THIAMINE ACCUMULATION INDUCED BY L-5-HYDROXY-TRYPTOPHAN IN RAT BRAIN

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Accepted May 8, 1973

It has been reported by Iwata et al. that the catecholamine contents in the brain, heart and spleen are increased in thiamine deficient rats, while the blood catecholamine is decreased (1, 2). An increase in the brain serotonin contents and decrease in the liver, stomach and blood serotonin contents have been found in the thiamine deficient rats by Kimura et al. and Itokawa et al. (3, 4). There is a concept that thiamine has a specific function in membrane transport in the nerve which is independent of its coenzyme role (5). Evidence for supporting this concept is the release of thiamine from the nerve preparation following electrical stimulation or application of neuroactive drugs (6). In this paper, effects of L-5-hydroxytryptophan (L-5HTP) on the brain thiamine level were studied and compared to those of L-dihydroxyphenylalanine (L-dopa).

Male Wistar rats, weighing 150-200 g, were maintained on a standard diet (CA-1, CLEA, Japan) with water ad libitum. Rats were administered i.p. L-5HTP (Kyowa Hakko) and L-dopa (Sānkyo) in doses of 1, 10 and 100 mg/kg. Drugs were suspended

REFERENCES

1) Koida, M. and Kaneto, H.: Folia pharmacol. jap. 68, 265P (1972) (in Japanese); 2) Nevo, A., de Vries, A. and Katchalsky, A.: Biochim. Biophys. Acta 17, 536 (1955); 3) Katchalsky, A., Danon, D. and de Vries, A.: Biochim. Biophys. Acta 33, 120 (1959); 4) Korn-guth, S.E. and Stahmann, M.A.: Cancer Res. 21, 907 (1961); 5) Ryp-P, H. J.-P.: Science 159, 390 (1968); 6) Mehrishi, J.N.: Europ. J. Cancer 5, 427 (1969); 7) Padawer, J.: J. Cell. Biol. 47, 352 (1970); 8) Martin, W.R.: Pharmacol. Rev. 19, 463 (1967); 9) Adler, T.K.: J. Pharmacol. exp. Ther. 140, 155 (1963); 10) Kaneto, H., Shimomura, K., Kamei, C. and Nakahashi, H.: Folia pharmacol. jap. 66, 487 (1970) (in Japanese)
in saline. The animals were sacrificed one hr after a single injection or one hr after the last of 7 daily injections. The brain and liver were removed and homogenized in 0.4 N perchloric acid for catecholamine assay or in 0.1 N hydrochloric acid for serotonin and thiamine assays. The amount of serotonin was estimated by the method of Bogdanski et al. (7) and catecholamines by the procedure of Anton and Sayre (8, 9). For fluorometric determination of thiamine, the alkaline cyanogen bromide method was used as described by Fujivara and Matsui (10).

Brain serotonin content was significantly increased one hr after a single i.p. injection of L-5HTP 100 mg/kg, but was not affected by L-5HTP in doses of 1 or 10 mg/kg. This elevation in the brain serotonin level was not enhanced by seven daily injections of L-5HTP. Brain thiamine content in the L-5HTP treated rats was increased in a dose-dependent manner. Seven daily injections of L-5HTP slightly enhanced the L-5HTP induced thiamine increase in the rat brain (Table 1). In the liver, L-5HTP induced an increase of serotonin but not thiamine.

| Treatment     | Serotonin Single inj. | Serotonin Daily inj. 7 days | Thiamine Single inj. | Thiamine Daily inj. 7 days |
|---------------|------------------------|------------------------------|----------------------|-----------------------------|
| None          | 0.50±0.02 (5)†         | 3.13±0.06 (17) µg/g         |                      |                              |
| L-5HTP 1 mg/kg | 0.46±0.03 (5)          | 0.56±0.02 (5)               | 3.17±0.15 (5)       | 3.35±0.07 (5)               |
| L-5HTP 10 mg/kg | 0.58±0.03 (5)         | 0.56±0.02 (5)               | 2.95±0.20 (5)       | 3.73±0.10 (5)               |
| L-5HTP 100 mg/kg | 1.83±0.07 (5)**       | 1.91±0.15 (5)**             | 3.69±0.35 (5)**     | 4.12±0.07 (5)**             |

