SODIUM-EXCRETORY AND ANTIHYPERTENSIVE EFFECT OF ACUTE HYPOXIA IN SPONTANEOUSLY HYPERTENSIVE ANIMALS

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UDC 616.12-008.331.1-055.5/.7-07:[616.12-008.331+616.632.33]-02:612.273.2.017.2

KEY WORDS: Hypertension; hypoxia; water and mineral metabolism.

An important role in the pathogenesis of the hypertension in spontaneously hypertensive rats (SHR) and in human essential hypertension is known to be played by disturbances of water and mineral metabolism and a steady-state increase in the sodium and water content in the body [1, 12]. Adaptation to high-altitude hypoxia leads to a decrease in secretion of antidiuretic hormone [4] and mineralocorticoids [5] and, as a result, leads to a decrease in the steady-state sodium and water content in the body [2, 11]. In this connection it has recently been found that such adaptation, if it begins in the early stage of ontogeny, inhibits the development of SHR [6].

The writers have suggested that the prophylactic effect of adaptation to hypoxia in SHR is due to the activating effect of hypoxia on sodium excretion by the kidneys of SHR. To test this hypothesis, the effect of acute hypoxia on sodium and water excretion by the kidneys in control Wistar rats and in SHR were compared.

EXPERIMENTAL METHOD

Experiments were carried out on 21 male albino rats age 6 months. Group 1 consisted of 10 Wistar rats weighing 328 ± 10 g, whose arterial blood pressure (AP) was 104 ± 10 mm Hg. Group 2 consisted of 11 SHR rats weighing 228 ± 14 g, whose AP was 157 ± 11 mm Hg. For the week before the investigation the animals were transferred to a standard sodium diet, and were given food and water ad lib. Urine was collected for 12 h from animals deprived of access to food and water and kept in single cages. Urine was collected twice from all rats: those kept under conditions of a normal oxygen concentration outside the pressure chamber, and those exposed to hypoxia in a pressure chamber, at an "altitude" of 4400 m above sea level. The interval between the times of taking the first and second samples of urine was 48 h. The diuresis was measured for a period of 12 h; the Na concentration in the urine and blood plasma were determined on the FPL-01 flame photometer and the creatinine concentration by the reaction with picric acid on the FÉK-60M photoelectric colorimeter. The filtration, reabsorption, and secretion of Na and water were calculated from the data.

To compare the sodium-excretory and antihypertensive effects of acute hypoxia, in the next stage of the experiment the animals of both groups were sent from Moscow to Terskol, to the Medico-Biological Station of the Academy of Sciences of the USSR, where the diet and all other conditions of keeping the rats were the same as in Moscow, but where the altitude was 2100 m above sea level. Before and after the transfer to a high altitude, the animals' blood pressure was measured on alternate days in the caudal artery by means of a physiograph (Narco Biosystems). These experiments were carried out two months after those to study the effect of hypoxia on sodium excretion. The body weight and blood pressure of the animals rose. The weight of the Wistar rats was 340 ± 5 g and AP was 113 ± 2 mm Hg; corresponding figures for the SHR were 315 ± 10 g and 196 ± 8 mm Hg.

The results were subjected to statistical analysis by two methods. The error of the arithmetic mean was calculated [8]; the significance of differences between the mean in the two groups compared was determined by calculation of the nonparametric U-criterion [3].

Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. Kemerovo Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 8, pp. 142-144, August, 1980. Original article submitted October 30, 1979.

TABLE 1. Effect of Acute Hypoxia on Diuresis and Sodium Excretion in SHR and Wistar Rats

Indices†	Wistar rats		SHR	
	before hypoxia	during hypoxia	before hypoxia	during hypoxia
Excretion of water, ml	1,7±0,02	1,0±0,3*	1,0±0,01*	1,8±0,6
Filtration of water, ml	124,4±1,2	52,1±14,0*	91,2±17,7	101,0±12,2
Reabsorption of water, ml	122,7±1,3	57,1±13,9*	90,2±17,8	99,2±12,3
Reabsorption of water, % of filtration	98,21±0,3	99,0±0,29	98,9±0,21	98,2±0,6*
Na^+ concentration, meq/liter	84,9±13,2	66,6±0,3*	121,2±16,8	82,5±5,1*
Na^+ excretion, meq	0,147±0,009	0,120±0,009*	0,126±0,004*	0,150±0,009*
Filtration charge, a^+	14,22±1,4	6,42±1,60*	9,51±1,85	10,53±1,37
Na^+ reabsorption, meq	14,07±1,4	6,30±1,60*	9,38±1,85	10,38±1,27
Na^+ reabsorption, % of filtration charge	98,96±0,30	98,1±0,30	98,67±0,30	98,57±0,38

*Differences significant.

