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EFFECT OF ADAPTATION TO HIGH ALTITUDE HYPOXIA ON CATECHOLAMINE METABOLISM IN SPONTANEOUSLY HYPERTENSIVE RATS

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Adaptation to periodic hypoxia under pressure chamber conditions is known to inhibit the development of spontaneous hereditary hypertension (SH) in spontaneously hypertensive rats (SHR) [5], the nearest model we have to essential hypertension in man [6]. An important pathogenetic mechanism of SH in its early stages is increased activity of the sympathetic nervous system, leading to increased vascular tone followed by structural changes in the vessel walls [10]. It has been suggested that one factor in this antihypertensive effect mentioned above is inhibition of activity of the sympathetic nervous system arising during adaptation to altitude hypoxia.

To test this hypothesis, parameters of function of the sympathico-adrenal system were studied in SHR during the development of hypertension and the effect of adaptation to hypoxia on these parameters was studied.

EXPERIMENTAL METHOD

Rats of both sexes 5 weeks old were divided into three groups. Group 1 contained 12 Wistar rats, group 2 contained 13 SHR rats; the animals of this group were not exposed to any outside influences. Group 3 consisted of 13 SHR rats which were placed for 6 h a day 6 times a week in a pressure chamber in which the pressure was reduced on the first day of the experiment to correspond to an altitude of 1100 m above sea level, on the 2nd day 2200 m, on the 3rd day 3300 m, and on the 4th and subsequent days 5000 m. The systolic pressure (BP) was measured once a week in the tail by a sphygmographic method on a "Narcobiosystem" physiograph. The concentrations of noradrenalin (NA) and adrenalin in the adrenals and of NA in the ventricles of the heart and the vas deferens were determined on the 40th and 70th days of the experiment by a fluorometric method after adsorption on columns with Dowex-50 ion-exchange resin [3]. The sensitivity of a segment of small intestine to NA and acetylcholine (ACh) was determined at the same times by determining the dissociation constant of the mediator-receptor complex [4]. On the 40th day the rate of synthesis of ^{3}H-NA and ^{3}H-dopamine from ^{3}H-tyrosine was estimated in the isolated atria [1]. The results were subjected to sta-

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TABLE 1. Effect of Adaptation to Periodic High Altitude Hypoxia on Concentration and Content of NA and Adrenalin in Tissues of SHR Rats (M ± m)

Group of animals	NA concentration in myocardium, ng/g		NA concentration in walls of vas deferens, ng/g		CA content in two adrenals, μg			
					NA		adrenalin	
	40 days	70 days	40 days	70 days	40 days	70 days	40 days	70 days
1. Wistar, unadapted*	613±75		13 116±345		8,73±1,14		32,35±3,71	
2. SHR, unadapted	1122±38	925±97	17 722±1017	16 750±670	7,86±0,11	3,72±0,32	40,72±1,54	24,19±1,92
3. SHR, adapted	913±79	843±69	15 693±887	15 540±697	8,40±1,00	5,00±0,64	35,88±1,62	22,30±0,61
P_{1-2}	<0,01	<0,02	<0,01	<0,01	>0,05	<0,01	<0,05	<0,05
P_{1-3}	<0,02	<0,05	<0,01	<0,01	>0,05	<0,02	>0,05	<0,02
P_{2-3}	<0,1	>0,05	>0,05	>0,05	>0,05	<0,05	<0,05	>0,05

*Rats of this group were tested once at the age of 13 weeks, i.e., on the 55th day of the experiment.

tistical analysis by Student's t test and by calculating the U criterion and Spearman's rank correlation coefficient [2].

EXPERIMENTAL RESULTS

The experiments showed that BP of SHR rats at the age of 5 weeks did not differ significantly from BP of the control animals at the same age (110 mm Hg). By the 11th week BP of the SHR rats averaged 155 mm Hg, and by the 15th week 206 mm Hg. Adaptation to altitude hypoxia prevented the rise of BP in SHR rats: After both 40 and 70 days of the experiment the mean value of BP was 110-120 mm Hg, the same as in normotensive Wistar rats.

The catecholamine (CA) concentration in SHR rats unadapted to hypoxia was significantly raised in the heart and vas deferens (Table 1); CA synthesis in the atria and responses of a segment of intestine to NA and ACh were not increased in this case. The shifts mentioned above were less marked 1 month later.

