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The effects of meldonium on microrheological abnormalities of erythrocytes in rats with obesity: An experimental study



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ABSTRACT

Background: The microrheological disorders of red blood cells in obesity is often missed by the researchers. This study aimed to report an experimental investigation on laboratory animals with developed obesity and to find out the effect of meldonium on the erythrocytes.

Methods: A total of 95 healthy male-rats of Vistar line were taken into the investigation, 29 animals had experienced no impacts and allocated as the control group, while 64 rats which had developed obesity induced by a cardioangioneuropathogenic semisynthetic diet into the obesity group. These rats were casually divided into an experimental (34 rats) group and the control group (30 rats). The rats of the experimental group in the next ten days were intragastrically injected with meldonium for 80 mg/kg. The biochemical, hematological and statistical methods of investigation were used in this study.

Results: During the formation of obesity and the use of meldonium, the body weight of the rats were gradually decreased to the normal level. On the obese rat's group receiving meldonium, the content of the lipids peroxidation products in erythrocytes progressively decreased and reached the level of the healthy control rats group. Moreover, there was a decrease in the number of erythrocytes-discoytes accompanied by an increase in the reversible and irreversible changes. These values were returned to the level of the healthy control rats group at the end of the observation. This pattern was observed in the total number of erythrocytes aggregate and free erythrocytes.

Conclusion: The application of meldonium eliminates the existing erythrocytes abnormal microrheological features in the rats with recently developed obesity.

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

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INTRODUCTION

Recently, the practical biology is actively studying the early manifestations of different pathologies and mechanisms of its development, given their different aspects.¹⁻⁵ The major formed elements of blood, and especially their most numerous group - red blood cells in various cardiovascular diseases and metabolic disorders have been in the focus of attention of various researchers.⁶⁻¹⁴ Among these disorders, the level of a particular blood cells component may rise under the influence of genetic predisposition, and the lifestyle changes such as the abdominal type of obesity accompanied by dyslipidemia, hypertension and metabolic syndrome.¹⁵⁻²⁰ It was noted that at hemodynamic and metabolic abnormalities we could notice a high activity of neutrophils, platelets and worsening of erythrocytes' microrheological features.²¹⁻²³ The microcirculation efficiency and metabolism intensity in the

tissues are lower than the healthy people.²⁴⁻²⁶ The inability to explore the earliest stages of the erythrocytes' microrheological abnormalities development in a human at the beginning of OB signs which is often to be missed by clinicians causes the need to conduct experimental investigations on laboratory animals with OB modeling in them.^{27,28}

A non-medication impact of regular muscle activity in an early stage of complicated metabolic abnormalities is highly efficient in lowering blood pressure, improve the weakened thrombocyte and the vascular dysfunctions and age changes.²⁹⁻³⁵ However, a regular muscle load is not acceptable for all patients, as not all of them agree to try it out. Therefore, it is essential to test the effectiveness of Meldonium cytoprotection against the microrheological properties of red blood cells at the onset of the development of obesity. The most realistic way

of getting the information is through an experiment which can be beneficial for the future of clinical investigations directed at its correctional impacts in the early development of OB.³⁶⁻³⁸ Thus, we aim to find out the effect of meldonium in the development process of erythrocytes' microrheological abnormalities in the experimental OB.

METHODS

This study was conducted in full correspondence with the 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 investigate a total of 95 healthy male-rats of Vistar line at the age of 2.5-3 months received from healthy females by the first-second farrow. The average weight of the rats at the start of the investigation was 208.2 ± 0.45 gram, with an abdominal circumference of 13.2 ± 0.26 Cm. Before the study, all the rats hadn't participated in any experiments and had suffered no diseases. Twenty-nine of them experienced no impacts and a composed control group of healthy rats. They were examined twice: at the beginning and the age of 5-5.5 months, i.e., simultaneously with the experimental group at the end of the investigation.

A total of 64 rats were put into small cages for 30 days to developed OB as the result of high caloric diet from a cereal mixtures (47%), sweet condensed milk (44%), vegetable oil (8%) and vegetable starch (1%).³⁸ Then, these rats were casually divided into experimental (34 rats) group and a control group of sick rats (30 rats). The rats from the experimental group received intragastrically with 80 mg/kg Meldonium (Pharmstandard-Leksredstva, Russia) for ten subsequent days.³⁹ The animals, which are composed of the control group of sick rats, were examined twice - at the moment when the pathological development observed in them and at the age of 5-5.5 months, i.e., at the same periods when we finished the investigation of rats with OB receiving meldonium.

