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CHANGES IN THE HEMOSTASIS AND FIBRINOLYSIS SYSTEM IN RATS WITH EXPERIMENTAL RENAL HYPERTENSION

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KEY WORDS: hemostasis; fibrinolytic system; renal hypertension.

In arterial hypertension resistance to the blood flow is increased [1, 8], due not only to anatomical changes in the microcirculatory bed (thickening of the walls, diminution of the lumen of the vessels), but also to changes in the rheologic properties of the blood. Some workers consider that an increase in viscosity of the blood plays an essential role not only in stable hypertension, but also in the initial stages of development of the disease [7]. The viscosity of the blood is significantly affected by the concentration and properties of its macromolecular proteins, namely fibrinogen, which can form aggregates with a molecular weight of up to 1000 kD, and fibronectin. An important role also is undoubtedly played by the fibrinolytic system, responsible for the hydrolysis of fibrinogen and of its high-molecular-weight fragments [10].

The aim of this investigation was to study concentrations of some plasma components of hemostasis and the role of the fibrinolytic system in experimental renal hypertension.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats. Renal hypertension was induced by Goldblatt's method: after removal of the left kidney, a nichrome coil with a lumen of 0.25 mm was applied to the right renal artery. Animals undergoing unilateral nephrectomy alone (group 1, mock operation) and intact animals (group 2) served as the controls. Twice a week the systolic blood pressure of all animals was measured by an indirect method [6] in the caudal artery. Blood for analysis was taken from the jugular vein. The following parameters were determined: fibrinogen concentration by Lazar's method, fibrinolytic activity (FA) by Niewierowski's method and on fibrin plates by the method of Astrup and Mullertz, the level of soluble fibrin monomer complexes (SFMC) by Stakhurskaya's

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TABLE 1. Parameters of Blood Clotting and Fibrinolysis in Experimental Rats, Rats Undergoing Mock Operation, and Intact Rats 2 Months after Operation to Produce Ischemia of the Kidney

Animals	Fibrinogen concentration, g/liter	SFMC content, g/liter	NF level, mm^2	Euglobulin lysis time, min	FA on fibrin plates, mm^2			Antithrombin III level, %	Antiplasmin content, %
					standard plates	heated plates	activity of plasmin activators		
Hypertensive (experimental; $n=17$)	3,96±0,38	0,24±0,04	54±14	176±21	4,5±0,8	2,1±0,3	2,4±0,8	156±24	108±14
	$p_1<0,02$	<0,01	<0,1	<0,001	<0,01	<0,5	<0,01	<0,02	>0,5
	$p_2<0,05$	<0,01	<0,02	<0,1	<0,5	<0,5	<0,5	<0,05	>0,5
Mock operation (n = 12)	2,32±0,28	0,066±0,008	86±22	83±11	24±3,1	4,4±0,4	20±3,1	88±12	92±9
	$p_2>0,5$	>0,5	<0,001	<0,5	<0,05	>0,5	<0,05	>0,5	>0,5
Intact (n = 10)	2,4±0,28	0,065±0,009	16,5±4,8	121±14	9,6±3,0	3,2±0,4	6,4±3,0	92±11	105±12

Legend. p_1) Significance of differences between parameters in hypertensive rats and rats undergoing mock operation; p_2) the same for hypertensive and intact animals.

method, antithrombin III (AT III) by Abildgard's method, nonenzymic fibrinolysis (NF) by the method of Kudryashov and Lyapina, and antiplasmins by Niewierowski's method [4].

EXPERIMENTAL RESULTS

Table 1 gives the results of determination of the biochemical parameters in the animals of three groups (one experimental and two control) 2 months after the operation to produce ischemia of the kidney in the experimental group, the average blood pressure (BP) being 170-190 mm Hg.

It will be clear from Table 1 that the fibrinogen concentration in the blood of experimental animals with high BP was increased by more than 1.5 times, SFMC was increased by more than 3 times, and NF, representing activity of complex compounds of heparin with fibrinogen and biogenic amines, also was strengthened. It is perfectly possible that the presence of these high-molecular-weight structures (fibrinogen, SFMC, heparin complexes) in the plasma of animals with hypertension, in the native or aggregated state, facilitates the strengthening of the viscous properties of the blood.

A distinguishing feature of this model of renal hypertension is the extreme functional load placed on the single residual organ, working under exceptional conditions, which leads to considerable pathological changes in the kidney [11] and, as a result, to a disturbance of metabolic processes in the animal [3]. By the 5th month of the experiment the body weight of the hypertensive animals was significantly increased and lipemia in the blood plasma was marked. The hemostasis system of the kidney showed changes, fibrin was deposited in the Malpighian glomeruli [9], and synthesis of plasminogen activators was disturbed [5]. Figure 1 shows FA of the cortex and medulla of the kidney of healthy animals and animals of the experimental groups 2 months after the operation to produce renal ischemia. FA of the renal cortex was considerably exhausted in the experiment, whereas the FA of the medulla was unchanged. Suppression of fibrinolysis in the kidney may facilitate deposition of fibrin in the capillaries, worsening of the microcirculation, and intensification of pathological changes in the organ, i.e., may consolidate the "vicious circle" of hypertension thus formed.

