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# MEDICAL SCIENCES

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## CHANGES IN INDICATORS OF FIBRINOLYSIS AND PROTEOLYSIS IN RATS WITH SPONTANEOUS HYPERTENSION DURING TREATMENT WITH RAMIPRIL

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**Abstract.** The article concerns investigation of the state of proteolytic and fibrinolytic activity in rats SHR series with ramipril treatment. The study found that SHR rats a reduction process fibrinolytic activity, and after treatment with this drug product level increases fibrinolysis and proteolysis.

**Key words:** proteolysis, fibrinolysis, spontaneously hypertensive rats-line SHR, lysis low-molecular proteins azoalbuminu, lysis collagen azokolu.

**Introduction.** Every year in the world, recorded 3 million deaths due to hypertension (AH) associated with the disease and its complications such as stroke, coronary heart disease (CHD), heart failure. In the study of pathophysiological mechanisms of these diseases, particular attention should rheological and coagulation destabilization in people with high blood pressure in terms of its participation in the

development of stroke, myocardial infarction. That is why one of the urgent problems of modern cardiology and neurology - early detection of changes in haemostatic balance and use adequate individual therapy. Coronary heart disease and stroke, of course, affects the growth processes of peroxidation and reduced antioxidant enzyme activity. Oxidative stress, underlying tissue degeneration can initiate many other pathogenic mechanisms. One of these mechanisms is proteo - tissue modification and fibrinolytic activity, the result of which may vary homeostasis at the cellular level, tissue, and whole organism level, hence the feasibility study proteo - reactions and fibrinolytic systems. Interaction of proteolysis and fibrinolysis largely determines the pathogenesis of various changes, the degree of cell damage, and adaptation and survival of the affected tissue.

In the treatment of hypertension is preferable to use those antihypertensive drugs, which can not only effectively reduce blood pressure, but also positively influence the process of fibrinolysis and proteolysis. However, the impact of certain antihypertensive drugs on the activity of certain products of proteolysis and fibrinolysis in patients with hypertension to date been insufficiently studied.

**The aim of the study.** Investigation of a comparative analysis of fibrinolysis and proteolysis in spontaneously hypertensive rats SHR series under the influence of drugs treatment of angiotensin converting enzyme.

**Material and methods.** Experiments conducted on laboratory rats 20 SHR series, weighing 0,248-0,431 kg (nursery of laboratory animals "Biomodelservis" m. Kyiv). In recent years, researchers raised specific transgenic lines with spontaneous hypertension rats (spontaneously hypertensive rats, SHR), which is an adequate model of the disease in humans. With this disease the animals are born, thereby increasing the possibility of a pilot study pathogenic mechanisms of hypertension and its possible farmakokorektsiyi [12]. Line rats with spontaneous hypertension SHR was launched in 1963 by Japanese scientists L. Okamoto and Aold of Wistar rats that have high blood pressure. Spontaneously hypertensive rats, SHR line in the first weeks of life have normal blood pressure. In this rat lines increased blood pressure observed in the age of 4-12 weeks. Hypertension occurs for no apparent reason in

100% of cases and is transmitted by heredity. In the process of aging animals raises blood pressure, myocardial hypertrophy develops. AG also accompanied by significant metabolic disorders of water-electrolyte metabolism [7].

During the acclimatization after transport from the nursery (14 days) and during the experiment, animals were kept in vivarium conditions at a constant temperature and humidity on the standard diet. [3] Determination of the total, and non-enzymatic fibrinolysis fermentatyvnoho in plasma was performed by lysis azofibrynu ( "Simko Ltd", Ukraine) [5]. Proteolytic activity of the plasma was determined by lysis azoalbuminu, azokazeyinu and azokolu [1]. The experimental group of animals was administered SHR series of angiotensin-converting enzyme (ACE). Ramipril dose was 5 mg / kg rat (Hoechst AG, Germany), which meet a range of daily doses for humans with the expectation conversion factor for rats. The drug was administered 1 time per day for 7 days with food (for short-term therapy) and for 21 days (for long-term treatment). 33nelikovanyh control group of rats SHR series of daily intragastric injected 0.9% sodium chloride in equivalent volume (0.2 mL / 200 g). All stages of the experiment conducted in compliance with the basic requirements of the European Convention for the humane treatment of animals.

Experimental data processed on personal computers software package EXCE-2003 (Microsoft Corp., USA). Statistical analysis was performed using applications "Statistica 8.0". For all indices calculated value of the arithmetic mean of the sample (s), its variance and average error (Sx). To identify differences probability results in the experimental and control groups of animals determined by Student coefficient (t), and then determine the probability of difference samples (p) and average confidence interval for the Student distribution tables. Considered likely value for which  $p < 0.05$ .