Changes in the CA content in the adrenals were of a different character. At the age of 11 weeks the changes were very small, but after 1 month, when BP of the SHR rats was significantly raised, the NA concentration in their adrenals was reduced by 74% and the adrenalin level by 51% compared with normotensive rats. Since CA synthesis in the adrenals and their liberation in SHR rats of this age are significantly increased [8, 9], the decrease in the CA concentration in the adrenals must evidently be interpreted as the result of their more rapid secretion than synthesis.

On the whole these results agree with the increase in activity of the sympathicoadrenal system in SHR rats established previously, as an important factor in the development of this hypertension [7].

Adaptation to altitude hypoxia caused changes in SHR rats directed toward normalization of CA metabolism (Table 1). For the vas deferens differences in the parameters of SHR rats adapted and not adapted to hypoxia were, however, not significant, and for the myocardium on the 40th day of the experiment they were on the borderline of significance. The prophylactic effect of adaptation on parameters of CA metabolism was clearly defined in the adrenals. For instance, adaptation for 40 days significantly reduced accumulation of adrenalin in the adrenals, whereas adaptation for 70 days did not significantly affect the changes in its content but led to a significant increase in the NA content, i.e., it brought this parameter close to the control level found in Wistar rats. This result is important because, of all the parameters of CA metabolism studied, only the concentration and content of NA in the adrenals correlated highly with the mean values of BP obtained during the preceding 10-day period of the experiment: on the 40th day of the experiment $r = -0.7$ ($P < 0.025$), on the 70th day $r = -0.85$ ($P < 0.005$); the lower values of BP corresponded to higher NA concentrations in the adrenals and vice versa. The NA secretion by the adrenals is evidently an important factor leading to the increase in BP in SHR rats: Adrenalectomy lowers or prevents the rise of BP in this type of hypertension [6].

Adaptation to altitude hypoxia thus inhibits changes in CA metabolism connected with the rise of BP in SHR rats, and this is evidently one of the mechanisms of the antihypertensive action of adaptation.

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RELATIONS BETWEEN KININASE AND ANGIOTENSIN-CONVERTING FUNCTIONS OF THE LUNGS IN RABBITS WITH CEREBROISCHEMIC AND VASORENAL ARTERIAL HYPERTENSION

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An important feature distinguishing the function of pulmonary microvessels is bradykinin inactivation and the conversion of angiotensin-I (A-I) into angiotensin-II (A-II). These two coupled processes take place with the participation of angiotensin-converting enzyme located in the membrane of the endothelial cells [6, 8, 10]. This enzyme is ascribed an important role in regulation of the arterial pressure (BP) under normal conditions, in arterial hypertension, and in other pathological states associated with circulatory disturbances [1, 3, 7, 9]. The development of hypertension is regarded by some workers as the result of a disturbance of the relations between pressor (angiotensin-dependent) and depressor (kinin-dependent) factors of humoral regulation [5, 11].

The object of this investigation was to study the kininase and angiotensin-converting function of the lungs as reflected in changes in depressor and pressor responses to these substances in rabbits with cerebroischemic and vasorenal arterial hypertension. This technique was used previously to study the metabolic function of the lungs in the course of experimental myocardial infarction [2].

EXPERIMENTAL METHOD

Experiments were carried out on three groups of Chinchilla rabbits (36 animals) weighing 2-3 kg: Group 1 consisted of intact animals (control), group 2 of animals with cerebroischemic hypertension (CIH), and group 3 of animals with vasorenal hypertension (VRH). The CIH was produced by unilateral ligation of branches of the left carotid artery above the carotid sinus [4]. The VRH was induced by bilateral application of a nichrome coil 0.6-0.8 mm in diameter to both renal arteries. The operations were performed under chloral hydrate anesthesia (200 mg/kg intravenously). The development of arterial hypertension was monitored by measuring the systolic BP in the auricular artery by the indirect Grant-Rothschild method.

The mean BP in the abdominal aorta was recorded graphically through a catheter introduced into the femoral artery by means of "Barovar" pressure transducer and "Alvar" electrocardiograph. Hemodynamic responses to injection of bradykinin and angiotensins were investi-

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