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EFFECT OF EXCESS OF ZINC IONS ON GABA METABOLISM AND FORMATION OF THE SENSOMOTOR CORTICAL EVOKED POTENTIAL

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Zinc is a trace element with a broad spectrum of action. Its ions affect various functions of the body, but a decisive aspect of the mechanism of action of zinc is its interaction with chemical transmitters of nervous and endocrine influences, including hormones, mediators, enzymes, and so on [1, 6, 8, 12].

On the basis of histochemical and electron-microscopic data, it has now been suggested that the zinc participates in synaptic transmission, only in mossy fibers [4]. At the level of the mossy fibers of the hippocampus zinc has been shown to play an important role of maintaining long-term potentiation of excitation [5].

The state of synaptic transmission in the sensomotor cortex and of the metabolism of GABA, a meditor of inhibition [11] which plays an essential role in the central mechanism of adaptation [2], has not been studied in the presence of an excess of zinc ions and, in our view, this is an interesting topic.

In this investigation changes in the sensomotor cortical evoked potential (EP) and in concentrations of GABA, glutamic, and aspartic acids (GA and AA, respectively), and activity of the enzymes glutamate decarboxylase (GDC) and GABA transaminase (GABA-T) were studied after single and prolonged injection of various doses of zinc chloride ($ZnCl_2$).

EXPERIMENTAL METHOD

Experiments were carried out on Chinchilla rabbits weighing 2.5-2.8 kg. EP were recorded on the focus of maximal activity of the sensomotor cortex in response to electrodermal stimulation of the contralateral limb. Single stimuli 0.5 msec in duration were used for stimulation. Potentials were recorded with a D-581 dual beam cathode-ray oscilloscope (Kryžik, Czechoslovakia), after preamplification. Potentials were recorded before and after intramuscular injection of $ZnCl_2$ (single or repeated) in doses of 0.1 and 1 mg/kg body weight (calculated as the pure metal). The primary somatosensory cortical response was recorded with respect to its amplitude and temporal characteristics.

To determine amino acids, the brain was removed and treated by the method in [14] with certain modifications [13]. Free amino acids — GABA, GA, and AA, were separated by electrophoresis on paper [10]. Activity of GDC II and GABA-T was determined [7].

Concentrations of amino acids and activity of the enzymes were determined before and 30 min after intramuscular injection, single or repeated (in the course of 7, 14, and 21 days), of $ZnCl_2$ in doses of 0.1 and 1 mg/kg. The numerical data were subjected to statistical analysis [9].

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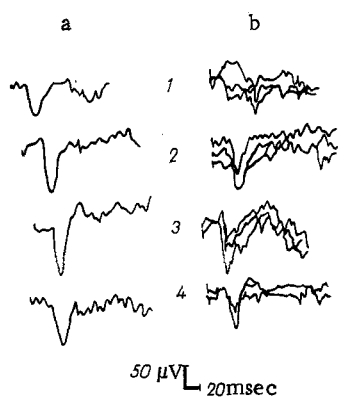

Fig. 1

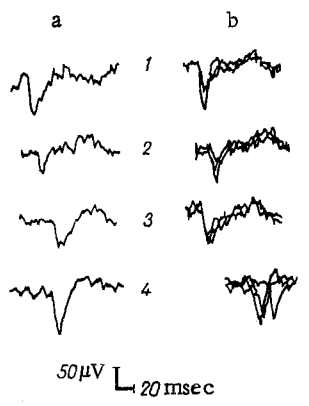

Fig. 2

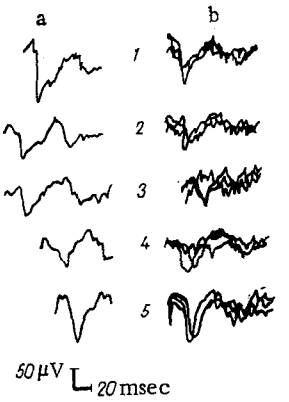

Fig. 3

Fig. 1. Sensomotor cortical EP after a single injection of $ZnCl_2$ in a dose of 0.1 mg/kg. a) Single potentials; b) superposition. 1) Background; 2) 30 min; 3) 1 h; 4) 2 h.

Fig. 2. Sensomotor cortical EP after repeated injections of $ZnCl_2$ in a dose of 0.1 mg/kg. Legend as in Fig. 1.

Fig. 3. EP after application of $ZnCl_2$ solution to sensomotor cortex. 1) Background; 2) 5 min; 3) 30 min; 4) 1 h; 5) 2 h. Remainder of legend as in Fig. 1.