Figure 2 shows the time course of some parameters during the development of hypertension from the 10th day to the 5th month. In the early hypertensive stage considerable mobilization of fibrinolysis could be seen as a process hydrolyzing high-molecular-weight fibrinogen aggregates and fibrinogen itself, and thus facilitating a decrease in viscosity of the blood plasma. A tenfold increase in the concentration of plasminogen activator 10 days after occlusion of the artery in the model used was described only during the first minutes in the case of electric shock [2]. Meanwhile, the fibrinogen concentration and SFMC level in the blood were reduced. Thus in the early stages of hypertension the fibrinolytic system acts as a protective, compensatory factor, preventing an increase in the concentration of high-molecular-weight proteins and the viscosity of the blood, and the development of hypertensive changes. Intensification of fibrinolysis in the first days of occlusion also disturbs fibrin deposition in the microvessels and their subsequent occlusion as

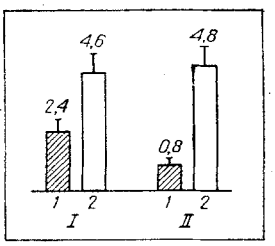

Fig. 1. FA (conventional units) of cortical (1) and medullary (2) zones of kidney in intact (I) and hypertensive (II) animals. Explanation in text.

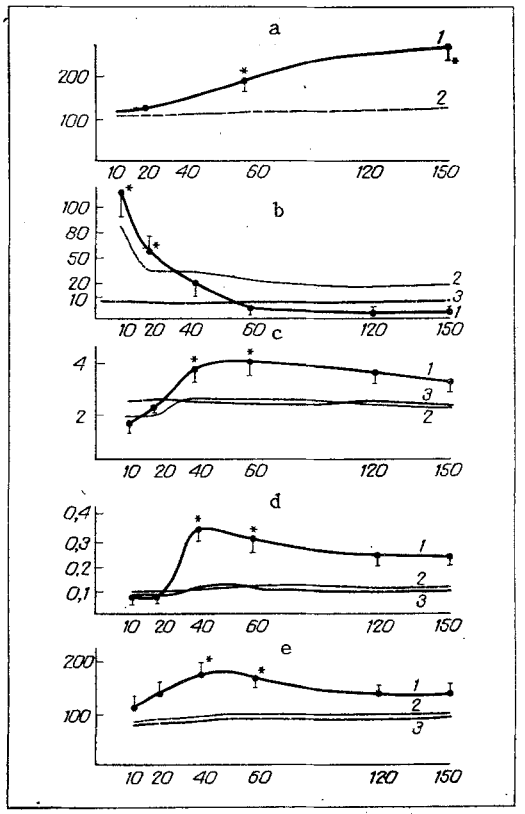

Fig. 2. Biochemical parameters of hemostasis and fibrinolysis at intervals during development of arterial hypertension. 1) Experimental animals, 2) mock operation, 3) intact. Abscissa, days of investigation; ordinate: a) BP, mm Hg; b) plasminogen activator (mm^2); c) fibrinogen, g/liter; d) SFMC, g/liter; e) AT III, %. Asterisk indicates statistically significant changes of parameters compared with control.

a result of microthrombosis, leading to a rise of BP. With the development of hypertension the plasma plasminogen activator level falls, whereas the concentration of fibrin and its high-molecular-weight aggregates rises. NF and AT III are considerably increased throughout the period of observation and give protection against possible thrombosis.

In the model of renal hypertension with unilateral nephrectomy and partial occlusion of the artery of the residual kidney, elevation of BP is thus accompanied by an increase in the concentration of high-molecular-weight plasma proteins, namely fibrinogen and its complexes with fibrin monomer, and by depression of FA of the blood, thereby leading to an increase in the viscous properties of the blood and the peripheral vascular resistance. At the same time, an increase in the concentration of high-molecular-weight proteins and inhibition of fibrinolysis may lead to occlusion of some microvessels, and may thus potentiate the reduction of the density of the microcirculatory bed. This last factor is an

essential component of the increase in vascular resistance in different forms of hypertension [12]. Consequently, an increase in the viscous properties of the blood leads directly and indirectly, through potentiation of the processes leading to a decrease in the density of the microcirculatory bed, to an increase in vascular resistance in the blood in hypertension, contributing to a further rise of BP. In the early stages of hypertension, the high fibrinolysis prevents these processes.

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TUBULOSTROMAL RELATIONS IN THE NORMAL RABBIT AND HUMAN KIDNEY

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KEY WORDS: normal kidney; tubules; stroma; tubulostromal relations.

The study of species differences in tubulostromal relations in the kidneys of laboratory animals and man is of considerable interest not only to anatomists, but also to pathologists because of the increased attention being paid in recent years to tubulo-interstitial lesions of the kidneys [3, 7, 8]. The aim of this investigation was to compare extraglomerular structural elements of the renal cortex and medulla in normal rabbits and man.

EXPERIMENTAL METHOD

Altogether 10 kidneys from male rabbits weighing 2-2.5 kg and 10 kidneys removed from eight men and two women, dying accidentally at the age of between 16 and 40 years, were studied. The cause of death of the human subjects in eight cases was asphyxia, and in two it was a road accident. The rabbits were killed by air embolism. Pieces for kidney for study were fixed in buffered 10% neutral formalin solution and embedded in paraffin wax. Paraffin sections were stained with hematoxylin and eosin, with picrofuchsine by Van Gieson's method, by Heidenhain's azan method, with Congo red, and by the PAS reaction. Frozen sections were treated by the direct Coons' method (with luminescent sera against human IgA,

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