EFFECT OF THE CARCINOGENIC TYROSIN METABOLITE, p-HYDROXYPHENYLLACTIC ACID, ON ASCORBIC ACID LEVELS IN MOUSE ORGANS AND BLOOD

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In connection with the possible etiologic role of endogenous carcinogens the study of the concrete mechanism of their formation and accumulation in man and animals is of the utmost interest.

Information has now been obtained on the important role of vitamin C as an activator of p-hydroxyphenylpyruvate hydroxylase, one of the key enzymes of tyrosine metabolism [6]. It has been shown [4] that the ascorbic acid (AA) concentration is sharply depressed in leukocytes and serum of patients with various forms of leukemias. Substantial disturbances of tyrosine metabolism also have been found, accompanied by accumulation of the endogenous carcinogen p-hydroxyphenyllactic acid (HPLA) in patients with hemoblastoses [2].

Since the causes of the AA deficiency in leukemic patients are not clear, it was decided to study whether the endogenous carcinogen HPLA, formed in large quantities and with great constancy by cancer patients, affects the basal AA level.

EXPERIMENTAL METHOD

Vaccinated noninbred male mice weighing 20-25 g were used. HPLA was injected intraperitoneally in a dose of 100 or 300 mg/kg in the form of aqueous solutions at pH 7.0, neutralized with 1 N NaCl. The AA concentration in the mouse plasma and organs was determined 18 h after the injection by the method in [5]. To determine the AA concentration in the blood plasma or organs, 0.2 ml of plasma or 50 mg of tissue was taken respectively. The results were subjected to statistical analysis by the method in [1].

The HPLA was synthesized at the D. I. Mendeleev Chemical Technology Institute, in the Department of Organic Chemistry (Professor N. N. Suvorova). The remaining reagents were of the analytically pure or chemically pure grades.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that 18 h after injection of HPLA into mice in a dose of 100 or 300 mg/kg the AA concentration fell in the liver by 15.0 and 25.4%, in the adrenals by 9.1 and 23.6% ($P > 0.1$), and in the blood serum by 22.3 and 39.9%, respectively. Thus the carcinogenic tyrosine metabolite HPLA, in a dose of 300 mg/kg, reduces the AA concentration significantly in the organs and blood of mice.

AA plays an important role in tyrosine metabolism on the principal catabolic pathway to fumaric and acetoacetic acids; the factors causing a fall of the AA concentration may therefore lead to serious disturbances of tyrosine metabolism, with the formation of its carcinogenic metabolites and, in particular, of HPLA.

The phenomenon of the fall in AA concentration in the organs and blood of mice discovered after injection of the carcinogenic tyrosine metabolite HPLA, and data on induction of tyrosine aminotransferase by this carcinogenic tyrosine metabolite obtained previously [3]

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TABLE 1. Effect of HPLA on AA Concentration in Organs and Blood Plasma of Mice

Substance	Dose, mg/kg	AA concentration, mg % ($\bar{x} \pm t \cdot S_{\bar{x}}$ at P = 0.05 level)			Decrease compared with control, %		
		liver	adrenals	blood plasma	liver	adrenals	blood plasma
Control	—	60,7±2,7	210,1±35,3	1,5±0,4	—	—	—
HPLA	100	51,6±4,4	190,9±22,2	1,2±0,2	15,0 $P>0,01$	9,1 $P<0,1$	22,3 $P<0,1$
	300	45,3±8,8	160,5±45,0	0,9±0,3	25,4 $P<0,001$	23,6 $P<0,002$	39,9 $P<0,002$

suggest that the formation of HPLA by man and animals and its accumulation in the body may take place on account of the functioning of two interconnected mechanisms: 1) intensification of the block at the ascorbate-dependent p-hydroxyphenylpyruvate hydroxylase level under conditions of AA deficiency, and 2) activation of tyrosine metabolism along the path of HPLA formation from p-hydroxyphenylpyruvate under conditions of induction of tyrosine aminotransferase by HPLA. A combination of these two mechanisms leads to acceleration and further accumulation of the carcinogenic tyrosine metabolite, which reduces the AA concentration even more and causes further activation of these two mechanisms in a closed cycle. To prevent the formation of the endogenous carcinogen HPLA, treatment with increased doses of AA is evidently necessary.

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