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Diagnostics of erythrocytes' microrheological features and early abnormalities of rats in the model of experimental hypertension development



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ABSTRACT

Difficulties in the early stage detection of erythrocytes' microrheological abnormalities during the development of hypertension are connected with falling out of clinicians' opinion of persons with first signs of this pathology. It dictates the necessity of experimental investigations' fulfillment on laboratory animals with just developed hypertension in them. Eighty-seven of healthy male rats of Wistar line at the age of 2.5–3 months were taken into the investigation. Twenty-nine animals of them had experienced no impacts and composed the control group. Fifty-eight rats had hypertension developed by prescribing them cardio-angioneuro pathogenic semisynthetic diet. For the purpose of investigation biochemical, hematological, and statistical methods were used. As a result of hypertension, the rats turned out to have developed an increase of systolic and diastolic pressure. At regular exercise, on the treadmill, the rats were noted to have a gradual decrease of their values during 60 days of investigation to the normal level. During hypertension

development lipids' peroxidation activated in rats' erythrocytes because the activity of their antioxidant protection weakened. When hypertension occurred in rats the erythrocytes-discocytes quantity in blood was found to have decreased. It was accompanied by an increase of reversibly and irreversibly changed erythrocytes quantity in the examined animals' blood. When hypertension occurred in rats a quick rise of erythrocytes' sum in aggregate was found and the rise in these aggregates' quantity was due to lowering of free erythrocytes' number. During experimental hypertension modeling, we noticed that there was a very early decrease in the quantity of erythrocytes-discocytes in the rat blood, and their level raised reversibly and irreversibly with the strengthening of their aggregative ability. It happened because of the weakening of erythrocytes' antioxidant protection, and activation of lipids' peroxidation in them.

Keywords: rats, erythrocytes, microrheological features, experiment, hypertension.

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INTRODUCTION

For further progressive development, modern medicine needs investigations of different early mechanisms of diseases causing pathogenesis¹⁻³ which can often be done only in experiments⁴⁻⁷ with compulsory consideration of their social aspects.⁸ The largest social significance at the modern stage of medical development as a science belongs to investigations of blood hemostasis-rheological aspects⁹⁻¹¹ including those of erythrocytes^{12,13} in pathological conditions and especially at heart's and vessels' diseases.¹⁴⁻¹⁷ Among this group of diseases in the whole civilized world, one of leading positions is occupied by Arterial hypertension (AH) leading to the wide invalidation of the population and contributing greatly to mortality figures of healthy persons.¹⁸ It was noticed that a detailed clinical picture of AH especially burdened by metabolic abnormalities is that there is high activity of platelets,^{19,20} neutrophils²¹ and worsening of erythrocytes' microrheological features.²² It significantly lowers microcirculation efficiency and metabolism

intensity in all the tissues.²³⁻²⁵ At the same time, the state of erythrocytes' microrheological characteristics at early stages of AH development is not yet studied enough.²⁶ Difficulties of the early stage detection of erythrocytes' microrheological abnormalities' development in a human being are connected with falling out of clinicians' opinion of persons with first signs of this pathology including AH.^{27,28} It dictates the necessity of experimental investigations' fulfillment on laboratory animals with its development modeling in them.^{29,30}

In this connection, we put the aim of our work: to observe for experimental conditions of AH in the development process of erythrocytes' microrheological features' abnormalities.

MATERIALS AND METHODS

All the investigations in the present work were conducted in full correspondence with ethical norms and recommendations on humanization of work with laboratory animals containing "The European Convention on the protection of vertebrate

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Table 1 Dynamics of arterial pressure, biochemical, and hematological parameters in experimental rats

Indicators	Experimental group, M±m		Control group, M±m
	initial state, n=58	end of Pathology modeling, n=58	healthy, n=29
systolic blood pressure, mm Hg.	110.1±0.29	155.3±0.46 p<0.01	110.3±0.36
diastolic blood pressure, mm Hg.	74.6±0.24	95.1±0.39 p<0.01	74.2±0.30
Acylhydroperoxides of plasma, D ₂₃₃ /l ml	1.62±0.017	1.91±0.034 p<0.01	1.63±0.019
Thiobarbituric acid-products of plasma, mkmol/l	3.71±0.036	4.22±0.047 p<0.01	3.69±0.32
Antioxidant activity of plasma, %	28.7±0.31	24.3±0.49 p<0.01	28.8±0.29
cholesterol of erythrocytes, mkmol/10 ¹² erythrocytes	0.92±0.022	1.00±0.031 p<0.05	0.92±0.023
common phospholipids of erythrocytes, mkmol/10 ¹² erythrocytes	0.67±0.024	0.65±0.036	0.68±0.022
cholesterol/common phospholipids of erythrocytes	1,37±0.020	1.56±0.029 p<0.01	1.35±0.019
acylhydroperoxides of erythrocytes, D ₂₃₃ /10 ¹² erythrocytes	2.76±0.019	3.36±0.024 p<0.01	2.74±0.017
malonic dialdehyde of erythrocytes, nmol/10 ¹² erythrocytes	0.90±0.016	1.12±0.029 p<0.01	0.91±0.018
catalase of erythrocytes, ME/10 ¹² erythrocytes	9870.0±12.6	8802.0±14.7 p<0.01	9880.0±11.9
superoxidismutase of erythrocytes, ME/10 ¹² erythrocytes	1820.0±3.74	1640.0±4.28 p<0.05	1830.0±4.05
erythrocytes-discocytes,%	83.8±0.39	72.7±0.48 p<0.01	84.0±0.34
reversibly modified erythrocytes,%	9.7±0.32	16.8±0.41 p<0.01	9.5±0.29
irreversibly modified erythrocytes,%	6.5±0.28	10.5±0.32 p<0.01	6.5±0.25
sum of all the erythrocytes in an aggregate	37.5±0.09	46.8±0.12 p<0.01	37.3±0.07
quantity of aggregates	8.7±0.10	11.8±0.09 p<0.01	8.8±0.04
quantity of free erythrocytes	248.1±0.56	229.0±0.67 p<0.01	249.2±0.52

