DYNAMICS OF URINARY EXCRETION OF 5-HYDROXYINDOLE-3-ACETIC ACID BY RATS DEVELOPING PRIMARY AND SECONDARY AVITAMINOSIS K

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The development of avitaminosis K in rats produced either by a vitamin K deficiency in the diet or by division of the bile duct, was accompanied by a sharp decrease in the daily excretion of 5-hydroxyindole-3-acetic acid in the urine. These disturbances disappeared or were considerably reduced when the vitamin K substitute vikasol was given to animals with avitaminosis K.

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A state of avitaminosis K has been shown to be accompanied by changes in the serotonin content in certain tissues and by an increase in the sensitivity of some smooth-muscle organs to it [2-4]. The results of these investigations could be interpreted more fully if the dynamics of excretion of 5-hydroxyindole-3-acetic acid (5HIA) were studied during the development of avitaminosis K in animals. The character of metabolism of this amine can be revealed only by combined determinations of serotonin and of its principal catabolite, 5HIA.

In the present investigation the dynamics of urinary excretion of 5HIA was studied in rats during the development of primary and secondary avitaminosis K.

EXPERIMENTAL METHOD

Experiments were carried out on 16 male albino rats weighing 150-240 g, with a similar level of 5HIA excretion. 5HIA in the 24 h urine was determined by the method of Udenfriend and co-workers [11]. The 24 h excretion of 5HIA was calculated per 100 g body weight.

The dynamics of 5HIA excretion were studied in 8 rats during the development of secondary avitaminosis K produced by ligation and division of the common bile duct, before the ligation operation, and during administration (subcutaneously, daily) of vikasol in a dose of 2 mg/100 kg body weight.

Primary avitaminosis K was produced in another 8 rats by keeping them in special metabolic cages to prevent coprophagy and on a diet free from vitamin K [9]. In rats with primary avitaminosis K the excretion of 5HIA was determined initially, during development of avitaminosis K, and after addition of vikasol to the vitamin K-free diet at the rate of 10 mg vikasol per 100 g diet.

Development of avitaminosis K was judged from a decrease in prothrombin activity of the blood. Blood was taken from the caudal vein and the determination was carried out by Lehmann's method [1]. In the experiments a lowering of the prothrombin activity of the blood to 20-30% was achieved.

EXPERIMENTAL RESULTS

The experiments showed that the development of avitaminosis K by means of a diet deficient in vitamin K or of division of the common bile duct is characterized by significant differences in the daily excretion of 5HIA in the urine.

Primary Avitaminosis K. The initial daily excretion of 5HIA was determined twice for each animal. The content of 5HIA in the 24 h urine of normal rats was 6.21 ± 0.2 μg/100 g weight, in agreement with figures given by other workers [5, 7, 8]. Keeping the rats on a diet deficient in vitamin K led to a gradual

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decrease in the 5HIA excretion in the urine. This decrease became significant (4.12 ± 0.32 μg/100 g body weight; $P < 0.001$) by the 21st day of keeping the rats on the vitamin K-deficient diet. By the 31st day the 5HIA excretion was 38.9% of its initial value. Addition of vikasol to the diet restored the original level of 5HIA excretion by the 7th day (6.31 ± 0.01 μg/100 g body weight).

Secondary Avitaminosis K. As in the preceding series of experiments, the original 5HIA excretion was determined twice for each rat before ligation of the bile duct. From the 11th day after ligation of the bile duct, a sharp increase in the excretion of 5HIA was observed, reaching 15.9 ± 1.45 μg/100 g body weight by the 14th day. Next followed a marked decrease in 5HIA excretion, falling to only 1.62 ± 0.08 μg/100 g, or 25.2% of the original level of 5HIA excretion, by the 28th day. After development of avitaminosis K for a period of 28 days, the rats of this group received vikasol by subcutaneous injection in a dose of 2 mg/100 g body weight. On the 5th day of administration of vikasol, the 5HIA excretion had not yet returned to its preoperative level, but it showed a statistically significant increase (to 5 ± 0.28 μg/100 g body weight) compared with the value of the 28th day of development of avitaminosis K ($P < 0.001$).

Consequently, in both primary and secondary avitaminosis K, in the period of intensive decrease of the clotting power of the blood (decrease in prothrombin activity to 20-30%), a disturbance of serotonin metabolism is observed. The excretion of 5HIA in the urine falls considerably when the body is deficient in vitamin K. Presumably the reason for this lies in inhibition of serotonin biosynthesis in animals with avitaminosis K. This hypothesis is confirmed by the results of our previous investigations [3] showing that avitaminosis K leads to a reduction in the serotonin content in the tissues, while administration of vikasol to animals with avitaminosis K or loading of intact animals with vitamin K causes an increase in serotonin content in the tissues above the initial level. Moreover, during analysis of the experimental results, allowance must be made for the formation of serotonin reserves by the tissues. We have as yet no direct proof that the binding of serotonin by the tissues is weakened in animals with avitaminosis K, but this view is supported by the fact that ATP plays an essential role in the fixation of serotonin [10], and we have found that biosynthesis of ATP is inhibited in avitaminosis K [6].

LITERATURE CITED

1. V. P. Baluda, V. N. Malyarovskii, and I. A. Oivin, Laboratory Methods of Investigation of the Clotting System of the Blood [in Russian], Moscow (1962), p. 93.
2. N. G. Bogdanov, Z. V. Urazaeva, and N. I. Yalovaya, Abstracts of Scientific Proceedings of the 10th Congress of the I. P. Pavlov All-Union Physiological Society [in Russian], Vol. 2, No. 1, Moscow-Leningrad (1964), p. 107.
3. N. G. Bogdanov and B. V. Polushkin, Byull. Éksperim. Biol. i Med., No. 11, 28 (1965).
4. N. G. Bogdanov and B. V. Polushkin, Vopr. Pitaniya, No. 4, 36 (1966).
5. Z. A. Popenenkova and D. A. Andreeva, Byull. Éksperim. Biol. i Med., No. 1, 48 (1966).
6. N. I. Yalovaya and N. G. Bogdanov, Abstracts of Proceedings of an All-Union Conference on Muscle Biochemistry [in Russian], Moscow-Leningrad (1966), p. 157.
7. G. Bertaccini and M. B. Nobili, Brit. J. Pharmacol., 17, 519 (1961).
8. V. Erspamer, J. Physiol. (London), 127, 118 (1955).
9. M. S. Mameesh and B. C. Johnson, Proc. Soc. Exp. Biol. (New York), 101, 467 (1959).
10. W. H. Prussoff, Brit. J. Pharmacol., 15, 520 (1960).
11. S. Udenfriend, E. Titus, and H. Weissbach, J. Biol. Chem., 216, 499 (1955).