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EFFECT OF SOMATOTROPHIC HORMONE IN SYNAPTOSOMAL MEMBRANE Na,K-ATPase IN THE YOUNG RAT BRAIN

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Somatotrophic hormone (STH) exhibits epileptogenic properties and plays an important role in processes of regeneration and formation of epileptic activity (EA), especially after trauma. The excitatory effect of STH, compensating for the synaptic deficit during recovery after local brain damage brings about hyperexcitability of this region and the development of EA [6, 9]. Hyperactivity of neurons, incidentally, is most characteristic of postnatal development, and the predisposition of the brain to seizures and the possibility of development of epilepsy are particularly great in childhood. STH has a decisive influence on the formation and differentiation of cells of the growing organism and, in particular of neurons [10].

According to the membrane hypothesis of development of EA [3, 4], an important role in the epileptization of neurons is played by structural changes in neuron membranes, leading to reversible inactivation of Na,K-ATPase which, in turn, is a trigger factor in the development of prolonged and persistent depolarization of neuron membranes and the formation of generators of pathologically enhanced excitation [5]. Inactivation of the Na,K-pump of neuron membranes is also a trigger factor coupling depolarization and secretion of mediators by nerve endings, i.e., it is a factor in not only pathological, but also physiological hyperactivity of neurons [2].

The action of STH inducing hyperactivity of neurons may be effected through receptors on the electrogenic Na,K-ATPase of neuron membranes.

The aim of the present investigation was to study the action of STH in experiments in vivo on the state of activity of transport Na,K-ATPase of synaptosomal membranes of the brain of young and adult rats.

EXPERIMENTAL METHOD

Unpurified, osmotically destroyed synaptosomes were obtained from formation of the brain stem and cerebral hemispheres of young male rats aged 3 weeks, weighing 35 g, and of

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TABLE 1. Effect of STH on ATPase Activity (in μmoles P_i/mg protein/h) of Brain Synaptosomes of Young and Adult Rats (M ± m)

Experimental conditions	Young rats (4-5)			Adult rats (2-3)		
	Ca-ATPase	Mg-ATPase	Na, K-ATPase	Ca-ATPase	Mg-ATPase	Na, K-ATPase
Control (without STH)	9,1±0,3	18,8±0,9	11,0±1,2	13,5	17,5	17,0
STH 0.00025 unit; 0.1 μg protein/ml; 5×10^{-9} M	9,7±0,5	21,6±0,5*	8,9±0,4	12,5	14,5	17,0
STH 0.0025 unit; 1 μg protein/ml; 5×10^{-8} M	9,8—0,3	22,2—0,1*	7,0—0,5*	18,0	20,00	—
STH 0.025 unit; 10 μg protein/ml; 5×10^{-7} M	13,4±0,3*	22,0±0,6*	6,8±0,9*	17,0	21,0	17,0
STH 0.25 unit; 100 μg protein/ml; 5×10^{-6} M	27,1±0,6*	28,6±0,6*	3,9±0,6*	27,0	28,0	10,0

Legend. *$p < 0.05$ compared with control. Number of experiments given in parentheses.

adult male rats weighing 230 g (aged 4.5-5 months) [8]. The fraction was preserved in 0.32 M sucrose, 50 mM Tris-HCl (pH 7.4) at 20°C for 1-2 weeks. Na,K-ATPase activity was judged by the quantity of inorganic phosphate (P_i) removed from the substrate (3 mM ATP) in the presence of 100 mM Na^+, 20 mM K^+, and 5 mM Mg^{++} or Ca^{++} [8]. In the experiments in vitro, crystalline human SDH, prepared by the "Biotekhnologiya" Research and Production Combine, Moscow, was used in a final concentration of $5 \cdot 10^{-9}$-$5 \cdot 10^{-6}$ M, containing 100 μg of synaptosomal protein in 1 ml of the sample. Protein was determined by Lowry's method.

EXPERIMENTAL RESULTS

In experiments in vitro, STH was shown to inactivate (by 37%; $p < 0.05$) membrane Na,K-ATPase of unpurified synaptosomes starting with a concentration of $5 \cdot 10^{-8}$ M (Table 1). With an increase in the STH concentration to $5 \cdot 10^{-6}$ M the inhibitory effect was increased.

