HYPOTENSIVE EFFECT OF INTENSIFICATION OF ALDOSTERONE METABOLISM IN DOGS WITH VASORENAL HYPERTENSION

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UDC 616.12-008.331-02: 616.136.7-007.272-092.9-085.357.453

The mechanisms of the hypotensive effect of portocaval transposition were investigated in dogs with vasorenal hypertension. Directing blood flowing from the kidneys and adrenals into the liver in dogs with vasorenal hypertension was found to increase aldosterone metabolism and, at the same time, to increase aldosterone secretion by the adrenals, as a result of which the level of the steroid in the peripheral blood returned to normal. Abolition of the syndrome of secondary hyperaldosteronism by portocaval transposition of the vessels takes place on account of increased aldosterone metabolism and leads to restoration of the normal arterial pressure.

KEY WORDS: aldosterone metabolism; experimental hypertension.

Secondary hyperaldosteronism is an important link in the pathogenesis of arterial hypertension. The object of the present investigation was accordingly to study the possibility of reducing the increased aldosterone concentration in the peripheral blood by stimulating its metabolism. It was postulated that this could be achieved by directing venous blood from the adrenals and kidneys into the blood flow of the liver, where components of the renin–angiotensin–aldosterone system are metabolized.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred dogs of both sexes, weighing 15-25 kg, and adapted to the experimental situation. The animals were given 70-90 meq sodium and 20-30 meq potassium daily with the diet and water ad lib. The model of vasorenal hypertension, developing after bilateral one-stage constriction of the renal arteries (CRA) was used. The animals of this group were studied weekly for 1 month. "Portalization" of blood draining from the kidneys and adrenals was carried out by portocaval transposition of the vessels (PCT) by the method described previously [1, 2]. The operation of PCT was carried out on intact, normotensive dogs (intact + PCT) and on animals with vasorenal hypertension 14 days after bilateral constriction of the renal arteries (CRA + PCT), at a time when the arterial pressure was permanently increased. The animals of both groups with PCT were investigated at intervals for 2 months after this operation. The results obtained by investigation of the intact animals and animals undergoing PCT were compared. The blood pressure was measured by a bloodless techooscillographic method on the Mingograph-34 (Sweden) apparatus. The plasma aldosterone concentration and plasma renin activity (PRA) were determined by radioimmunological methods [5, 7]. The metabolic clearance and the rate of secretion of aldosterone were determined by the method of Tait et al. [8], using a single injection of [^{3}H]aldosterone (in dogs with CRA) and continuous infusion of [^{3}H]aldosterone (in the animals of both groups with PCT). In dogs with PCT the infusion of the labeled hormone was given by two methods: by injection of aldosterone into the general circulation and directly into blood flowing into the liver. The last method enabled the true secretion of aldosterone by the adrenals and the coefficient of aldosterone extraction by the liver could be calculated. [^{3}H]Aldosterone was isolated by the

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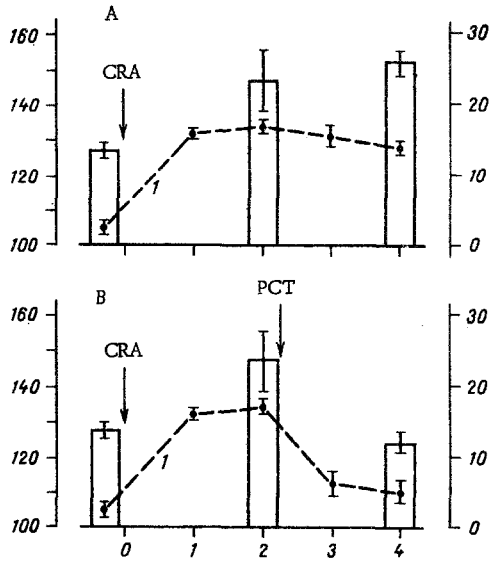

Fig. 1. Effect of PCT on mean arterial pressure (1) and aldosterone concentration (columns) in peripheral blood of dogs with vasorenal hypertension (CRA). A) Dogs with CRA; B) dogs with CRA + PCT. Abscissa: time after CRA (in weeks); ordinate: on left – arterial pressure (in mm Hg), on right – aldosterone concentration (in ng %). Values of M ± m given.

method of Kliman and Peterson [6] in the modification described in [3]. The radioactivity of the samples was determined in 10 ml of toluene scintillator on a Mark II scintillation counter (Nuclear Chicago, USA).

