CHANGES IN PROTEIN SYNTHESIS IN DIFFERENT PARTS OF THE BRAIN OF RATS WITH EXPERIMENTAL NEUROSENSITIZATION

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The important role of neuroautoimmune processes in the pathogenesis of some nervous and mental diseases has now been established [8, 10]. However, the mechanisms leading to the development of the pathological changes during neurosensitization and, in particular, the characteristics of protein metabolism in the brain, have been inadequately studied. Different workers who have studied incorporation of labeled amino acids into brain proteins in experimental allergic encephalomyelitis have obtained contradictory results [4, 11, 12]. Adjuvants used in the induction of encephalomyelitis may affect indices of protein metabolism [1]. Despite the marked antigenic differences between different parts of the CNS [2, 5], the effect of sensitization by antigens from individual brain structures on protein metabolism in the brain is not discussed in the literature.

The object of this investigation was to study the characteristics of protein renewal in different parts of the brain in rats sensitized with antigens from various brain formations.

EXPERIMENTAL METHOD

A saline extract of whole allogeneic brain, cerebral cortex, cerebellum, or medulla, in a volume of 0.5 ml, was injected intraperitoneally daily for 3 days into noninbred female albino rats weighing 200-250 g. Control animals received physiological saline by the same scheme. On the 10th-12th days, at the end of sensitization, a solution of methionine-^{35}S with a total activity of 15-20 μCi was injected intraperitoneally into the rats. The animals were decapitated 1 h later and ten different brain structures were isolated on ice; total proteins were precipitated from these structures with 10% TCA, they were then washed with 5% TCA, nucleic acids were removed, and lipids were extracted with alcohol and ether. Tissue homogenates also were prepared from the same brain structures. Radioactivity of the tissue homogenates, dried proteins, and TCA-supernatant was measured on PP-8 and DP-100 radiometers with end-window type BFL-25 counters. The relative specific activity of proteins was calculated, allowing for the radioactivity of the TCA-supernatant, and the ratio of activity of the tissue homogenates to activity of blood also was determined. Titers of antibrain antibodies were estimated in the complement fixation test, using the same antigens for immunization as the test antigen, and also an extract of rat liver (control). The results were subjected to statistical analysis by means of the Wilcoxon–Mann–Whitney nonparametric criterion. Altogether 92 rats were used in the experiments.

EXPERIMENTAL RESULTS

Different results were obtained in the four series of experiments on rats immunized with antigens from different parts of the brain.

In rats sensitized with whole brain antigen, antibodies against whole rat brain and its different parts were found in the blood (titer 1:10-1:20). A considerable (by 70%, $P < 0.05$) increase in incorporation of methionine-^{35}S into proteins of the hippocampus and, to a lesser degree, into proteins of the hypothalamus ($P > 0.05$), was observed. Incorporation of the amino acids into proteins of the thalamus and cerebellum was depressed (Fig. 1).

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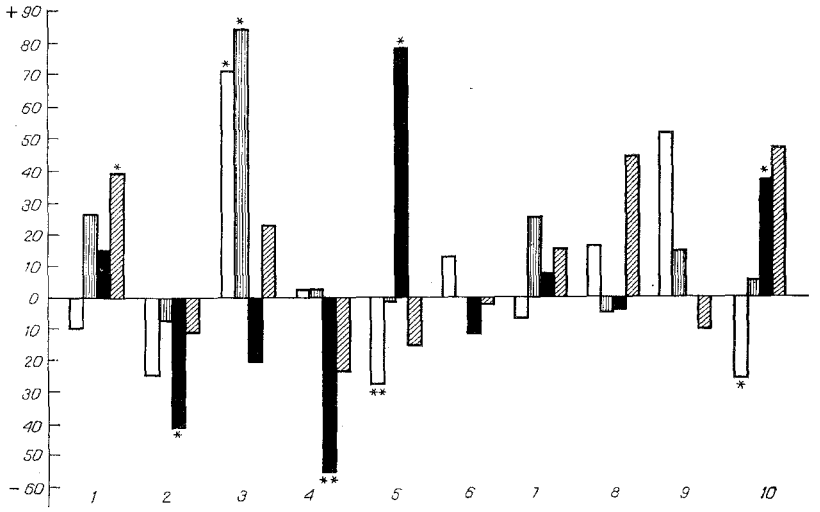

Fig. 1. Incorporation of methionine-^{35}S into total proteins of different parts of the brain of sensitized rats. Unshaded column — sensitization of rats with whole brain, vertically shaded columns — sensitization with cortex, black columns — sensitization with cerebellum, obliquely shaded columns — sensitization with medulla. Abscissa, parts of brain investigated: 1) cortex, 2) olfactory lobes, 3) hippocampus, 4) basal ganglia, 5) cerebellum, 6) corpora quadrigemina, 7) spinal cord, 8) medulla, 9) hypothalamus, 10) thalamus. Ordinate, relative specific activity (in percent of control; control taken as 0%). * — differences from control significant ($P < 0.05$).

