NEW VITAMIN B_1 ANTAGONISTS WITH NEUROTROPIC ACTIVITY

Yu. M. Ostrovskii, T. I. Zimatkina,
D. A. Oparin, and N. I. Morgacheva

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Antivitamins are universally used in experimental biochemistry for specific inhibition of enzyme reactions [3]. Certain pharmacological agents have also been developed on this basis and are widely used [2]. Among the antimetabolites of thiamine, pyrithiamine and hydroxythiamine have achieved the greatest popularity. The first is known for its high neurotoxicity [8], which is unconnected with the corresponding diphosphate formed from it; the latter, which is less toxic, does not pass through the blood-brain barrier [9]. The experimental study of the role of thiamine diphosphate-dependent reactions in maintenance of metabolic homeostasis in nerve tissue is thus hampered by great difficulties.

The search for antimetabolites of thiamine with the desired properties was based on synthesis of new derivatives of hydroxythiamine which are esters of this compound with dichlorodiethylaminopropionic (HTCP) and dichlorodiethylaminophenylbutyric (HTCPB) acids. The antivitamin activity of the two compounds was compared with that of hydroxythiamine (HT) against the enzyme transketolase, which is particularly sensitive [5] to HT diphosphate.

EXPERIMENTAL METHOD

Experiments were carried out on male albino mice weighing 18-20 g, kept on a balanced diet. The animals were deprived of food for 12 h before decapitation. Aqueous solutions of the compounds, in a volume of 0.2 ml, were injected subcutaneously in single doses, equimolar relative to HT in a dose of 100 mg/kg. Control mice received injections of the same volume of physiological saline. Transketolase activity (in μ moles sedoheptulose-7-phosphate/g tissue/h) was determined by Bruns' method [4]. The toxicity of the new compounds was determined by the method of Litchfield and Wilcoxon [7].

EXPERIMENTAL RESULTS

By subcutaneous injection LD_{50} for albino mice was found to be: for HTCP 460 mg/kg, for HTCPB 495 mg/kg, and for HT itself 1430 mg/kg.

The compounds acted similarly to HT on tissues of the liver, kidneys, spleen, heart, and muscles, and their strongest inhibition of transketolase activity was exerted on the 3rd day after injection (Fig. 1a). A different picture was observed in the brain (Fig. 1b). In the case of HT, activity of the enzyme in brain tissue did not differ significantly from the control at all times of investigation. After injection of HTCP and HTCPB, however, transketolase activity was considerably reduced compared both with the control and with data for groups of animals receiving HT. The antivitamin effects of the new compounds were strongest, just as on other tissues, on the 3rd day of the experiments.

The results are evidence that the compounds undergo hydrolysis in the brain at the ester bond, and the HT which penetrates into the brain tissue is converted by the corresponding kinase reaction [1, 6] into HT diphosphate, which inhibits transketolase.

After injection of HT in doses equimolar to those contained in the HTCP and HTCPB, significant inhibition of enzyme activity was not observed at any stage of the investigation. It can accordingly be concluded that the blood-brain barrier is permeable only for HT esters. The ability of the new compounds to penetrate into brain tissue in all probability is the

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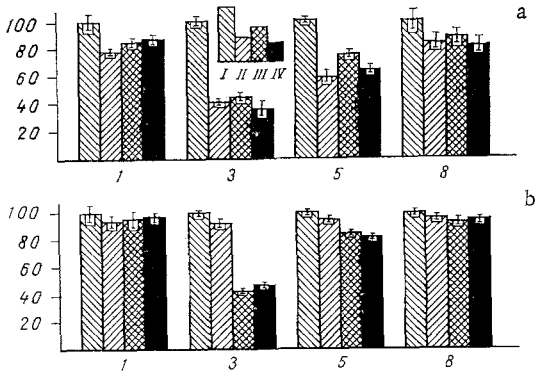

Fig. 1. Transketolase activity in liver (a) and brain (b) tissues of albino mice at different times of investigation after injection of HT (II), HTCP (III), and HTCPB (IV) in % of control (I). Abscissa, time (in days); ordinate, transketolase activity (in % of control).

reason for their higher toxicity than that of HT.

The suggested compounds can thus be used successfully as preparations specifically inhibiting the functioning of the pentose cycle in nerve tissue at the transketolase level.

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RNA CONTENT IN STRUCTURES OF THE AUTONOMIC NERVOUS SYSTEM OF RABBITS IN ACUTE EMOTIONAL STRESS

A. V. Gorbunova, S. I. Kashtanov, and V. V. Portugalov

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Changes in protein metabolism in the extramural ganglia of the autonomic nervous system were demonstrated previously in rabbits in acute experimental stress. Since RNA plays a primary role in protein biosynthesis, it appeared important to study whether the RNA content changes in neurons of the parasympathetic ganglion nodosum and sympathetic stellate ganglion of rabbits with acute emotional stress.

EXPERIMENTAL METHOD

Emotional stress was induced in immobilized rabbits by simultaneous aperiodic stimulation of negative emotiogenic centers of the hypothalamus (ventromedial nuclei) and electrodermal stimulation in accordance with a specially developed stochastic scheme. The ventromedial hypothalamic nuclei were stimulated by bipolar nichrome electrodes, and electrodermal stimulation was carried out through steel needles inserted under the skin of one of the ani-

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