EXPERIMENTAL RESULTS

Analysis of the electrophysiological data on the effect of $ZnCl_2$, in the doses used, and when administered by different methods, indicate the essential role of this element in the formation of the sensomotor cortical EP.

A single injection of zinc chloride in doses of 0.1 and 1 mg/kg led, after 30-60 min, to the appearance of potentials with increased amplitude and with some lengthening of their latent period. After 2 h these parameters returned to their original background level (Fig. 1). After repeated injections (5-7 days) $ZnCl_2$ caused a decrease in amplitude of EP with considerable lengthening of the temporal parameters (Fig. 2), but only in a dose of 0.1 mg/kg, 30 min after the last injection. Changes described in sensomotor cortical potentials were recorded for 1 h. A tendency for the amplitude of the potentials to recover, with lengthening of the latent period, was observed 2 h after the injection.

The changes described above in the potentials were observed also when $ZnCl_2$ solution was applied in a dose of 0.1 mg/kg directly to the sensomotor cortex. Potentials with very low amplitude were recorded 5 min after application, although the time of their appearance and their duration remained unchanged. A similar state of the sensomotor cortical potentials also was observed for 1 h. Their amplitude was almost restored after 2 h (Fig. 3).

Thus, a single injection of $ZnCl_2$ in a dose of 0.1 and 1 mg/kg increases the amplitude of the potentials and lengthens the time of their appearance, whereas multiple injections and applications of $ZnCl_2$ to the sensomotor cortex were accompanied by a decrease in the amplitude of EP and by lengthening of the time of their appearance. Identical changes in sensomotor cortical potentials were observed by the present writers during a change in the GABA level in brain structures [3], and for that reason the results of the electrophysiological investigations given above provided a basis for determination of GABA level in brain tissue after a single injection or during prolonged administration of $ZnCl_2$.

The results of these investigations showed that a single injection of $ZnCl_2$ in doses of 0.1 and 1 mg/kg was accompanied by a sudden increase in the GABA concentration in the sensomotor cortex. The concentrations of GABA, GA, and AA in thos zone of the cortex 30 min after injection of these doses were higher than in the control. Activity of the enzymes of GAGA metabolism, namely GDC and GABA-T, was correspondingly increased (Table 1).

Prolonged administration (for 7, 14, and 21 days) of $ZnCl_2$ in a dose of 0.1 mg/kg increased the GABA concentration by 2-3 times, and this was accompanied by an increase in GDC

TABLE 1. Concentration of GABA, GA, and AA (in μmoles /g wet weight of tissue) and Activity of Enzymes GDC (in μmoles GABA) and GABA-T (in μmoles GA) in Sensomotor Cortex after Injection of Zinc (M ± m, n = 10)

Experimental conditions	GABA	GA	AA	GDC	GABA-T
Control	1,65±0,19	3,75±0,37	1,72±0,13	60,3±1,4	29,6±4,0
Single injection					
0.1 mg/kg	2,66±1,12*	4,45±2,9	2,55±0,71*	30,6±2,1*	26,2±5,0
1 mg/kg	2,36±0,87*	2,78±0,97	2,76±2,80*	13,1±0,9*	30,6±1,7
Repeated injections in a dose of 0.1 mg/kg					
7 days	3,36±2,0*	6,30±3,4*	3,68±2,2*	23,5±1,0*	17,2±2,0*
14 days	3,51±2,3*	5,76±4,0*	3,92±2,5*	24,1±1,3*	48,6±1,3*
21 days	4,18±1,5*	5,80±1,5*	4,24±1,7*	23,9±4,6*	43,4±1,7*

Legend. *P < 0.05 compared with control.

activity and a decrease in GABA-T activity. Later, on the 14th and 21st days after injection of zinc chloride, the GABA-T activity rose a little (Table 1).

Consequently, with an increase in the dose and duration of administration of zinc a sudden increase in the GABA concentration was observed, accompanied by a corresponding change in activity of the enzymes concerned in its metabolism. Consequently, prolonged administration of zinc has a marked effect on GABA metabolism in the sensomotor cortex. It may be that zinc, by its influence on activity of the enzymes of GABA metabolism, brings about a corresponding shift in functional activity of the synapses of the sensomotor cortex through them, and this is also manifested electrographically.

This conclusion is confirmed by data obtained by other workers [5, 15], who showed that an increase in the concentration of zinc ions, by inhibiting oxidation of pyridine nucleotides in mitochondria, creates the conditions for increased synthesis of GA, which is a raw material for GABA formation. The increase in the GABA concentration observed in the sensomotor cortex may therefore, perhaps, be the result of this activating effect of zinc ions on glutamate formation. All these considerations together determine the functional activity of synapses in the sensomotor cortex, and this is expressed as a corresponding change in EP.

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