EFFECT OF HYPERCAPNIA ON TYROSINE AND TRYPTOPHAN METABOLISM

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UDC 612.398.192:[547.587.42+547.557].015.36-06:616.127.3

Experiments on rats showed that an increase in the CO_2 concentration in the inspired air (3.8%) leads to disturbances of tyrosine and tryptophan metabolism: Activity of tryosine aminotransferase and tryptophan oxygenase in the liver rises, the concentration of free tyrosine and of free total tryptophan in the blood serum falls, but the level of free tryptophan obtained by dialysis rises. The possible significance of these abnormalities in endogenous carcinogenesis is discussed.

KEY WORDS: hypercapnia; tyrosine; tryptophan; tyrosine aminotransferase; tryptophan; oxygenase.

During the metabolism of tyrosine and tryptophan in man and animals biologically active substances are formed, some of which are carcinogenic: p-hydroxyphenylpyruvic, p-hydroxyphenyllactic, and 3-hydroxyanthranilic acids, 3-hydroxykynurenin, etc. [1]. These metabolites may accumulate in the body in certain pathological states [2].

In this investigation the effect of hypercapnia on tyrosine and tryptophan metabolism was studied in order to discover whether the endogenous formation of the above-mentioned carcinogenic metabolites can take place.

EXPERIMENTAL METHOD

Experiments were carried out on 128 female albino rats. Hypercapnia was produced by ventilating special cages with air containing 1-5% CO_2. The CO_2 concentration in the atmosphere of the cages averaged 0.2% and 3.8% in different series of experiments. In the acute experiments the increased CO_2 concentration in the air was created once only, for 2, 4, and 8 h. In the chronic experiments it was maintained for 8 h daily for 3 weeks. The pH of the blood (micro-Astrup apparatus), the serum free tyrosine [11], and the activity of tyrosine aminotransferase (EC 2.6.1.5) [8] and tryptophan oxygenase (EC 1.13.1.12) [5] in the liver were determined. Free tryptophan in the serum was determined by the method of Spies and Chambers [9], but in samples of smaller volume. Dialysis was carried out during centrifugation of 4-5 ml serum in cellulose bags at 37°C for 5 h at 1500 rpm. The results of trial determinations agreed with data in the literature [4] obtained by a spectrofluorometric method.

EXPERIMENTAL RESULTS AND DISCUSSION

When the CO_2 concentration in the inspired air was increased (3.8%) the pH of the blood fell (from 7.385 ± 0.046 to 7.310 ± 0.067; $P < 0.002$). When the CO_2 concentration in the air was 0.2% there was virtually no change in pH.

Changes in the indices of tyrosine and tryptophan metabolism in rats inhaling air containing 0.2 and 3.8% CO_2 were similar in direction, but in the first case they did not reach statistical significance. Differ-

Laboratory of Endocrinoloogy, Latvian Research Institute of Experimental and Clinical Medicine, Ministry of Health of the Latvian SSR, Riga. (Presented by Academician of the Academy of Medical Sciences of the USSR N. A. Kraevskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 81, No. 4, pp. 416-418, April, 1976. Original article submitted June 25, 1975.

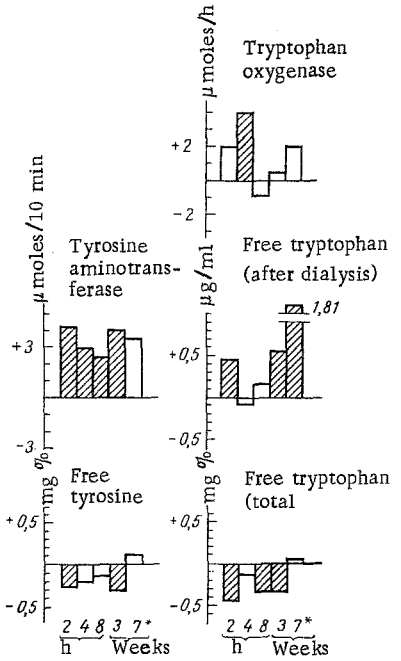

Fig. 1. Changes in content of free tyrosine and tryptophan in blood serum and activity of tyrosine aminotransferase and tryptophan oxygenase in liver during inhalation of air containing 3.8% CO_2. Shaded columns show values differing statistically significantly ($P < 0.05$) from control. Group of animals inhaling air containing 3.8% CO_2 for 3 weeks, followed by ordinary air for 4 weeks, marked by asterisk. Zero line in each case represents control.

ences between the results obtained with the experimental and control rats at each time of testing are shown in Fig. 1. During hypercapnia the tyrosine aminotransferase and tryptophan oxygenase activity in the liver increased, i.e., increased amounts of p-hydroxyphenylpyruvic acid and kynurenin were evidently formed. Similar results have been obtained in mice during high altitude hypoxia [3]. The concentration of free tyrosine and free total tryptophan in the serum fell during hypercapnia. Conversely, the concentration of free tryptophan obtained by dialysis increased. This part of the free tryptophan is known to undergo intermediate metabolism and it not only increases tryptophan oxygenase activity in the liver but it also blocks the further metabolism of its own derivatives at the 3-hydroxyanthranilic acid oxidase level [2]. Consequently, in hypercapnia, conditions are created in the body not only for increased breakdown of tryptophan, but also for the greater accumulation of its derivatives, including the carcinogenic compounds 3-hydroxykynurenin, 3-hydroxyanthranilic acid, etc. These disturbances were still present 4 weeks after the end of the experiments.

It has not yet been proved that during hypercapnia endogenous carcinogenic metabolites of tyrosine accumulate in the body; only the possibility of their more rapid formation has been demonstrated (increased tyrosine aminotransferase activity in the liver). However, characteristically in hypoxia in man the excretion of p-hydroxyphenyllactic acid with the urine is increased [6]. Since many metabolic disturbances are the same in hypercapnia and hypoxia [7, 10], it can be postulated that hypercapnia is also accompanied by the accumulation of p-hydroxyphenylpyruvic and p-hydroxyphenyllactic acids in the body.

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