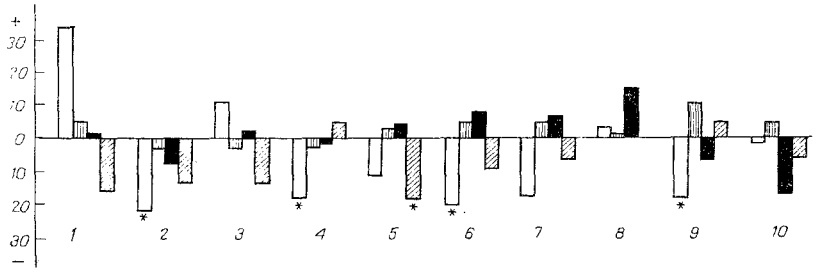

Fig. 2. Incorporation of methionine-^{35}S into tissue homogenates from different parts of brain of sensitized rats. Ordinate, relative activity (in percent of control). Remainder of legend as to Fig. 1.

Immunization of the rats with antigen from the cerebellum led to a significant increase in radioactivity of proteins of the cerebellum and thalamus, whereas incorporation of labeled methionine into proteins of the basal ganglia and olfactory lobes simultaneously fell. Antibodies against the cerebellum were present in the blood of these animals.

On immunization of the rats with antigens from the medulla, antibodies against this structure appeared in low titers (1:5-1:10). Incorporation of methionine into proteins of the medulla and spinal cord, thalamus, and hippocampus ($P > 0.05$) and sensomotor cortex ($P < 0.05$) was increased; in the other structures a tendency was observed for radioactivity of the proteins to be reduced.

Data obtained during the investigation of incorporation of radioactivity into brain tissue homogenates are given in Fig. 2. Sensitization of the rats with antigen of whole brain led to a decrease in incorporation of methionine-^{35}S in the tissues of the olfactory lobes, basal ganglia, corpora quadrigemina, and hypothalamus ($P < 0.05$), whereas accumulation of labeled methionine in the tissues of the cerebral cortex was increased. When animals were

sensitized with antigens of the cortex, cerebellum, and medulla no significant changes in incorporation of methionine into the tissues of the various structures of the CNS were observed.

The experimental results are evidence of changes in protein renewal in different parts of the brain during experimental neurosensitization. An increase in incorporation of methionine into proteins of brain structures corresponding to the antigens used for sensitization, and also into proteins of certain other structures, was observed. When the possible mechanisms of the change in the rate of protein renewal during neurosensitization are examined it must be remembered that antibrain antibodies can penetrate from the blood into the brain [7], exhibiting affinity for the corresponding parts of the brain, where they can induce changes in processes of tissue metabolism and, in particular, of protein biosynthesis. Activation of protein synthesis found in some structures of the CNS is in harmony with the results of investigations showing an increase in the intensity of protein biosynthesis in other organs and tissues when exposed to autoimmune action, such as bone tissue [6] and myocardium [3].

No parallel was observed in the present experiments between changes in incorporation of labeled methionine into proteins and its accumulation in the tissues of individual brain structures. This indicates that changes in the incorporation of methionine into proteins of different parts of the brain were not directly connected with increased penetration of the amino acids into the tissue of these structures, but they reflect the special features of protein biosynthesis in the CNS during neurosensitization. The writer previously demonstrated a selective increase in permeability of the blood–brain barrier (BBB) for ^{32}P in parts of the brain corresponding to the antigen used for sensitization [9]. No such relationship was found for methionine-^{35}S, evidence of a certain selectivity in the changes in functions of the BBB relative to different metabolites under certain conditions.

The changes observed in protein synthesis in different parts of the brain in experimental neurosensitization may play an important role in the pathogenesis of lesions of the CNS accompanied by neuroautoimmune disturbances.

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