Conventions: p - found reliability of indices' differences with control group.

animals used for experiments or in other scientific purposes" (Strasbourg, 1986).

We took into investigation 87 healthy male rats of Wistar line at the age of 2.5–3 months received from healthy females by the first-second farrow. Animals' body mass at the time of taking them into investigation composed 210.6±0.52 gr, their abdominal circumference 13.8±0.28sm. Before the investigation, all the rats had not participated in any experiments and had suffered no diseases. Twenty-nine animals among them did not experience any impacts and composed control group of rats.

According to researched methods³¹ 58 rats we developed hypertension by subjecting them to cardio angioneuro pathogenic semisynthetic diet for 2 weeks, enriched by cholesterol, burdened by salts of twice-substituted sodium phosphate water and deficient in potassium and magnesium. Daily intramuscular administration of hydrocortisone acetate suspension - 1.5 mg on 100 gr of animal's body mass, changing water for drinking with 1% salt solution, and cold impact at 4°C during 4 hours on animals for 2 weeks.

Measuring of animals' arterial pressure (AP) was fulfilled noninvasively with the help of the MLU/4c501 device by the method of tail cuff application (MedLab, China).

The level of lipids peroxidation (LPO) in animals' plasma was found according to the quantity of thiobarbituric acid (TBA)-active products in it. With the help of "Agat-Med" and according to the content of acylhydroperoxides (AHP)³² taking into consideration the level of antioxidant activity (AOA) of liquid blood part.³³ Lipid peroxidation in erythrocytes was defined with the help of malonic dialdehyde (MDA) and AHP concentrations in them.³² We estimated the level of common cholesterol (CS) enzymatically by "Vitaldiagnostikum" (Russia) and found the concentrations of common phospholipids (CPL) according to phosphorus content with the calculation of the ratio CCS/CPL. In erythrocytes, we defined the activity of catalase and superoxide dismutase (SOD).³²

Cytoarchitectonics of red corpuscles was defined with the help of light phase-contrast microscopy. All the erythrocytes were subdivided into discocytes, reversibly deformed, and irreversibly changed forms. Erythrocytes' aggregative activity was found out with the help of light microscope in Goriajev's.³⁴

The results were processed by Student's criterion (t) and systematic multifactorial analysis.

RESULTS

As the result of AH formation in rats there developed in them stable increase of systolic and diastolic pressure levels (Table 1).

At experimental AH development in rats, we noticed an increase of AHP and TBA-active products' quantity in plasma. The quantity of plasma TBA-products in experimental animals underwent the analogical dynamics. Found LPO increase at AH modeling in rats turned out to be possible because of plasma AOA weakening on 18.1% (table 1).

At AH development in experimental rats cholesterol quantity in erythrocytes rose a bit (to 1.00 ± 0.031 mkmol/ 10^{12} ar.), while the content of CPL in their membranes had a tendency to decrease (to 0.65 ± 0.036 mkmol/ 10^{12} ar.), what led to a reliable increase of the gradient CS/CPL.

During AH development LPO activated in rats' erythrocytes owing to activity weakening of their antioxidant protection (Table 1).

At AH development in rats, we found a reliable decrease of erythrocytes-discocytes quantity in the blood which was accompanied by the blood of experimental animals by corresponding quantity dynamics of reversibly and irreversibly changed erythrocytes, increasing at AH development. At AH development in rats, we found some increase of red corpuscles in aggregate and quantity of these aggregates.

Having applied systematic multifactorial analysis, we managed to calculate separately in experimental rats the pro-aggregative potential of erythrocytes (PPE) and their de-aggregative potential (DPE). Found the degree of impact on them with all the registered parameters, and to realize the calculation of the common erythrocytes' aggregative potential value (CAPE).

