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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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TABLE 1. Doses of Bradykinin and A-I Inducing Standard Changes in Mean BP when Injected into the Right and Left Ventricles of Rabbits with CIH and VRH (M ± m)

Parameter	Intact animals	Bradykinin	
		cerebroischemic (n = 12)	vasorenal (n = 13)
Initial level of BP, mm Hg	91,2±5,4	113,5±4,3	136,9±5,8
Bradykinin			
Standard change in BP, mm Hg	—20,2±1,7	—20,8±0,9	—19,0±1,2
Dose of bradykinin (in mg/kg) injected into ventricle:			
left	108,9±21,4	50,2±8,7	18,8±3,1
right	471,2±96,2	411,5±41,8	286,8±42,0
Difference between doses for right and left ventricles, μM	340,0±75,7	340,1±35,6	252,8±42,8
Ratio between doses	1:4,4	1 : 8,2	1 : 15,8
Angiotensin			
Standard change in BP after injection of A-II, mm Hg	20,0±0,6	19,2±0,6	19,0±0,5
Dose of A-II injected intravenously, ng/kg	391,7±43,5	300,1±40,8	202,5±28,4
Standard change in BP following injection of A-I, mm Hg	14,1±1,0	15,8±1,2	16,5±1,1
Dose of A-I (in ng/kg) injected into ventricle:			
left	527,3±51,8	522,0±42,3	491,0±19,6
right	163,6±25,9	503,3±51,4	484,8±19,1
Difference between doses for right and left ventricles, μM	245,1±53,2	13,4±22,7	4,4±4,9
	3,3 : 1	1 : 1	1 : 1

gated under urethane anesthesia (1.5 g/kg, intravenously) on the 30th-40th days of development of hypertension. A polyethylene catheter, connected to a pressure transducer, was introduced into the right external jugular vein and, on the appearance of the characteristic intraventricular pressure curve, it was concluded that the catheter was in the right ventricle. It was then fixed. A catheter was introduced similarly through the left carotid artery into the left ventricle. Injection of all drugs began into the left ventricle, to produce a linear change in BP and a maximal response of 15-20 mm Hg. Each subsequent injection was given 3-5 min after BP had returned to its original level (±5 mm Hg). The drugs were dissolved in 0.5-1.0 ml physiological saline for injection. After responses to injection into the left ventricle had been recorded, an injection was given into the right ventricle, and in this case also linearity and standardization of the responses at a value of 15-20 mm Hg were secured. The kininase or angiotensin-converting function of the lungs could thus be estimated from the change in the dose of the drug inducing the standard hemodynamic response.

The following preparations were used: synthetic bradikinin was from Reanal, Hungary; A-I and A-II were from Sigma, USA. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

The results given in Table 1 show that the original mean BP level was moderately raised in CIH and considerably (by 50%) increased in VRH. Comparison of the doses of bradykinin causing a standard fall in BP when injected into the left ventricle shows that the presence of hypertension is accompanied by an increase in reactivity of the vessels to this substance. In animals with CIH and VRH these doses were 2.1 and 5.7 times respectively below that inducing the same reaction in intact animals. Comparison of doses of bradykinin injected into the right and left ventricles shows that the conventional quantity of the polypeptide inactivated by the lungs did not differ from the control in rabbits with CIH and was considerably lower in rabbits with VRH. However, the ratio between the doses of bradykinin injected "before the lungs" and "after the lungs" in the animals with hypertension changed very considerably: Wehn the reactivity of the vessels was increased, the "cost" of depressor activity of each unit of bradykinin destroyed in the lungs was significantly higher. Ultimately this pathophysiological mechanism can be regarded as progressive limitation of the depressor function of kinins during the development of hypertension.

Similar experiments with A-II showed that the presence of arterial hypertension was accompanied by an increase in the pressor reactivity of the vessels also. In CIH and VRH doses inducing a standard response were 1.3 and 1.9 times lower respectively than in the control rabbits. However, no such difference was found when A-I, the unconverted form of the preparation, was injected into the left ventricle. Comparison of doses of A-I injected into the right or left ventricles and inducing a standard increase in BP revealed depression of the angiotensin-converting function of the lungs in both forms of experimental hypertension. The ratio between the doses of A-I for the right and left ventricles was not as high as for bradykinin. The development of arterial hypertension due to chronic cerebral and renal ischemia thus leads to changes in the properties of the pulmonary microcirculation, that are manifested, on the one hand, as an increase in destruction of the depressor polypeptide, bradykinin, and on the other hand, by sharp inhibition of conversion of A-I. These changes must be examined together with the other important pathophysiological mechanism of development of arterial hypertension, namely increased sensitivity of the vessels to bradykinin and to A-II. The patterns observed imply that given equal activation of the kallikrein-kinin and renin-angiotensin systems of the blood, factors of depressor action obtain the advantage. However, the existence of the mechanism for restricting the depressor function of kinins in arterial hypertension thus revealed may be one factor disturbing equilibrium between the pressor and depressor components of BP regulation. Definite confirmation of this suggestion is given by the more marked changes of vascular reactivity and metabolic function of the lungs with respect to bradykinin and A-I in VRH, characterized by a greater rise in BP. A wider examination of the neurohumoral factors leading to the development of essential hypertension must also take into account the role of other groups of physiologically active substances of plasma and renal origin such as prostaglandins and catecholamines.

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