EXPERIMENTAL RESULTS

Bilateral CRA leads to a permanent rise of arterial pressure and of the aldosterone level in the peripheral blood of dogs (Fig. 1; Table 1). The PRA of these animals, after being raised for a short time (for 1 week), returned to normal (Table 1). No changes in the metabolic clearance of aldosterone were found 7-10 days after the CRA operation: 28.8 ± 2.6 and 29.3 ± 3.1 $ml \cdot kg^{-1} \cdot min^{-1}$ in the control and experimental series, respectively (n = 7). On the other hand, the calculated values of secretion of the hormone during this period differed significantly: 3.2 ± 0.2 $ng \cdot kg^{-1} \cdot min^{-1}$ in the control and 7.7 ± 0.9 $ng \cdot kg^{-1} \cdot min^{-1}$ in the experimental series (n = 7; $P < 0.05$).

Portalization of the venous blood from the kidneys and adrenals in dogs with arterial hypertension caused restoration of the normal arterial pressure after 1-2 weeks. Under these circumstances the plasma aldosterone concentration also fell to normal (Fig. 1; Table 1). No change in PRA was observed in these animals (Table 1). Meanwhile it was found that PCT both in intact dogs and in animals with bilateral CRA caused a sharp (tenfold) increase not only in the metabolic clearance of aldosterone, but also in the rate of its secretion (Table 2).

The results suggest that normalization of the arterial pressure in animals with vasorenal hypertension as the result of portalization of blood draining from the adrenals leads to the abolition of the syndrome of secondary aldosteronism through the increased inactivation of aldosterone in the liver. At the same time, the impression is obtained that the operation of PCT, when carried out on intact dogs, does not affect the rate of aldosterone inactivation in them, for the aldosterone concentration in the peripheral blood of these dogs was unchanged after the operation (Table 1). However, as Table 2 shows, the normal aldosterone level in dogs of both groups with PCT was due to a simultaneous and balanced increase in metabolic clearance and secretion of the hormone.

In the animals with secondary hyperaldosteronism the high plasma aldosterone level was due to the higher than normal secretion of the hormone by the adrenals. After the operation of PCT these differences in

TABLE 1. Effect of PCT on Aldosterone Concentration and Plasma Renin Activity in Intact Dogs and Dogs with Bilateral CRA

Experimental model	Aldosterone concentration, ng %		Plasma renin activity, $ng \cdot ml^{-1} \cdot h^{-1}$	
	$M \pm m$	n	$M \pm m$	n
Intact	15,5±1,5	43	1,84±0,21	38
Intact + PCT	14,4±1,8	18	1,15±0,28	17
CRA:				
7 days	29,0±2,5*	13	4,26±0,60*	13
14 "	23,5±4,4*	7	1,64±0,48	7
21 "	22,7±2,3*	8	1,82±0,46	8
30 "	26,0±1,4*	7	2,10±0,64	7
CRA + PCT	12,3±1,1	4	0,78±0,32	8

*Difference from control (intact) statistically significant ($P < 0.05$).

TABLE 2. Effect of PCT on Metabolic Clearance and Rate of Secretion of Aldosterone in Intact Dogs and Dogs with Bilateral CRA

Experimental model	Metabolic clearance of aldosterone, $ml \cdot kg^{-1} \cdot min^{-1}$	Rate of aldosterone secretion, $ng \cdot kg^{-1} \cdot min^{-1}$
Intact (n = 22)	38,0±2,1	8,76±1,31
Intact + PCT (n = 6)	374,5±98,1*	72,50±21,60*
CRA + PCT† (n = 2)	516,0*	65,0*
	606,0*	93,0*

*Difference from control (intact) statistically significant ($P < 0.001$).
†Results of individual observations made on two dogs.

