INDUCTION OF TYROSINE AMINOTRANSFERASE BY CARCINOGENIC METABOLITES OF TRYPTOPHAN AND TYROSINE

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The effect of endogenous carcinogenic substances (3-hydroxyanthranilic and parahydroxyphenyllactic acids) and their noncarcinogenic analogs (anthranilic and phenyllactic acids) on tyrosine aminotransferase activity was compared in rat liver. The carcinogenic metabolites were found to have the property of sharply inducing activity of the enzyme. This phenomenon and existing data on the role of the increase in tyrosine aminotransferase and tryptophan oxygenase activity in tyrosine and tryptophan catabolism in the direction of the possible formation of carcinogenic metabolites suggest that there is a "chain reaction" of accumulation of endogenous carcinogens in the body.

KEY WORDS: endogenous carcinogens; tyrosine aminotransferase; tyrosine; tryptophan.

The carcinogenic activity of some tryptophan metabolites has been known for a long time. The highly carcinogenic properties of some tyrosine metabolites have been established more recently. The excretion of phenolic acids in patients with leukemias has been shown to correspond to the carcinogenic activity of these acids. The substance with the highest activity is parahydroxyphenyllactic acid, the excretion of which is increased in all patients with various types of leukemias [3, 5].

From the standpoint of the possible etiological role of endogenous carcinogenic substances investigations into the concrete mechanisms of their formation and accumulation in man and animals are of fundamental importance. Information on the mechanisms of disturbances of particular enzyme systems and of the coenzyme functions of vitamins, leading to the accumulation of carcinogens during tryptophan catabolism via the kynurenin pathway and tyrosine catabolism to fumaric or acetoacetic acid has now been obtained [2, 4]. It can be concluded from the analysis of these data that the activity of tryptophan oxygenase and tyrosine aminotransferase has a role of special importance in the phenomenon of increased catabolism of tryptophan and tyrosine in the direction of the possible formation of carcinogenic metabolites from them.

Experiments showing the strong inducing effect of 3-hydroxyanthranilic, xanthurenic, and quinolinic acids, which possess carcinogenic properties, on the activity of tryptophan oxygenase and tyrosine aminotransferase are particularly interesting. Anthranilic acid, which is carcinogenically inert, did not cause the activity of these enzymes to increase [6].

With this information in mind a comparative study was made of the effect of two metabolites of tryptophan and tyrosine, mainly 3-hydroxyanthranilic and parahydroxyphenyllactic acids, with high carcinogenic activity, was compared with that of anthranilic and phenyllactic acids, which are carcinogenically inert, on the activity of tyrosine aminotransferase.

EXPERIMENTAL METHOD

Experiments were carried out during the morning (9 a.m.-1 p.m.) on noninbred male albino rats weighing 80-100 g. The substances for study were injected intraperitoneally into the animals 4 h before sacrifice in a volume of 2 ml as a neutral solution or suspension. Control rats received an intraperitoneal of 2 ml of 0.9% NaCl solution.

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TABLE 1. Effect of Some Tryptophan Metabolites and Phenolic Acids on Tyrosine Aminotransferase Activity in Rat Liver

Substance injected and dose	No. of animals	Activity, of enzyme, e.u. (M ± tm, P = 0.05)	Induction of enzyme, % (mean values)
Control	4	71±31	
Anthranilic acid, 250 mg/kg	4	134±83	89 ($P<0,001$)
3-Hydroxyanthranilic acid, 250 mg/kg	4	218±57	207 ($P<0,001$)
Phenyllactic acid: 250 mg/kg	4	59±24	−17 ($P>0,5$)
750 mg/kg	3	63±23	−11 ($P>0,5$)
Parahydroxyphenyllactic acid: 250 mg/kg	4	77±27	8 ($P>0,5$)
750 mg/kg	3	193±24	172 ($P<0,001$)

Tyrosine aminotransferase activity was determined in liver tissue homogenate by a colorimetric method [1]. The unit of enzyme activity was taken to be the formation of 1 μmole parahydroxyphenylpyruvate during incubation for 1 h at 37°C. Activity of the enzyme was expressed in extinction units (e.u.) per gram liver tissue. The degree of induction of tyrosine aminotransferase activity was determined from the increase in activity of the enzyme compared with the control, expressed as a percentage.

