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Diagnostics of erythrocytes' early microrheological abnormalities in rats with experimentally developed obesity



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ABSTRACT

Background: Difficulties of the earliest stages' detection of erythrocytes' microrheological abnormalities' development at obesity are connected with falling out of clinicians' field of view of persons with first signs of this pathology. It dictates the necessity of experimental investigations' fulfillment on laboratory animals with just developed obesity in them.

Methods: 91 of healthy male-rats of Vistar line at the age of 2.5-3 months were taken into an investigation. 29 animals of them had experienced no impacts and composed the control group. In 62 rats after their putting into small cages (one specimen - in a cage) during 30 days there was developed OB as the result of giving them of high-caloric diet from combined feed (47%), sweet condensed milk (44%), vegetable oil (8%) and vegetable starch (1%). There were used biochemical, hematological and statistical methods of investigation. During obesity development lipids' peroxidation activated in rats'

erythrocytes because of activity weakening of their antioxidant protection.

Results: At obesity development in rats, there was found reliable decrease of erythrocytes-discocytes quantity in blood. It was accompanied by the increase of reversibly and irreversibly changed erythrocytes' quantity in examined animals' blood. At obesity development in rats, there was found the quick rise of erythrocytes' sum in aggregate and these aggregates' quantity at lowering of free erythrocytes' number.

Conclusion: During experimental obesity modeling we noticed very early in rats' blood decrease of erythrocytes-discocytes' quantity, the level rise of their reversibly and irreversibly varieties with the strengthening of their aggregative ability. It takes place in the background of a weakening of erythrocytes' antioxidant protection and activation of lipids' peroxidation in them.

Keywords: rats, erythrocytes, microrheological features, experiment, obesity

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INTRODUCTION

Further deepening of medical knowledge about mechanisms of the earliest pathology development stages is impossible without the active usage of numerous experimental models on animals^{1,2,3,4} with obligatory consideration of main social⁵ consequences of examined pathology. Taking into consideration fundamental significance for a body's vital activity provision of functional and rheological features of basic regular blood elements^{6,7,8} and especially their most numerous population - erythrocytes^{9,10} at different diseases^{10,11} including very widespread in developed countries cardio-vascular pathology, researchers pay great attention to them.^{12,13,14} As a serious basis for this pathology, we consider now obesity (OB) which having genetic^{15,16} and behavioral component¹⁷ causes metabolic abnormalities in the whole body^{18,19} sometimes promoting firm invalidation of a person in the nearest future.²⁰ It is caused by the

fact that developing in a patient's body dysfunctions lead to activation of neutrophils,²¹ platelets²² and change microrheological peculiarities of erythrocytes²³ worsening metabolism in all the tissues.^{24,25,26} However, the state of erythrocytes' microrheological characteristics at early stages of OB development is not yet studied well enough. Complexity in the finding of the earliest stages of erythrocytes' microrheological abnormalities in a human being with initial signs of obesity is connected with these persons' fall out of clinicians' field of view.^{27,28} It dictates the need of conducting of experimental investigations on laboratory animals with modeling of this pathology development in them.^{29,30} Conducting of such experiments will allow to trace the dynamics of the body's common state³¹ in tight connection with early hemostatic and hemorheological³² and also early vascular dysfunctions.^{33,34} Besides, conducting of experimental investigations

on obesity models can help in working out of rational and effective approaches for early removal of initial rheological abnormalities and activation of hemostasis system.^{35,36}

In this connection we put the following aim for our work: to estimate appearing at experimental obesity development early changes in erythrocytes' microrheological features.

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

We took into investigation of 91 healthy male-rats Vistar line at the age of 2.5-3 months received from healthy females by the first-second farrow. Animals' body mass at the moment of taking them into investigation composed 209.7 ± 0.49 gr, their abdominal circumference – 13.5 ± 0.24 sm. Before the investigation, all the rats hadn't participated in any experiments and had suffered no diseases. 29 animals of them experienced no impacts and formed the control group of rats.

