EFFECT OF CARCINOGENIC METABOLITES OF AROMATIC AMINO ACIDS ON OXIDATIVE PROCESSES IN LIPIDS IN VITRO AND IN VIVO

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As a result of disturbance of metabolism of aromatic amino acids in patients with leukemias and certain solid tumors, carcinogenic metabolites of tyrosine and serotonin are formed and accumulate in large quantities [8, 10]. One possible mechanism of the harmful action of carcinogens on the body is their effect on the lipid peroxidation (LPO) system and, in particular, on one parameter of that system, namely the antioxidative activity (AOA) of lipids, which is closely connected with the system of natural antioxidants. The value of AOA correlates with proliferative activity of the cells [3] and with the onset and growth of malignant neoplasms [1, 4-6]. In particular, it has been shown that exogenous carcinogens such as benzpyrene derivatives, o-aminoazotoluene, and benzanthracene, cause significant and regular changes in LPO, connected with changes in the morphological picture during carcinogenesis.

With this information in mind it was decided to compare the effect of metabolites of tyrosine and serotonin, namely p-hydroxyphenyl-lactic and 5-methoxyindolyl-3-acetic acids, with high carcinogenic activity [7, 9], and phenyl-lactic and 5-hydroxyindolyl-3-acetic acids, which are carcinogenically inert, on oxidative processes in lipids.

EXPERIMENTAL METHOD

Vaccinated noninbred male mice weighing 20-25 g were used. The compounds were injected in the form of aqueous solutions at pH 7.0, depending on the animal's body weight. To determine AOA of the lipids in the organs of control animals and after injection of the compounds, a methyl oleate model was used [2, 11]. The antioxidative properties of the lipids were assessed by their effect on the oxidation reaction of the methyl ester of oleic acid at 54°C. AOA was calculated by the equation:

$$\text{AOA} = \frac{\tau - \tau_0}{C} = \frac{\Delta\tau}{C},$$

where τ_0 and τ denote periods of induction of oxidation of pure methyl oleate and of methyl oleate with lipid extract respectively, and C the concentration of lipids in methyl oleate (in g/ml). To determine the antioxidative properties of the compounds themselves, the tyrosine and serotonin metabolites were dissolved in definite concentrations in methyl oleate and oxidation of the substrate and determination of AOA of the compounds were carried out by the method described above.

The p-hydroxyphenyl-lactic, 5-methoxyindolyl-3-acetic, and 5-hydroxyindolyl-3-acetic acetic acids were synthesized at the D. I. Mendeleev Chemical Technologic Institute in Professor N. N. Suvorov's Department. The remaining preparations were of the analytically pure or chemically pure grades.

EXPERIMENTAL RESULTS

The test substances, when introduced in equimolar concentrations (10^{-4} M) into the methyl ester of oleic acid, had different effects; the carcinogenic metabolites p-hydroxy-

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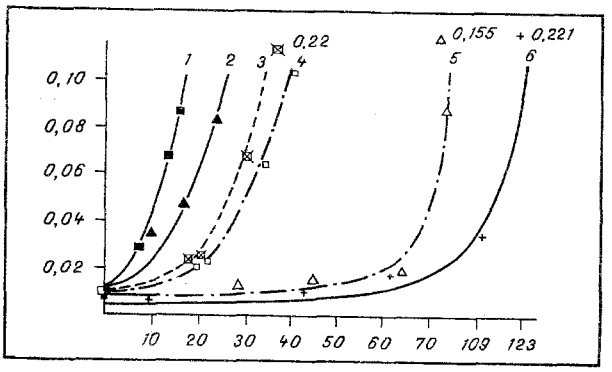

Fig. 1. Effect of carcinogenic metabolites of tyrosine and serotonin and their noncarcinogenic analogs on oxidative processes in lipids in experiments in vitro. Abscissa, incubation time (in h); ordinate, level of LPO products (in mmoles/g tissue). 1) 5-Methoxyindolyl-3-acetic acid, 2) p-hydroxyphenyl-lactic acid, 3) control, 4) phenyl-lactic acid, 5) 5-hydroxyindolyl-3-acetic acid, 6) ionol.

