbances in the adrenergic structures were generalized in character. It will be noted that the decrease in the ST and catecholamine concentrations was not accompanied by an increase in MAO activity, which suggests that the possible cause of inhibition of the monoaminergic system was disturbance of biosynthetic processes and not the intensification of catabolism of the monoamines. This conclusion is supported by the observed fall of the ST level in the brain of guinea pigs with allergic encephalomyelitis in the absence of any changes in the content of 5-hydroxyindoleacetic acid [16]. However, data showing the opposite have also been obtained [8, 17].

Analysis of the dynamics of the ST and catecholamine content in the brain showed that the changes in the preparalytic period are opposite in direction: as the ST level falls the concentration of catecholamines rises. At the stage of clinical manifestations the changes remain opposite in direction in the hypothalamus

and cerebral cortex, but in the white matter all the indices are lowered. In the group of dogs without clinical manifestations of encephalomyelitis a tendency was observed for the concentration of both monoamines to decrease; MAO activity, however, was increased.

Although the view of Brodie and Shore that relations between serotoninergic and adrenergic structures are antagonistic is not regarded as sufficiently well-grounded [2], there is no doubt about the existence of definite relations between the content of biologically active monoamines in the brain, characterizing biochemical and functional status of particular structures. Allergic alteration of the brain and development of inflammatory and demyelinizing changes are accompanied by disturbance of these relationships, and this leads ultimately to inhibition of both serotoninergic and adrenergic structures of the white matter – the "target" of immune aggression.

Changes in the monoamine contents in the hypothalamus – the central regulator and integrator of automonic functions – are particularly interesting. They may have a bearing, in particular, on the severe disturbances of activity of the cardiovascular system observed in EAE [3, 6].

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