Biotransformation of Hepatic Xenobiotics in Rats with Various Resistance to Hypoxia Exposure to after Cold

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Hepatic monooxygenase activity was studied in rats with various resistance to hypoxia during adaptation to cold. Cold-induced change in the concentrations of cytochromes P-450 and b_5 and the activity of microsomal metabolism of amidopyrine and aniline were shown to be associated with individual resistance to hypoxia. The content of microsomal cytochromes in highly resistant rats did not change on the fifth day of cold exposure. However, the intensity of metabolic reactions decreased. In low-resistance rats, a cold-induced decrease in the concentration of the cytochromes was not accompanied by significant changes in metabolic rates of amidopyrine and aniline.

Key Words: *individual resistance to hypoxia; hepatic monooxygenases; cold; adaptation*

Changes in the functional activities of oxidases in mixed of the liver fractions depend on individual resistance to hypoxia [4]. Cytochrome P-450 is represented by several isoforms with various substrate specificity and immunochemical, catalytic, and spectral characteristics [2].

The set of cytochrome P-450 isoforms depends on the species, sex, and age of the animal and particularities of effects of xenobiotics entering the body [3,6]. The intensity and the rate of the synthesis if several cytochrome P-450 isoforms increase during adaptation to cold. The role of cytochrome P-450 and its isoenzyme composition in animals with various resistance to hypoxia during adaptation to cold received little attention.

Here, we studied the activities of hepatic monooxygenases in rats with various resistance to hypobaric oxygenation under cold exposure.

MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 160-180 g. According to their resistance to hypoxia, the rats were divided into highly resistant (HR) and low resistant (LR) groups. One week later, the rats were placed into cold room (0-2°C) for 5 days. Material for investigation was collected on fifth days of the cold procedure and on the third day of the post-cold recovery period. The animals kept at 21°C served as control. the content of microsomal cytochromes was measured [7]. Hydroxylase and demethylase activities of the endoplasmic reticulum enzymes were determined with aniline and amidopyrine substrates [5]. Data were analyzed statistically.

RESULTS

The concentrations of cytochromes P-450 and b_5 in LR rats were 1.6 and 1.4 times higher, respectively, than those in HR rats. Cold exposure led to various changes in the contents of cytochromes P-450 and b_5 in hepatic microsomal fractions animals with various resistance to hypoxia. In LR rats, the content of cytochrome P-450 decreased by 14% (compared with control) the fifth day of adaptation to cold and did not differ from control on the third day of the post-cold period. The content of cytochrome P-450 in HR rats did not differ significantly from the control level throughout the entire observations period and tended to decrease on the fifth day of cold exposure. The microsomal concentration of cytochrome b_5 in LR animals decreased by 1.6 times on the fifth day of cold expo-

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TABLE 1. Changes in the Contents of Cytochromes P-450 and b_5 (nmol/mg protein) in Hepatic Microsomes in HR and LR Rats during Adaptation to Cold ($M\pm m$, n=4-8)

Experimental conditions	Cytochrome	LR rats	HR rats
Control	P-450	0.788±0.02	0.502±0.06*
	b_5	0.922±0.06	0.678±0.05*
Cold exposure, the fifth day	P-450	0.691±0.07+	0.491±0.02*
	b_5	0.640±0.04+	0.607±0.03*
Recovery period, the third day	P-450	0.767±0.05	0.532±0.03*
	b_5	0.898±0.03	0.646±0.04*

Note. Here and in Table *p<0.05 compared with LR rats; +p<0.05 compared with control.

TABLE 2. Changes in the Activities of Aniline p-Hydroxylase and Amidopyrine N-Demethylase in Hepatic Microsomes in HR and LR Rats during Adaptation to Cold ($M\pm m$, n=4-8)

Experimental conditions	Indices	LR rats	HR rats
Control	Aniline p-hydroxylation	0.41±0.04	0.31±0.02*
	Amidopyrine N-demethylation	3.36±0.21	2.71±0.22*
Cold exposure, the fifth day	Aniline p-hydroxylation	0.39±0.08	0.03±0.03+*
	Amidopyrine N-demethylation	4.64±0.98	2.09±0.11+*
Recovery period, the third day	Aniline p-hydroxylation	0.29±0.04+	0.28±0.04
	Amidopyrine N-demethylation	3.02±0.3	2.78±0.67

Note. The rate of aniline p-hydroxylation is expressed in nmol p-nitrophenol/min/mg microsomal protein; the rate of amidopyrine N-demethylation is expressed in nmol HCHO/min/mg microsomal protein.

sure and returned to the control level on the third day of the recovery period. The content of cytochrome b_5 in HR animals did not change significantly and tended to decrease on the fifth day of cold exposure (Table 1).The intensity of aniline hydroxylation in LR animals did not change significantly on the fifth day of cold exposure. In these rats, aniline p-hydroxylase activity decreased by 1.4 times on the third day recovery period. there was a 1.2-fold decrease in the rate of hydroxylation in HR rats on the fifth day of cold exposure. The activity of aniline p-hydroxylase in these rats did not differ from the control level on the third day of the recovery period.

In LR rats the activity of amidopyrine N-demethylase was constant. In HR this activity rats decreased by 26% on the fifth day of cold exposure (Table 2).

These data indicate that reactions of the hepatic monooxygenase enzymes to cold exposure are different in rats with various resistance to hypoxia. In HR rats, the contents of cytochromes were similar to the levels on the fifth day of cold exposure. However, N-demethylase and p-hydroxylase activities decreased significantly in these animals. Obviously, the cold-induced decrease in N-demethylase and p-hydroxylase activities is the adaptive metabolic reaction which contributes to the shift of oxygen consumption to maintaining temperature homeostasis. In LR rats, there was a significant cold-induced decrease in the contents of cytochromes P-450 and b_5. However, this was not accompanied by a decrease in the rates of metabolism of aniline and amidopyrine. Such a response of LR rats to cold exposure provides the conditions necessary for intense oxygen consumption during metabolic transformation of xenobiotics. This decreases the possibility of the shift of oxygen consumption to maintaining temperature homeostasis.

Thus, the initial functional activity of the hepatic monooxygenase enzyme complex is constitutionally determined and associated with the resistance to hypoxia. This contributes to various adaptive responses to acute cold exposure.

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