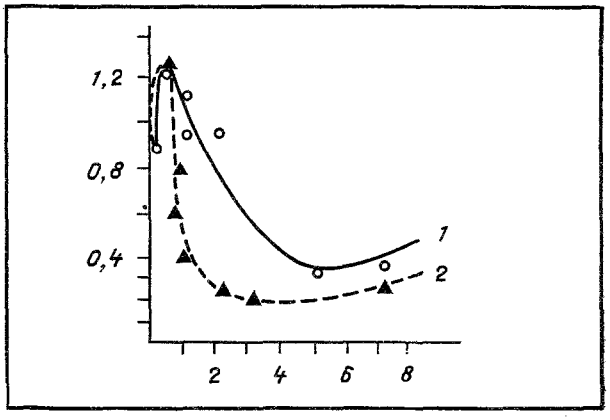

Fig. 2. Effect of p-hydroxyphenyl-lactic acid in doses of 100 (1) and 300 mg/kg (2), on AOA of mouse liver lipids. Abscissa, time after injection of compound (in days); ordinate, relative AOA (in relative units). AOA of control preparations taken as one relative unit.

phenyl-lactic and 5-methoxyindolyl-3-acetic acids accelerated oxidative processes whereas the noncarcinogenic analogs had either a weak oxidative (phenyl-lactic acid) or a significant antioxidative action (5-hydroxyindolyl-3-acetic acid), comparable with the effect of the known synthetic antioxidant ionol (Fig. 1). It was shown previously, on the same oxidative model in vitro [6], that carcinogenic derivatives of anthracene and o-aminoazotoluene have a weak antioxidant action, but their noncarcinogenic analogs have no effect on oxidation. Our results differ from those obtained in the investigations cited above and they indicate that carcinogens belonging to different classes have different effects on lipid oxidation in model systems.

On the basis of our results of experiments in vitro it might be expected that carcinogenic metabolites of tyrosine and serotonin would interfere with the course of oxidative reactions of lipids in the animals' liver and modify their rate substantially. We studied changes in AOA of mouse liver lipids after a single intraperitoneal injection of p-hydroxyphenyl-lactic acid in doses of 100 and 300 mg/kg (Fig. 2). It was found that 3-8 h after injection of the compound the value of AOA of the liver lipids was reduced by 20%. After 18 h AOA began to fall sharply, and after 2-5 days it was 2.5-5 times less than normal.

Comparison of our results with data in the literature on the effect of exogenous carcinogens on the AOA level of liver lipids [5] indicates a definite analogy between them. In fact, we also found that the changes in AOA under the influence of p-hydroxyphenyl-lactic acid take place in a complex series of stages, and this confirms the hypothesis put forward previously regarding the "bifunctional" character of the effect on AOA in vivo as an essential condition for the manifestation of carcinogenic activity. It can thus be stated that substances possessing carcinogenic properties differ in their effects on lipid oxidation in vitro; in vivo, however, a feature common to them is, probably, their ability to both raise and lower the AOA level of lipids in the organs and tissues.

We know that AOA of lipids depends directly on the content of natural antioxidants in the body. The results obtained in experiments in vivo indicate that the endogenous carcinogen p-hydroxyphenyl-lactic acid, in doses of 100 and 300 mg/kg, cause a sharp fall in the level of natural antioxidants in the liver after only 1-2 days, as is shown by the marked decrease in AOA of the liver lipids. This leads to acceleration of LPO and to the accumulation of toxic peroxides of unsaturated fatty acids. The use of natural and synthetic antioxidants or of substances raising the AOA level of the lipids, can evidently lead to normalization of LPO in the animal liver and can abolish the pro-oxidative action of p-hydroxyphenyl-lactic acid.

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