**Results and discussion.** Activity of proteolysis and fibrinolysis depends on the consistency of activators and inhibitors. As excessive activation and inhibition of proteolysis and excessive fibrinolysis may result in the development of some pathological processes [1]. Disbalance protease-antiproteases is part of the pathogenesis of many tissue damage [2]. Tkanynna fibrinolytic activity plays a

crucial role in the destruction of cells in ischemic angiogenesis and vascular remodeling [10]. Proteolytic system of the body is actively involved in the regulation of blood circulation and blood flow to various organs [8]. Fibrin is the structural basis of blood clots. Just the co platelets in endothelial damage. Increased levels of fibrinogen is of some importance in the development of thrombotic complications. It was found that increased levels of fibrinogen increase in the number of times the risk of heart attacks the brain and heart. Increased levels of fibrinogen are unfavorable prognostic factor associated with increased risk of death in patients with atherosclerotic vascular lesions of the brain and heart.

The use of ramipril caused significant changes fibrinolytic activity and processes of proteolysis in blood plasma (at system level) rats series SHR.

The results of the comparative analysis of fibrinolysis and proteolysis in spontaneously hypertensive rats SHR series under the influence of drugs treating angiotensin converting enzyme ramipril presented in Tables 1-2.

Lysis low molecular weight proteins in the blood suffered tendency to increase in comparison with the control of high-protein lysis experienced somewhat more pronounced activation - 17.5% compared with the control, while the lysis of collagen decreased by 16.8% compared with the control group.

Use of the drug ramipril led to the likely growth rates lysis of high protein and collagen - in 51.7% and 22.06% respectively compared with the control, and low molecular weight compounds lysis conversely experienced downward trends. Presumably such changes may be associated with a strong activation of oxidative modification of proteins, which primarily causes damage to the high-protein, followed by lysis [6].

Use of the drug ramipril has had the most pronounced effect on proteolytic processes for collagen, hardly touching the other indicators. Thus, compared with ramipril in normal schiruv lysis of collagen in blood plasma increased by 12.1%, but the overall effect on the lysis of collagen preparatuyi is common in both species and manifests its decline compared to the control group. Changes lysis of low molecular weight proteins exhibit opposite direction, while the high-performance lysis proteins



are consistently higher than the control for all applied research impacts. Changes proteolytic processes in terms of the drug ramipril may indicate a more significant its damaging effect.

The total fibrinolytic activity (SFA) for the actions of plasma ramipril varied depending on a series of rats (Table 2). The observed increase in plasma SFA by 22.3% in terms of the drug was likely caused by increased enzymatic fibrinolysis (32.8%) with a simultaneous increase in the intensity of NFA.

**Table 1.**

**Changes proteolytic processes in the plasma of rats SHR series combined with the usual line of rats in the treatment of ramipril ( $M \pm m$ ).**

Number of	Terms experiment	Lysis of low-molecular proteins azoalbuminu mg / ml per hour	Lysis collagen azokolu mg / ml per hour	Lysis of high-protein, mkg azokazeyinu
1 control	Rats SHR series n = 6	2,83±0,0282	0,274±0,0506	2,21 ±0,102
2	Normal rats, n = 10	3,04±0,0831*	0,228±0,0224*	2,60±0,1209
3	Rats series SHR, who received ramipril n = 8	2,86±0,0685	0,255±0,0240*	2,64±0,0988*

Note. Here in after: \* - probably for a group 1 (control), ( $p < 0.05$ ).

**Table 2.**

**Changes of fibrinolytic processes in the plasma of rats SHR series combined with the usual line of rats in the treatment of ramipril ( $M \pm m$ ).**

Number of	Terms experiment	Lysis of low-molecular proteins azoalbuminu mg / ml per hour	Lysis collagen azokolu mg / ml per hour	Lysis of high-protein, mkg azokazeyinu
1 control	Rats SHR series n = 6	0,599±0,0223	0,299±0,0103	0,299±0,0135
2	Normal rats, n = 10	0,736±0,0674*	0,338±0,0204*	0,398±±0,0557*
3	Rats series SHR, who received ramipril n = 8	0,686±0,0317*	0,329±0,0118*	0,357±0,0246*

**Conclusion.** Reduced blood anticoagulant activity and inhibition of fibrinolysis inhibitors due to higher content of the activation of plasminogen and antiplasmin, including rapid action is observed in most patients with chronic coronary insufficiency due to atherosclerotic lesions express coronary arteries irrespective of

hypertension syndrome. Changing the fibrinolytic system shows the reaction of all the endothelium and does not carry information about the immediate prognosis of the disease. System increase plasminogen activator inhibitor is not equivalent to the local activation processes of blood coagulation, as well as increase the production of plasminogen activator is not indicative of local fibrinolysis enhancing.

In SHR rats observed changes in systemic and local fibrinolysis and proteolysis, which may be due to the activation of the adaptive response.

The use of ramipril led to activation of proteolytic activity especially high-protein while azokolu and lysis of collagen in the use of the drug increased, but the figures were lower than the control group.

In SHR rats a reduction process fibrinolytic activity, and after treatment with this drug levels of fibrinolytic activity recovers, but remains lower than in the control group animals.

The use of ramipril showed a mixed impact on fibrinolysis and proteolysis. Prospects for further research. Clarify the characteristics of changes in fibrinolysis and proteolysis in spontaneously hypertensive rats, provided rampirylom treatment is important for the knowledge of the mechanisms of occurrence and development of pathological conditions that will enable to improve early diagnosis, improved treatment of cerebrovascular disease and timely preventive measures.

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