Activity of Mg- and Ca-ATPase with low affinity for the bivalent cation was increased by the action of STH; activation of Mg-ATPase was observed by STH beginning with a concentration of $5 \cdot 10^{-9}$ M, and activation of Ca-ATPase, beginning with a concentration of $5 \cdot 10^{-7}$ M STH. Considering that activity of both Mg- and Ca-ATPase in preparations of osmotically destroyed synaptosomes can characterize the ATPase function of components of the cytoskeleton and cytoplasmic organelles, it can be postulated that these ATPases participate in the realization of the modulating and neurotropic action of STH. The study of the effect of STH on brain synaptosomal ATPase activity in adult rats showed that inactivation of Na,K-ATPase is exhibited only by comparatively high STH concentrations: $5 \cdot 10^{-6}$ M (Table 1). These facts are evidence of the specificity of action of STH in low concentrations on the Na,K-ATPase of neuronal membranes of the rat brain.

The results indicate that STH may exert a membranotropic action. The effect of STH on Na,K-ATPase is evidently mediated through ligand-receptor interaction. The presence of receptors for STH has been demonstrated in the plasmalemma of various target cells [1, 10, 11]; the functioning of this receptor with the ligand, moreover, depends on the Ca^{++} and Mg^{++} concentrations in the medium [1]. We know that STH in the brain modifies electrogenesis [1, 7, 10]. In brain synaptosomes STH induces activation of cyclic nucleotide phosphodiesterase and inhibition of adenylate cyclase. It is difficult at present to say whether this effect is connected with the phenomenon we now describe. It can be tentatively suggested that inactivation of Na,K-ATPase of brain synaptic membranes through the action of STH is a manifestation of the neurotropic, modulating action of this neuropeptide in ontogeny, aimed at increasing the effectiveness of synaptic transmission. The possibility likewise cannot be ruled out that if excessive accumulation of STH in the brain tissue takes place, hyperactivity may be converted into pathological hyperactivity of the neurons, leading to the development of EA.

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EFFECT OF ADAPTATION TO PERIODIC AND CONTINUOUS ANOXIA ON DISTURBANCE OF THE ELECTRICAL STABILITY OF THE HEART IN POSTINFARCTION CARDIOSCLEROSIS

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Research published previously yielded evidence that marked disturbances of electrical stability of the heart, usually developing during postinfarction cardiosclerosis, and including lowering of the electrical threshold of fibrillation and enhancement of ectopic activity of the heart, can be abolished by adaptation of animals to periodic anoxia under pressure chamber conditions [4, 5]. However, the question whether this result can be achieved by adaptation of animals at average altitudes in the mountains has not hitherto been studied.

The aim of this investigation was to compare the effect of adaptation to periodic anoxia under pressure chamber conditions and adaptation to anoxia at average altitudes in the mountains on disturbances of electrical stability of the heart during postinfarction cardiosclerosis.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 180-200 g. Under ether anesthesia the descending branch of the left coronary artery was ligated by the method in [10], after which the animals gradually developed postinfarction cardiosclerosis in the form of a massive scar in the wall of the left ventricle. In the first stage of the experiment, adaptation to anoxia in the pressure chamber began in the case of animals 2 weeks after ligation of the coronary artery: the 1st and 2nd days at an altitude of 1000 m above sea level for 2 h, then every 2 days later the altitude was increased by 1000 m up to 5000 m. The duration of stay in the pressure chamber was then increased daily by 1 h up to 6 h. Altogether the rats were exposed to anoxia 45 times. The experiments were done in March and April.

At the second stage of the experiment, done in July and August, 2 weeks after ligation of the coronary artery the animals were taken up to the base laboratory of high-altitude physiology, A. A. Bogomolets Institute of Physiology, Academy of Sciences of the Ukrainian SSR, in the village of Terskol at an altitude of 2100 m above sea level, where they remained for 30 days in the animal house, under conditions identical with those in Moscow, after which they were returned to Moscow, where experiments to study parameters of the electrical stability of the heart were carried out during the first 3 days.

The electrical threshold of fibrillation of the heart was determined in acute experiments under pentobarbital anesthesia after thoracotomy. By means of the SFN-3201 stimulator (Nihon Kohden, Japan), triggered by the R wave of the ECG, the heart was stimulated by

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