In PPE of experimental rats with developed AH the following values were rather heavy: the average aggregate's size (Pi=586.7), aggregates' quantity (Pi=476.8). The quantity of irreversibly transformed erythrocytes (Pi=427.8), index of aggregation (Pi=426.3) and the sum of all the erythrocytes being in aggregates (Pi=403.1). The value of suspended average PPE estimating on the whole phenomena providing erythrocyte aggregation in rats with AH was equal to 0.112. Very significant in DPE structure in rats with AH were the following values: the activity of erythrocyte SOD (Pi=518.3), the quantity of erythrocytes-discocytes (Pi=522.6), and catalase functional ability (Pi=531.5). The value of suspended average DPE, estimating the state of mechanisms which do not allow erythrocytes to aggregate, in the case of rats with AH was equal to 0.083, and the level of common aggregative potential of their erythrocytes was equal to 0.029.

DISCUSSION

Despite the fact that on the basis of AH development in human population it depends not only environmental impacts but also presence of different

genetic abnormalities,³⁵⁻³⁸ the applied model can be considered as quite adequate for the achievement of the work involved.

In the result of experimental AH development in rats, we created pathological state very near to the one that genetically determined AH.^{39,40} At the same time, AOA of blood weaken promotes an increase in the quantity of AHP and TBA-products and negatively influencing metabolism in tissues. Besides, activation of LPO processes in the liquid part of blood causes alteration of vascular endothelium^{41,42} of regular blood elements in the outer structure^{43,44} which includes their population - erythrocytes, thereby negatively influencing their different functions.^{13,14} It is burdened by hypoxia that inevitably develops in rats with AH⁴⁵ and forming membranopathy in erythrocytes with an increase of CS in them due to the lowering of CPL on simultaneous activation of lipids' peroxidation in erythrocytes as a result of their antioxidant protection lowering.

Transformation mostly promotes the loss by a part of erythrocytes of normal biconcave form which makes their movement along capillaries difficult.²² Transformation changes in erythrocytes lead to their increase in the blood of their reversibly and irreversibly changed forms.²⁵ So, in rats by the moment of AH development in them, the quantity of erythrocytes transformed by echinocytosis into spheres, with the appearance of different forms "acanthas" on their surface and stomatocytosis to unilaterally arched disk, significantly exceeds the same at the beginning. Further transformation inevitably goes in the direction of spherocytocytosis, spherostomatocyte and, finally, spherocyte which soon must be destroyed.¹³

In rats with AH strengthening of erythrocytes' aggregation the charge on their membrane changes because of the degradation of a glycoprotein on it. They have a negative charge on the background of active LPO.⁴⁶ Intensification of oxygen active forms' generation in these conditions provides the rats with AH by oxidative alteration of membrane's structures at the simultaneous damage of plasma globular proteins are able to be connected in the form of "bridges" between separate erythrocytes and continue the process of their aggregation. Besides, LPO products gradually increase the threshold of erythrocytes' deaggregation on behalf of erythrocytes' adhesion strengthening in aggregates, accelerating the rise of aggregation process between itself and platelets on the background of oxidative damages of their membrane's lipids.^{47,48}

It becomes clear that very early rise of erythrocytes' aggregation in rats was found with developing AH is mostly connected with the impact of catecholamines, the concentration of which, as it is

known, from the first development stages of cardiovascular pathology and especially AH significantly increases.⁴⁹ As a result of α_1 -receptors' activation in these conditions functions as a mediator in the Ca^{2+} -calmodulin system with involvement into the cascade of phosphatidyl inositol's intracellular reactions. Activation of α_2 -adrenoreceptors takes place by adenylate cyclase suppression owing to the impact of a receptor-agonist on Gi-proteins leading to lowering of cAMP quantity in a cell and stimulating Ca^{2+} inflow into a cell^{50,51} which additionally increases the erythrocytes' aggregation.

The rising number of freely circulating aggregates in the blood of rats with AH aggregates leads to damage of endothelial bed of their vessels promoting exposure of subendothelial structures what "start" the hemostasis processes.⁵²⁻⁵⁴ Disrupts metabolism⁵⁵⁻⁵⁷ and significantly worsens the processes of blood rheology.⁵⁸⁻⁶⁰ Rising number of freely circulating aggregates can block the part vasa vasorum,⁶¹ thereby significantly weakening vascular metabolism, promoting depression of de-aggregates' output in endothelial cells.⁶²⁻⁶⁴

CONCLUSION

During experimental AH modeling in rats' blood we noticed very early lowering of erythrocytes-discocytes content, a rise in the level of their reversibly and irreversibly changed variants with the strengthening of their aggregative ability. It happens in the background of an increase in the gradient of cholesterol/common phospholipid in erythrocytes, weakening of their antioxidant protection and activation of lipids' peroxidation in them.

CONFLICT OF INTEREST

No Conflict of interest to declare.

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