

INHIBITION OF ADAPTIVE FORMATION OF TRYPTOPHAN PEROXIDASE IN RATS BY ETHIONINE

by

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KNOX has shown the parenteral administration of L-tryptophan to rats to effect, within 3 to 5 hours, a 10-fold increase in the tryptophan peroxidase activity of liver homogenates¹. The rapid nature of this response and the specificity of the provoking stimulus strongly indicated that this was an example of the adaptive control of enzyme formation. It is in view of these results that the question of mechanism arises; namely, does this adaptation phenomenon represent the alteration of pre-existing protein molecules or does it represent a form of a *de novo* synthetic process involving constituent amino acids. We have investigated this question by using DL-ethionine to block the utilization of methionine. If the adaptive formation of tryptophan peroxidase represents a *de novo* synthesis, the administration of ethionine prior to tryptophan injection should have an inhibitory effect; should the mechanism of protein alteration be operative, this analog should not be inhibitory.

Female Sprague-Dawley rats, weighing approximately 200 grams, were injected with 0.77 mM of DL-ethionine (E) in divided doses over a period of several hours. Two hours before sacrifice 1 mM of L-tryptophan (T) was administered intraperitoneally. A control series, in which saline was substituted for ethionine, was similarly treated. Upon sacrifice the livers were rapidly removed and homogenates were assayed for tryptophan peroxidase activity¹. Since the specificity of this phenomenon could only be demonstrated in the adrenalectomized animal¹, a second set of experiments was devised in order to demonstrate the reversibility of this inhibition by L-methionine (M). The results are presented in Table I.

TABLE I

<i>Treatment of rats</i>	<i>Number of animals in each experiment</i>	<i>μM Kynurenine formed per h per g liver</i>	<i>% inhibition of adaptation</i>
Intact			
1. Control + T, 1 mM	4	1.65	27
2. E, 0.77 mM + T, 1 mM	4	1.21	
Adrenalectomized			
1. T, 1 mM	3	0.43	42
2. E, 0.77 mM + T, 1 mM	3	0.25	
3. E, 0.77 mM + M, 0.77 mM + T, 1 mM	3	0.34	
4. E, 0.77 mM	3	0.03	

E = ethionine; T = tryptophan; M = methionine

It is apparent that in the intact rat ethionine administration inhibited the increase in tryptophan peroxidase activity which was seen in the control series. Furthermore, in the adrenalectomized animals, it can be seen that ethionine administration alone caused no significant change in enzyme activity and that administering methionine simultaneously with ethionine effected a partial reversal of inhibition. These results support the following hypothesis: ethionine inhibits the adaptive production of tryptophan peroxidase in rat liver by interfering with the utilization of methionine for enzyme synthesis. This work was completed prior to the publication of the investigations of HALVORSON AND SPIEGELMAN² and constitutes a confirmation, in mammals, of their observations using yeast.

REFERENCES

- ¹ W. E. KNOX, *Brit. J. Exptl Path.*, 32 (1951) 462.
- ² H. O. HALVORSON AND S. SPIEGELMAN, *J. Bact.*, 64 (1952) 207.

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