†Calculated for a period of 12 h and per 100 g body weight.

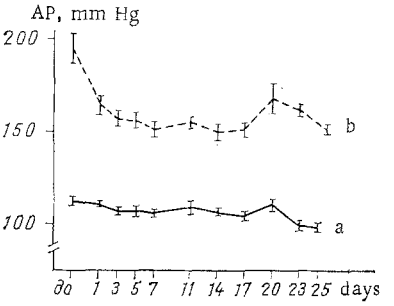

Fig. 1. AP (in mm Hg) of Wistar rats (a) and SHR (b) before and after ascent to a high altitude.

EXPERIMENTAL RESULTS

The results (Table 1) show that during exposure to a normal oxygen concentration (outside the pressure chamber) the diuresis, i.e., the water excretion of the SHR was reduced by about 40% compared with the control (Wistar rats). This decrease was due both to a reduction in water filtration in the glomeruli and to an increase in the percentage of water reabsorbed in the tubules. Meanwhile, a decrease in Na^+ excretion was observed, but this was small and amounted to only 16%. This decrease in Na^+ excretion took place on account of a considerable reduction in the filtration charge of the ion and was small because of the simultaneous decrease in Na^+ reabsorption in the tubules. Since the diuresis was considerably reduced, the small decrease in the excretion of Na^+ was combined with a considerable increase in its concentration in the urine. It is important to note that the retention of Na^+ in SHR confirms the results of previous investigations [9] and is associated with hypersecretion of mineralocorticoids in SHR [10]. Even on the assumption that disturbance of sodium excretion by the kidneys is compensated to some extent by activation of extrarenal pathways of sodium excretion, it may nevertheless be accompanied by retention of sodium and water in the body. Retention of this sort has been proved to take place in SHR [13]. The main result of this experiment was that in response to acute hypoxia, diuresis and sodium excretion were reduced in the control Wistar animals, whereas in SHR these parameters, on the contrary, were increased. As Table 1 shows, under the influence of acute hypoxia the excretion of water by Wistar rats fell by 40% on account both of a decrease in filtration and a decrease in the percentage of reabsorbed water. The Na^+ excretion also was reduced, mainly on account of a great decrease in filtration charge. As a result of a simultaneous decrease in the percentage of reabsorbed Na^+, the net decrease in Na^+ excretion was small, namely 20%. This effect of hypoxia, observed in adult animals at the 5th year of life, is in agreement with data in the literature on inhibition of excretion of water and electrolytes under the influence of acute hypoxia, and it suggests that retention of sodium and water may play a definite role in the elevation of the arterial pressure that is usually observed in man and animals immediately after ascent to a high altitude.

The qualitatively opposite action of acute hypoxia in SHR was expressed primarily as an increase of 80% in water excretion. This great diuretic effect was due to the fact that the filtration of water increased more than its reabsorption. Meanwhile, a sodium-excretory effect was observed. However, the increase in Na^+

excretion under these circumstances was about 20%, whereas the filtration charge of Na^+ rose much less than the filtration of water.

In SHR, characterized by some retention of Na^+ and water in the body, unlike in the control animals, acute hypoxia thus did not cause retention of Na^+ and water, but gave a significant diuretic and sodium-excretory effect. This suggests that the increased sensitivity of the SHR to the sodium-excretory and diuretic action of acute hypoxia may play a role in the mechanism of the prophylactic effect of prolonged hypoxia against the development of spontaneous hypertension.

The effect of high-altitude hypoxia, with an acute onset and protracted course, on AP of both groups of rats agreed with this hypothesis. The curves in Fig. 1 are evidence that AP in SHR 1-2 days after the beginning of exposure to hypoxia was already reduced from 200-190 mm Hg to about 150 mm Hg, i.e., by 40-50 mm Hg, whereas in the control rats the AP level showed no significant change. Acute hypoxia of moderate intensity, acting for 24 h, thus has a hypotensive effect in SHR but has no such effect on Wistar rats. Taken as a whole, these data indicate that the antihypertensive effect of prolonged and moderate hypoxia, demonstrated previously in animals [6] and man [7], may depend on its sodium-excretory action and may be formed of two components: the sodium-excretory effect of acute hypoxia and the sodium-excretory effect of adaptation to hypoxia, combined with manifestations of adaptation hypoaldosteronism [5].

This interpretation of the antihypertensive effect of adaptation to hypoxia is in agreement with the view that agents promoting sodium excretion combined with restriction of the dietary sodium intake are being successfully used for the treatment of hypertension in man. In this connection the well-marked sodium excretory effect of hypoxia in SHR ought to be taken into account when an attempt is made to explain the fact that hypertension is less common among mountain dwellers, and that the AP level in patients with initial forms of hypertension falls during residence at moderately high altitudes in the mountains [7].

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