In 62 rats after putting them into small cages (one specimen - in a cage) for 30 days, there was developed OB as the result of giving them of high-caloric diet from combined feed (47%), sweet condensed milk (44%), vegetable oil (8%) and vegetable starch (1%).³⁸ Given model allows modeling in maximal degree all the obesity peculiarities relevant to a human being.³⁹

Measuring of animals' arterial pressure (AP) was fulfilled noninvasively with the help of the device MLU/4c501 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 a set "Agat-Med" and according to the content of acylhydroperoxides (AHP)⁴⁰ taking into consideration the level of antioxidant activity (AOA) of blood liquid part.⁴¹ LPO in erythrocytes was defined with the help of concentrations in them of malonic dialdehyde (MDA) and AHP.⁴⁰ We estimated in them enzymatically the level of common cholesterol (CCS) by a set "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).⁴⁰

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.⁴² Erythrocytes' aggregative activity was found out with the help of light microscope in Goriajev's box by their aggregates' quantity, the quantity of aggregated and not having entered the aggregation red corpuscles in the meal of washed erythrocytes.⁴³

The results were processed by Student's criterion (t).

RESULTS

In the result of OB model's reproduction, the rats have developed a stable increase of body mass and the bulk of abdominal cavity (table 1).

At experimental OB development in rats, we noticed the increase of AHP and TBA-active products' quantity in plasma. The quantities of plasma TBA-products in experimental animals underwent the analogical dynamics. Found LPO increase at OB modeling in rats turned out to be possible because of plasma AOA weakening on 18,1% (table 1).

At OB development in experimental rats cholesterol quantity in erythrocytes rose a bit (to 1.06 ± 0.027 mkmol/ 10^{12} ar.), while the content of CPL in their membranes tended to decrease (to 0.61 ± 0.034 mkmol/ 10^{12} ar.), what led to a reliable increase of the gradient CS/CPL.

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

At OB development in rats, we found a reliable decrease of erythrocytes-discocytes quantity in blood which. It was accompanied in blood of experimental animals by corresponding quantity dynamics of changed reversibly and irreversibly erythrocytes, increasing at OB development. At OB development in rats we found sum increase of red corpuscles in aggregate and quantity of these aggregates at simultaneous number lowering of free red corpuscles (table 1).

DISCUSSION

Despite the fact that in the basis of OB development in human population lie not only environmental impacts but also presence of different genetic abnormalities,^{44,45} the applied model can be considered as quite adequate for the achievement of putting in the work purpose.

In the result of experimental OB development in rats, we created pathological state very near to such one as genetically determined OB.^{46,47} At the same

Table 1 Dynamics of Body Mass, Biochemical and Hematological Indices of Experimental Rats (Conditional signs: p - found reliability of indices' dynamics on the background of experimental pathology development)

Indicators	Experimental group, M±m		Control group, M±m healthy, n=29
	initial state, n=62	end of pathology modeling, n=62	
Value of body mass, kg	224.1±0.48	281.3±0.34 p<0.01	215.1±0.43
Abdominal cavity, cm	13.9±0.24	16.9±0.27 p<0.01	215.1±0.43
Acylhydroperoxides of plasma, D ₂₃₃ /l ml	1.60±0.012	1.92±0.032 p<0.01	1.63±0.019
Thiobarbituric acid-products of plasma, mkmol/l	3.68±0.031	4.29±0.044 p<0.01	3.69±0.32
Antioxidant activity of plasma, %	28.9±0.29	24.4±0.44 p<0.01	28.8±0.29
cholesterol of erythrocytes, mkmol/10 ¹² erythrocytes	0.91±0.019	1.06±0.027 p<0.01	0.92±0.023
common phospholipids of erythrocytes, mkmol/10 ¹² erythrocytes	0.67±0.022	0.61±0.034 p<0.01	0.68±0.022
cholesterol/common phospholipids of erythrocytes	1.36±0.032	1.74±0.037 p<0.01	1.35±0.019
acylhydroperoxides of erythrocytes, D ₂₃₃ /10 ¹² erythrocytes	2.75±0.016	3.51±0.025 p<0.01	2.74±0.017
malonic dialdehyde of erythrocytes, nmol/10 ¹² erythrocytes	0.92±0.015	1.16±0.027 p<0.01	0.91±0.018
catalase of erythrocytes, ME/10 ¹² erythrocytes	9920.0±14.9	8750.0±17.3 p<0.01	9880.0±11.9
superoxidismutase of erythrocytes, ME/10 ¹² erythrocytes	1835.0±2.90	1600.0±4.65 p<0.01	1830.0±4.05
erythrocytes-discocytes,%	84.4±0.35	71.8±0.49 p<0.01	84.0±0.34
reversibly modified erythrocytes,%	9.5±0.34	17.0±0.48 p<0.01	9.5±0.29
irreversibly modified erythrocytes,%	6.1±0.24	11.2±0.31 p<0.01	6.5±0.25
sum of all the erythrocytes in an aggregate	37.2±0.08	46.2±0.11 p<0.01	37.3±0.07
quantity of aggregates	8.6±0.07	12.0±0.10 p<0.01	8.8±0.04
quantity of free erythrocytes	247.5±0.52	226.1±0.64 p<0.01	249.2±0.52