† Mean ± S.E. (number of rats)
Significant difference from control value using the Student’s t-test; *P<0.05, **P<0.01

| Treatment     | Dopamine | Noradrenaline | Thiamine |
|---------------|----------|---------------|----------|
| None          | 0.86±0.04 (9)† | 0.40±0.04 (4) | 3.13±0.06 (17) µg/g |
| L-dopa 1 mg/kg | 1.82±0.29 (4)** | 0.52±0.03 (5)* | 2.84±0.25 (5) |
| L-dopa 10 mg/kg | 1.83±0.23 (5)** | 0.48±0.09 (5) | 3.13±0.11 (4) |
| L-dopa 100 mg/kg | 3.52±0.33 (11)** | 0.49±0.02 (5)* | 2.67±0.11 (17)** |

† Mean ± S.E. (number of rats)
Significant difference from control value using the Student’s t-test; *P<0.05, **P<0.01

The accumulation of brain dopamine without that of noradrenaline was observed in the L-dopa treated rats. On the other hand, the brain thiamine content was slightly decreased in this group of rats (Table 2). Liver catecholamines were markedly increased only in the L-dopa 100 mg/kg treated rats among the three groups and the thiamine content remained unchanged.

The free and total thiamine in brain and liver of the 5HTP treated rats were also determined. The ratio of free thiamine to total thiamine in the brain of the L-5HTP treated rats and the control rats was 5.5% and 5.3% respectively. Ratio in the liver was 3.6%
and 3.5%. It is therefore suggested that most of the increased thiamine induced by L-5HTP is the phosphorylated form and presumably binds to tissue protein as the usual tissue thiamine.

Possible interpretations for a dose-dependent increase of brain thiamine induced by L-5HTP are: 1) an increase of thiamine uptake into the brain, 2) acceleration of the synthesis of thiamine pyrophosphate from thiamine and the binding of thiamine to tissue protein, 3) an inhibition of thiamine pyrophosphatase which converts thiamine pyrophosphate to free thiamine. Since increase of liver thiamine was not induced by L-5HTP injection to rats, it is most probable that the uptake process of thiamine into the brain is accelerated by L-5HTP itself, serotonin converted from L-5HTP or serotonin metabolites.

On the other hand, a slight decrease in brain thiamine induced by L-dopa may be a non-specific effect as this decrease is small and not dose-dependent. A full paper including data is in preparation.

REFERENCES
1) IWATA, H., WATANABE, K., NISHIKAWA, T. AND OHHASHI, M.: Europ. J. Pharmacol. 6, 83 (1969); 2) IWATA, H., FUJIMOTO, S., NISHIKAWA, T. AND HANO, K.: Experientia 24, 378 (1968); 3) KIMURA, M., IKEDA, H., ITOKAWA, Y. AND TANAKA, C.: Vitamins 45, 1 (1972); 4) ITOKAWA, Y., TANAKA, C. AND KIMURA, M.: Metabolism 21, 375 (1972); 5) VON MURALT, A.: Nature 154, 767 (1944); 6) ITOKAWA, Y., SCHULZ, R.A. AND COOPER, J.R.: Biochim. Biophys. Acta 266, 293 (1972); 7) BOGDANSKI, D.F., PLETSCHER, A., BRODIE, B.B. AND UDENFRIEND, S.: J. Pharmacol. exp. Ther. 117, 82 (1956); 8) ANTON, A.H. AND SAYRE, D.F.: J. Pharmacol. exp. Ther. 145, 326 (1964); 9) ANTON, A.H. AND SAYRE, D.F.: J. Pharmacol. exp. Ther. 138, 360 (1962); 10) FUJIWARA, M. AND MATSUI, K.: Analyt. Chem. 25, 810 (1953)