SPECIFICITY AND MECHANISM OF STIMULATION OF ADENYLATE DEAMINASE ACTIVITY BY SEROTONIN

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The adenylate deaminase activity of the mitochondrial fraction of rat liver was stimulated in vivo not only by serotonin (5-HT) or other biogenic and synthetic indolylalkylamines, but also by phenyl- and imidazolealkylamines. 5-HT also stimulated adenylate deaminase activity of the liver mitochondria of CBA mice. Actinomycin D or cycloheximide, inhibitors of protein biosynthesis, prevented the stimulation of adenylate deaminase activity by 5-HT. Theophylline, a phosphodiesterase inhibitor, gave a similar effect only in the presence of a high degree of stimulation of adenylate deaminase activity.

KEY WORDS: serotonin; adenylate deaminase; cycloheximide; actinomycin D; theophylline.

A previous investigation [1] showed that adenylate deaminase activity is stimulated in the mitochondrial fraction of the liver after administration of serotonin (5-HT) to rats.

The object of this investigation was to reproduce this phenomenon by means of other amines in other species of animals and also when protein biosynthesis is blocked.

EXPERIMENTAL METHOD

The conditions of administration of 5-HT and determination of adenylate deaminase activity were described previously [1]. All preparations were injected intraperitoneally.

Actinomycin D was given as a single dose (1.5 mg/kg [2] 20 min before 5-HT), cycloheximide as four injections (each of 10 mg/kg [3], the first injection 20 min before 5-HT, then every 2 h thereafter), and theophylline as two injections (each of 75 mg/kg [4], the first injection 20 min before 5-HT, the second 4 h after injection of 5-HT).

EXPERIMENTAL RESULTS AND DISCUSSION

Stimulation of adenylate deaminase activity in the liver was well marked 8 h after injection of 5-HT both into rats (noninbred or of the August strain) and into CBA mice; however, the maximal effect in mice was produced by a dose of the amine 10 times higher than in rats (Table 1). Besides 5-HT, other natural or synthetic indolylalkylamines, as well as phenyl- and imidazolealkylamines tyramine and histamine, stimulated adenylate deaminase activity, but the optimal conditions for the obtaining of this effect differed with different amines (Table 1).

Blocking protein biosynthesis with actinomycin D or cycloheximide prevented the stimulation of adenylate deaminase activity by 5-HT (Table 2); theophylline, a phosphodiesterase inhibitor, produced a

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TABLE 1. Stimulation of Adenylate Deaminase Activity of Mitochondrial Fraction of Liver after a Single Intraperitoneal Injection of Amines (M±m)

Amine	Dose (in mmoles/kg)	Species of animal	Time after injection (in h)	Stimulation of AMP deamination (in % of control, without amines)	p*
Serotonin creatinine sulfate	0,15	August rats	8	173±10,2 (6)	<0,001
The same	1,50	CBA mice	8	153±12,6 (4)	<0,01
» »	0,15	Noninbred rats	8	203±7,9 (14)	<0,01
Tryptamine·HCl	0,30	The same	8	161±2,4 (3)	<0,01
5-Methoxytryptamine·HCl	0,15	» »	8	150±7,4 (7)	<0,002
4,5-Benztryptamine·HCl	0,30	» »	8	193±9,2 (3)	<0,001
6,7-Benztryptamine·HCl	0,15	» »	8	136±1,9 (4)	<0,02
6-Methoxytryptamine·HCl	0,15	» »	1	126±6,4 (4)	<0,05
α-Methyltryptamine·HCl	0,075	» »	8	147±2,6 (3)	<0,002
Tyramine	0,60	» »	1	152±5,8 (4)	<0,001
Histamine	0,15	» »	8	153±4,6 (5)	<0,01

* Differences between values obtained after injection of amines (experiment) or physiological saline (control).

Legend. Number of experiments in parentheses. In the control, liberation of ammonia (in nmoles/min/mg protein) was 2.12±0.11 (14) in experiments with noninbred rats, 3.04±0.24 (4) in August rats, and 2.94±0.08 (5) in CBA mice.

TABLE 2. Prevention by Actinomycin D, Cycloheximide, or Theophylline of Stimulation of Adenylate Deaminase Activity of Mitochondrial Fraction of Rat Liver 18 h after a Single Intraperitoneal Injection of 0.15 mmole/kg Serotonin Creatinine Sulfate (M±m)

Series of expts.	Conditions	Number of expts.	Deamination of AMP (in nmoles ammonia/min/mg protein)	Ratio expt./control (degree of stimulation of AMP deaminase activ.)
I	Control	9	2,39±0,18 $P<0,001$	—
	5-HT	9	3,73±0,14	1,56
	Actinomycin D	4	2,57±0,03	—
	Cycloheximide	4	2,39±0,27	—
	Actinomycin D + 5-HT	7	2,89±0,17	—
	Cycloheximide + 5-HT	4	2,51±0,23	—
II	Control	4	1,75±0,17 $P<0,01$	—
	Experiment (5-HT)	4	3,36±0,21	1,92
	Control (theophylline)	5	2,44±0,21	—
	Experiment (theophylline + 5-HT)	4	2,24±0,17	0,92
III	Control	3	1,95±0,05 $P<0,002$	—
	Experiment (5-HT)	3	3,00±0,09	1,54
	Control (theophylline)*	5	2,44±0,21	—
	Experiment (theophylline + 5-HT)	3	3,31±0,10	1,41

* Identical with corresponding control to experiments of series II.

similar effect in only those rats in which adenylate deaminase activity was stimulated by a factor of 1.8-1.9 by 5-HT (Table 2).

Amines evidently stimulate adenylate deaminase activity because they stimulate the synthesis of the appropriate enzyme. Activation of adenylate cyclase by amines [5] may modify the ratio between the adenosine phosphates in favor of AMP [6], and this could stimulate adenylate deaminase synthesis. Theophyl-

line, which blocks the hydrolysis of cyclic adenosine-3',5'-phosphate to AMP [5], can prevent this process (Table 2). However, there is probably another and less effective (see Table 2) mechanism of stimulation of adenylate deaminase activity by amines.

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