time, AOA of blood weakens very fast promoting quantity increase in it 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^{48,49} of regular blood elements' outer structures^{50,51} including the most numerous their population - erythrocytes, thereby negatively influencing their different functions.^{10,11} It is burdened by hypoxia inevitably developing in rats with OB⁵² and forming in erythrocytes membranopathy having in its basis increase of CS in them in them

with the tendency to CPL lowering at simultaneous activation in erythrocytes of lipids' peroxidation in the result of their antioxidant protection lowering.

Forming situation mostly promotes the loss by a part of erythrocytes of normal biconcave form what makes the process of their moving along capillaries difficult.¹⁹ Forming changes in erythrocytes lead to quantity increase in the blood of their reversibly and irreversibly changed forms.²² So, in rats by the moment of OB 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 spherocytosis, spherostomatocyt and, finally, spherocyte which soon must be destroyed.¹⁰

Found in rats with formed OB strengthening of erythrocytes' aggregation has mostly in its basis appearing changes of their membrane's charge because of glycoproteins' degradation on it. They have the negative charge on the background of active LPO.⁵³ Intensification of oxygen active forms' generation in these conditions provides the rats with OB by oxidative alteration of membrane's structures at the simultaneous damage of plasma globular proteins able to be connected in the kind of "bridges" between separate erythrocytes and realize the process of their aggregation. Besides, LPO products gradually increase the threshold of erythrocytes' deaggregation on behalf of erythrocytes' adhesion strengthening in aggregates, speed rise of aggregation process between itself and platelets on the background of oxidative damages of their membrane's lipids.^{54,55}

It becomes clear that found the very early rise of erythrocytes' aggregation in rats with developing OB 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 OB significantly increases.⁵⁶ As the result of α_1 -receptors' activation in these conditions as mediator functions the system Ca^{2+} -calmodulin with involvement in 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^{57,58} what additionally rises erythrocytes' aggregation.

The number rise of freely moving in the blood of rats with OB aggregates leads to damage of endothelial bed of their vessels promoting exposure of subendothelial structures what "start" hemostasis processes, disrupts metabolism and significantly worsens the processes of blood rheology.^{54,59} Rising number of freely circulating aggregates can block the part vasa vasorum, thereby significantly weakening vascular metabolism, promoting depression of deaggregates output in endothelial cells.^{60,61}

In this connection even recently developed obesity should be considered as very dangerous state connected with the development of metabolic abnormalities complex^{62,63} able to worsen headlong erythrocytes' microrheological features and so weaken hemodynamics in capillaries. As it was

shown earlier, such abnormalities can cause evident activation of hemostasis system's components^{64,65} significantly increases the risk of thrombosis coming.⁶⁶ All these demands from clinicians to pay more attention to initial forms of obesity.

CONCLUSION

During experimental OB modeling in rats' blood, we noticed very early lowering of erythrocytes-discocytes content, raise the level of their reversibly and irreversibly changed variants with the strengthening of their aggregative ability. It happens in the background of increase in erythrocytes of cholesterol/common phospholipids' gradient, weakening of their antioxidant protection and activation of lipids' peroxidation in them. For this reason, brief existence of obesity in a body can lead to the development of metabolic abnormalities' complex able to worsen headlong erythrocytes' microrheological features and, so, break hemodynamics in capillaries.

CONFLICT OF INTEREST

All authors declare there is no conflict of interest regarding publication of this manuscript.

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