MECHANISM OF ACTION OF DELTA SLEEP-INDUCING PEPTIDE INJECTED AFTER L-DOPA

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The regulating action of peptides on metabolism of biologically active substances in the brain is mediated through the state of neurotransmitter systems. It cannot be exhibited when these are functioning normally, but has a more marked effect during changes in state of the bodily functions [1, 2]. Depending on the character of the experimental model, on the initial type of emotional-behavioral reactivity of the animal, and the dose and time of the investigation peptides exhibit a definite cytotropic action, which can be described as psychoactivating, tranquilizing, or antidepressive [3]. There is biochemical and physiological evidence of the regulatory effect of delta sleep-inducing peptide (DSIP) in various extremal states (hypoxia, alcoholic motivation, cold and emotional stress) [6, 7, 13, 15]. In this connection it is interesting to study the effect of this peptide during administration of drugs giving rise to psychopathological deviations in animals [8].

In this investigation the state of the neurotransmitter systems was assessed by the level of activity of enzymes involved in neurotransmitter utilization (monoamine oxidase, type A and B, acetylcholinesterase) in the sensomotor cortex and caudate nucleus of rabbits at the subcellular level, under the influence of DSIP, in an experimental model of enhanced, nonmotivated anxiety and aggression following administration of L-dopa [9, 10].

EXPERIMENTAL METHOD

Experiments were carried out on 20 animals (two groups): group 1 consisted of control rabbits weighing 1800-2000 g, of the chinchilla breed; group 2 consisted of experimental rabbits receiving L-dopa by intraperitoneal injection in a dose of 50 mg/kg body weight. The animals were used in the experiments 60 min after receiving a single injection. DSIP, synthesized at the M. M. Shemyakin Institute of Bio-organic Chemistry, Academy of Sciences of the USSR, was injected suboccipitally into rabbits of both groups in a dose of 50 μg/kg body weight, and the animals were decapitated 30 min later. The test object consisted of subfractions of "light" and "heavy" synaptosomes (C and D) and free mitochrondria (E) from the sensomotor cortex and caudate nucleus of rabbits of both groups. The protein concentration (by Lowry's method) and activity of acetylcholinesterase (AChE) and of the molecular isozymes of monoamine oxidase (MAO), type A (serotonin as the substrate) and type B (paranitrophenylethylamine as the substrate) were determined spectrophotometrically in these subfractions. The results of each series of experiments were subjected to statistical analysis and expressed in units of specific enzyme activity per milligram protein of each fraction and as the change, in %, of the test parameters.

EXPERIMENTAL RESULTS

The effect of DSIP on enzyme systems of neurotransmitter metabolism in different parts of the animal brain was demonstrated by the writer previously. It took the form of marked activation of type A MAO in subfractions of both brain structures studied and reciprocal inhibition of type B MAO activity in subfractions of the sensomotor cortex compared with normal. These changes were less marked in subfractions of the caudate nucleus and were

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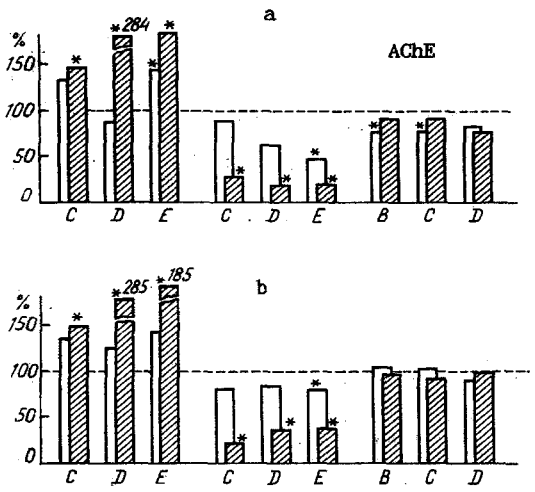

Fig. 1. Effect of DSIP on enzyme activity in subfractions of sensomotor cortex (a) and caudate nucleus (b) under normal conditions and after previous injection of L-dopa. C) "Light" synaptosomes, D) "heavy" synaptosomes, E) free mitochondria from cells. Unshaded columns – change in enzyme activity due to DSIP relative to control; shaded columns – change in enzyme activity under the influence of DSIP and L-dopa.

statistically significant only in subfractions of mitochondria (E) [4]. Under the influence of DSIP, preceded by a single injection of L-dopa, marked changes in MAO activity were obtained compared with their level under the influence of L-dopa, which was taken as 100%: type A MAO activity in subfractions of both formations increased by 150-300% and activity of type B MAO was inhibited by 60-80%. AChE activity was not statistically significantly changed under these conditions (Fig. 1).

Thus the action of the peptides on the state of neurotransmitter systems in a model of psychomotor excitation was considerably strengthened and was exhibited unequally in the case of different enzymes, evidence of the selective character of the effect.

Changes in activity of an enzyme may be due to several factors, and these data accordingly do not permit the direct action of the peptide on the enzyme to be confirmed. On the basis of data in the literature, interaction of this kind can be postulated not with the active center of the enzyme, but with its regulatory site, which may be one possible mechanism of the modulating effect of the peptide [3]. In the present experiments this applied primarily to activation of type A MAO and to inhibition of type B MAO, i.e., to inactivation of biogenic amines. Relative to AChE, whose activity was unchanged by the action of DSIP, it can be tentatively suggested that this peptide does not affect the mechanisms of cholinergic transmission.

DSIP as it were coordinates the functioning of different components of the monoaminergic systems. When the program of activity of the animal is disturbed, the effects of the regulatory peptides become stronger. Evidently under these conditions the peptides form a quick-acting adaptive system, realized by their neuroregulatory action. The effect of DSIP, especially when preceded by L-dopa, is thus manifested not as normalization of enzyme activity, but, on the contrary, as enhancement of changes in MAO activity compared with the control. Parameters of activity of the enzyme systems in this case adequately reflect the functional state of the animals. By changing the membrane potential in the synapses and conductance of neurons, peptides can regulate the effectiveness of action of mediators. A prolonged change in synaptic processes under the influence of regulatory peptides can lead to normalization of neuronal activity and of animal behavior [1, 11].

When the mechanism of action of regulatory peptides are discussed there is reason at present to suggest that peptides interact directly with receptors specific for other ligands, for example, for neurotransmitters.

The writer postulated previously that under the influence of DSIP something resembling inhibition of perception of external sensory stimuli takes place, which is evidently based on a mechanism of activation of the serotoninergic system [5].

After preliminary administration of L-dopa, which reduces the animal to a state of enhanced, nonmotivated anxiety, injection of DSIP has a regulating effect, as it were potentiating its own screening action, which is particularly clear in structures of the caudate nucleus.

Activation of type A MAO may be one of the possible mechanisms lying at the basis of the effect of DSIP. A considerable increase in the concentration of 5-hydroxyindoleacetic acid, the end product of serotonin metabolism, has been found in synaptosomes of the sensomotor cortex and, in particular, of the caudate nucleus, in the absence of any appreciable changes in the concentration of the neurotransmitter itself [13]. This effect may perhaps be determined by activation of serotonin synthesis, as has been demonstrated for tryptophan hydroxylase under the influence of a synthetic opioid analog [12].

Evidently the whole serotoninergic system can be activated by the action of DSIP. This activation, at the behavioral level, abolishes the animal's psychomotor excitation. There is evidence that serotonin is involved in the regulation of sexual behavior, of the sleep – waking cycle, and reactivity, and it may probably play definite role in the development of various clinical states, including affective disorders and depression [14].

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