STIMULATION OF ADENYLATE DEAMINASE ACTIVITY BY SEROTONIN

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After a single intraperitoneal injection of serotonin into rats adenylate deaminase activity in the mitochondrial fraction of the liver was stimulated. The conditions under which a twofold increase in the deamination of AMP occurred, after serotonin administration, were determined. Preliminary blocking of monoamine oxidase activity did not prevent this effect of serotonin.

KEY WORDS: serotonin; adenylate deaminase; monoamine oxidase; liver mitochondria.

The mechanism by which enzyme activity is regulated by serotonin and the other biogenic amines has still received only a little study [4]; the effects ascribed to amines may be due in fact to the action of biogenic aldehydes and other compounds formed by their deamination [7, 12]. In the writers' investigations of deamination reactions of biogenic amines and also of nucleotides, a definite interconnection was found between the enzymes catalyzing these reactions [1, 6]. It is also known that serotonin (like many other biologically active compounds) activates adenylate kinase [5], an enzyme catalyzing the formation of cyclic adenosine-3'5'-monophosphate, the excess of which is hydrolyzed with the aid of phosphodiesterase to AMP, the substrate of adenylate deaminase. It can therefore be postulated that the administration of biogenic monoamines acting on the metabolism and content of nucleotides and evidently inducing adaptive changes in the activity and properties of monoamine oxidase (MAO) [10] would have a definite regulatory effect, in experiments in vivo, on adenylate deaminase activity.

To test this hypothesis the adenylate deaminase activity of the liver, into the tissue of which the exogenous amine penetrates freely, was studied after the parenteral administration of serotonin to rats.

EXPERIMENTAL METHOD

Solutions of serotonin creatinine-sulfate (Merck, West Germany) or serotonin adipinate (synthesized in the Department of Organic Chemistry, D. I. Mendeleev Institute of Chemical Technology) in 0.5 ml 0.05 M potassium-phosphate buffer, pH 7.4, were injected into fasting male rats (150-180 g body weight). Control rats received the same volume of the buffer solution. The methods of isolating the mitochondrial fractions and of determining their protein content and adenylate deaminase activity, estimated from the rate of liberation of ammonia during incubation of the mitochondria with AMP, were described earlier [1].

EXPERIMENTAL RESULTS AND DISCUSSION

After the parenteral injection of serotonin (as the creatinine-sulfate or adipinate) into the rats the adenylate deaminase activity of liver tissue homogenates was stimulated. Differential centrifugation of these homogenates [11] showed that after injection of serotonin the adenylate deaminase activity in fact increased in the mitochondrial fraction and was highest (twice the control level) after intraperitoneal injection of 0.15 mmole serotonin per kilogram body weight (Fig. 1, II) and 8 h after the moment of the injection (Fig. 2, III).

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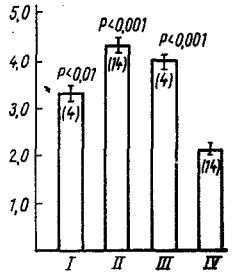

Fig. 1

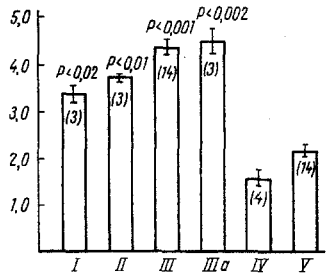

Fig. 2

Fig. 1. Stimulation of adenylate deaminase activity of rat liver mitochondria 8 h after a single intraperitoneal injection of serotonin creatinine-sulfate. Abscissa – doses of serotonin creatine-sulfate (in mmoles/kg): I) 0.075; II) 0.15; III) 0.225; IV) control. Ordinate – rate of deamination of AMP (in nmoles ammonia liberated per minute per milligram protein). Mean values (M ± m) are shown. Number of experiments in parentheses.

Fig. 2. Stimulation of adenylate deaminase activity of rat liver mitochondria at different times after serotonin administration (0.15 mmole/kg body weight). Abscissa – time after injection of serotonin: I) 2 h; II) 5 h; III) 8 h; IIIa) 1 h before receiving the serotonin the rats were given an intraperitoneal injection of pargyline (110 mg/kg) in 0.5 ml of neutralized aqueous solution; IV) 16 h; V) control. Remainder of legend as in Fig. 1.

Preliminary administration of the MAO inhibitor pargyline (N-methyl-N-benzylpropinylamine hydrochloride) to the rats in a dose producing considerable inhibition of the deamination not only of tyramine but also of serotonin [8, 13] did not prevent the stimulation of adenylate deaminase activity observed after the injection of serotonin (Fig. 2: compare III and IIIa). These results indicate that the effect of serotonin on the adenylate deaminase activity of the liver mitochondria, unlike certain previously studied effects [3, 9] of biogenic amines on γ-amylase (acid α-glucosidase) activity, is unconnected with the formation of serotonin deamination products.

Evidently not only serotonin but also many compounds related to it can stimulate the adenylate deaminase activity of the mitochondria, but the optimal conditions for the manifestation of this effect differ considerably, depending on the chemical structure of the compounds.

An increase in the rate of deamination of AMP in the mitochondria is evidently accompanied by uncoupling of tissue oxidation and oxidative phosphorylation. Uncoupling agents with different chemical structures are known to stimulate adenylate deaminase activity in bovine liver mitochondria [2]. Loss of ATP in the mitochondria could limit the formation of cyclic adenosine-3',5'-monophosphate, through which the amines exert their action on the functions of many enzyme systems [5]. Stimulation of adenylate deaminase activity after administration of amines in vivo could therefore play an important role in limiting the possible toxic effect of the exogenous amine through limitation of the formation of cyclic adenosine-3',5'-monophosphate.

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