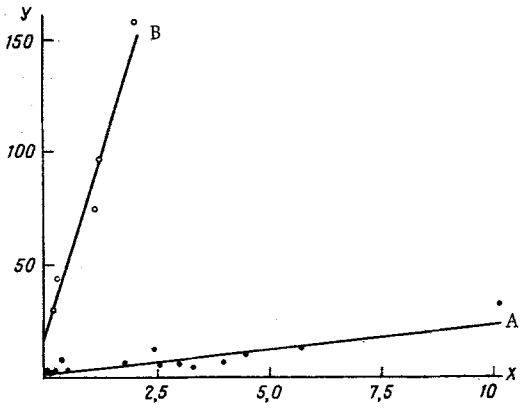

Fig. 2. Correlation between PRA and rate of aldosterone secretion in intact dogs (A) and in dogs with PCT (B). A) $y = 2.6 \cdot x + 1.4$ ($r = 0.90$; $P < 0.001$); B) $y = 64.8 \cdot x + 17.5$ ($r = 0.98$; $P < 0.05$). Abscissa, PRA) in $ng \cdot ml^{-1} \cdot h^{-1}$; ordinate, rate of aldosterone secretion (in $ng \cdot min^{-1} \cdot kg^{-1}$).

secretion of the hormone virtually disappeared (Table 2), and the level of secretion was established at a new, increased level, maintaining the normal aldosterone concentration in the plasma as the result of a simultaneous sharp increase in the intensity of aldosterone metabolism. The high secretion of aldosterone in animals with transposition of the vessels cannot be due to a high secretion of renin, for the plasma renin activity in the dogs with PCT was no higher than in the control (Table 1). However, analysis of relations between PRA and the rate of aldosterone secretion showed that the adrenals of these dogs have high sensitivity to angiotensin: The coefficient of regression after PCT was almost 25 times higher than normally (Fig. 2) and, in addition, in dogs with PCT the basal rate of aldosterone secretion, calculated for a PRA value of zero, also was increased (by 13 times) in the dogs with PCT (Fig. 2). This indicates that in animals with transposition of the vessels, besides renin, other factors including possibly ACT participate in the regulation of aldosterone secretion. Portalization of adrenal venous blood in fact leads to increased inactivation not only of aldosterone, but also of glucocorticoids in the liver [2]. The reduction in the blood glucocorticoid concentration must, in turn, lead to an increase in ACTH secretion by a negative feedback mechanism. A morphological study of the adrenals in dogs with PCT revealed hyperplasia of all three zones of the adrenal cortex [2].

It is also interesting to note that, despite this marked increase in aldosterone secretion in animals with transposition of the vessels, the liver is able effectively to inactivate the hormone reaching it from the adrenals, although it is present in 10 times more than the normal amount. The value of the coefficient of

extraction of aldosterone from blood passing through the liver is 0.81 in the animals with PCT, corresponding to the level of extraction of aldosterone in the liver of intact dogs [4]. Consequently, under conditions of portocaval transposition of the vessels the enormous metabolic capacity of the liver shows itself.

After portocaval transposition of the vessels there is thus an increase in the metabolic clearance of aldosterone and, at the same time, a balanced increase in secretion of the hormone by the adrenals. This correspondence between the metabolism and secretion of aldosterone in PCT leads to a reduction in the aldosterone concentration in the peripheral blood and, accordingly, to restoration of the normal blood pressure in animals with vasorenal hypertension caused by bilateral CRA. The results of these experiments, in the writers' view, are of considerably clinical importance: Instead of the total adrenalectomy as performed for malignant hypertension, an operation based on the principle of "portalization" of blood from the kidneys and adrenals can be used.

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PHOSPHOINOSITIDE CONTENT IN ERYTHROCYTE MEMBRANES OF RATS WITH SPONTANEOUS HYPERTENSION

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UDC 616.12-008.331.1:591.1.05

The content of triphosphoinositides (TPI) and monophosphoinositides (MPI) per milligram of membrane protein in ghost erythrocytes of rats with spontaneous hypertension (SHR) is 178 and 74%, respectively, of the content of these lipids in ghost erythrocytes of normotensive rats (NR). The total phosphoinositide content in ghost erythrocytes of NR is more than 120% of the total content of these lipids in ghost erythrocytes of SHR.

KEY WORDS: spontaneous hypertension; erythrocytes; phosphoinositides.

The difference in the permeability of erythrocytes of SHR and normotensive Wistar rats in their permeability to monovalent cations Na^+ and K^+, discovered previously [7], conforms with the hypothesis of spontaneous hypertension as a disease of cell membranes [1]. Investigation of the molecular mechanisms of abnormal permeability of the erythrocyte membranes of rats with spontaneous hypertension was undertaken in order to study the biochemical manifestations of this pathology.

Fourth Main Board, Ministry of Health of the USSR. (Presented by Academician of the Academy of Medical Sciences of the USSR E. M. Chazov.)

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 84, No. 8, pp. 155-156, August, 1977. Original article submitted January 19, 1977.