The following reagents were used: anthranilic, 3-hydroxyanthranilic, phenyllactic, and parahydroxyphenyllactic acids (synthesized in Professor N. N. Suvorov's laboratory at the D. I. Mendeleev Chemical Technological Institute); sodium diethyldithiocarbamate ($C_5H_{10}NS_2Na \cdot 3H_2O$), analytically pure and recrystallized from ethyl alcohol with ether (USSR product); trichloroacetic acid (Xenon Lodz, Poland). The other reagents were all of the analytically pure and chemically pure grades.

EXPERIMENTAL RESULTS AND DISCUSSION

Activities and levels of induction of tyrosine aminotransferase under the influence of the test substances are given in Table 1. Clearly tyrosine aminotransferase activity differed significantly under the influence of noncarcinogenic and carcinogenic compounds. For instance, anthranilic acid, a noncarcinogenic tryptophan metabolite, although it increased the activity of the enzyme, did so much less than the carcinogenic metabolite 3-hydroxyanthranilic acid. Very demonstrative differences were found through the action of phenolic acids, and in this case a threshold effect was observed. In a dose of 250 mg/kg no changes in activity of the enzyme were found, but with an increase in the dose up to 750 mg/kg, phenyllactic acid (a noncarcinogenic metabolite) as before did not affect the enzyme activity, whereas parahydroxyphenyllactic acid (a highly carcinogenic metabolite) almost doubled its activity.

Comparison of the results of these experiments with those obtained by Hardeland [6] reveals a very striking fact regarding the induction by carcinogenic metabolites of tryptophan and tyrosine of the key enzymes responsible for the catabolism of these amino acids via the formation of those same carcinogenic metabolites. It is also interesting to note that cross induction of tyrosine aminotransferase and tryptophan oxidase can take place by carcinogenic metabolites of tryptophan and tyrosine. The observed coupling of disturbances of tryptophan and tyrosine metabolism in patients with leukemias may correlate to some degree with this last phenomenon [2].

A unique "chain reaction" thus arises: Carcinogenic metabolites of tryptophan or tyrosine, once formed, increase the activity of tyrosine aminotransferase and tryptophan oxygenase, so that the conditions are created for the formation of more of the same carcinogenic metabolites. This must lead to considerable accumulation of the carcinogens.

The complex mechanisms of formation and accumulation of endogenous carcinogens are not, of course, confined to the phenomenon described above. Investigations of these mechanisms are continuing and the results of the present investigation merely emphasize once again how complex and at times unexpected the individual stages and pathways of formation of endogenous carcinogens may be.

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EFFECT OF RESTORATION OF VISUAL IMPULSES ON ENERGY METABOLISM IN THE VISUAL SYSTEM OF THE BRAIN IN DARK-REARED ANIMALS

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Changes in the rate and character of energy metabolism in the mitochondria of the visual system of the brain induced by prolonged visual deprivation (from birth until the age of 2.5 months) were shown to be reversible. The degree of normalization differed for mitochondria of the visual cortex and superior colliculus. During the 2-week recovery period (when the animal was transferred to ordinary conditions of illumination) the rate of these processes increased, when glutamic acid was used as the substrate, and reached the control level or exceeded it somewhat. The rate of electron transport in the cytochrome c–cytochrome oxidase section of the succinate oxidase oxidation chain, which was increased during deprivation, diminished in the recovery period and came close to the control level. The role of specific impulse activity in the formation of mitochondrial energy processes in the brain with age is discussed.

KEY WORDS: mitochondria of rabbit brain; postnatal development; visual deprivation; bioenergetic processes.

Exclusion of visual afferentation before completion of the structural, functional, and biochemical differentiation of the visual system leads to physiological, morphological and biochemical changes in that system at the tissue, cellular, and subcellular levels [1, 2, 6-8]. The writer has shown that mitochondria of the visual system of the brain in animals reared in the dark until the age of 2.5 months differ in several indices of their energy metabolism from controls. The differences are connected with changes in the relative importance of individual substrates in the energy balance and, in particular, an increase in the role of succinic acid and an increase in the efficiency of the final section of the succinate oxidase oxidation chain. The fact that such changes in the mitochondria of the visual system exceed those found in the mitochondria of other parts of the cortex has suggested an important role of visual afferentation in the formation of the energy metabolism of the developing brain [3].

The object of this investigation was to discover whether energy processes in the mitochondria of the visual system (visual cortex, superior colliculus, and, for comparison, the "remaining" cortex), if altered by light deprivation, can be restored to normal.

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