The level of lipids peroxidation (LPO) in animals' plasma was determined using the quantity of thiobarbituric-acid (TBA)-active products with the help of a set "Agat-Med" and the content of acylhydroperoxides (AHP) taking into consideration the level of antioxidant activity (AOA) of blood liquid part.^{40,41} The LPO in erythrocytes was defined with the help of the concentrations of malonic dialdehyde (MDA) and AHP.⁴⁰ In erythrocytes, we determined the activity of catalase and superoxide dismutase (SOD).⁴⁰

The Cytoarchitectonics of red corpuscles was defined with the help of light phase-contrast microscope. All the erythrocytes were subdivided into discocytes, reversibly deformed and irreversibly changed forms.⁴ The erythrocytes' aggregative activity was examined under the light microscope in Gorjaev'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). Statistical processing of received information was made with the help of a programme package "Statistics for Windows v. 6.0", "Microsof Excel". Differences in data were considered reliable in case of $p < 0.05$.

RESULTS

In the conclusion of OB model's reproduction, the rats developed a stable increase in body mass and bulk of abdominal cavity. There is no marked changes in their mean body mass and abdominal circumference between the Meldonium group and OB group (table 1). Example: There is a significantly higher mean body mass between the mean body mass of the experimental group at the end of pathology modeling and the initial state for 282.3 ± 0.39 kg and 208.2 ± 0.45 kg, respectively ($p < 0.01$).

In the OB rats group, we noticed an increase in AHP and TBA-active products level in plasma. In the course of the observation rats with OB, AHP concentration in plasma gradually decreased towards the end of the investigation for 1.63 ± 0.026 D₂₃₃/1 ml. The level of plasma TBA-products in experimental animals was found to be similar with the rats with OB. The LPO level was increased in the OB modeling rats because of plasma AOA weakening for 13.7%. The use of meldonium has led to the increase in the given index level from $24.8 \pm 0.46\%$ to $28.2 \pm 0.31\%$ at the day-60 of investigation ($p < 0.01$) (table 1).

During the OB development, the LPO was activated in rats' erythrocytes due to the weakening of their antioxidant protection. The administration of meldonium progressively lowered the AHP content in erythrocytes of rats with OB and reached the control level of healthy rats by the 60th day of the experiment. The experimental rats follow the same pattern regarding the concentration of erythrocyte MDA for 0.92 ± 0.019 nmol/10¹² at the day-60 of the research which is corresponded to the values of the healthy rat's control group. The changes in the LPO activity of erythrocytes in the OB experimental animals may result from the changes in their antioxidant system which can be measured from the catalase and superoxide dismutase activities. The

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

Indicators	Experimental formation of pathology (M±m)		Use of meldonium in rats with formed pathology (M±m, n=34)				Control (M±m)	
	initial state, (n=64)	end of pathology modeling (n=64)	initial state	20 days	40 days	60 days	Sick (n=30)	Healthy (n=29)
Value of body mass, kg	208.2±0.45	282.3±0.39 p<0.01	281.7±0.42 p<0.01	276.8±0.56 p<0.01	272.0±0.31 p<0.01	271.1±0.49 p<0.01	284.6±0.58 p<0.01	215.1±0.43
Abdominal cavity, Cm	13.2±0.26	16.6±0.22 p<0.01	16.8±0.26 p<0.01	16.8±0.35 p<0.01	16.6±0.25 p<0.05	16.4±0.32 p<0.01	17.2±0.46	13.1±0.45
Acyhydroperoxides of plasma, D ₂₃₃ /l ml	1.60±0.014	1.94±0.035 p<0.01	1.93±0.032 p<0.01	1.85±0.029 p<0.01	1.70±0.035 p<0.05	1.63±0.026	1.96±0.032 p<0.01	1.63±0.019
Thiobarbituric acid-products of plasma, mkmol/l	3.68±0.032	4.32±0.040 p<0.01	4.35±0.037 p<0.01	4.12±0.030 p<0.01	3.92±0.034 p<0.01	3.73±0.022	4.28±0.041 p<0.01	3.69±0.32
Antioxidant activity of plasma, %	28.9±0.27	24.6±0.42 p<0.01	24.8±0.46 p<0.01	25.7±0.40 p<0.01	26.5±0.33 p<0.05	28.2±0.31	24.0±0.49 p<0.01	28.8±0.29
Acyhydroperoxides of erythrocytes, D ₂₃₃ /10 ¹² erythrocytes	2.75±0.012	3.52±0.027 p<0.01	3.50±0.028 p<0.01	3.26±0.032 p<0.01	3.10±0.026 p<0.05	2.81±0.024	3.55±0.039 p<0.01	2.74±0.017
Malonic dialdehyde of erythrocytes, nmol/10 ¹² erythrocytes	0.92±0.014	1.17±0.025 p<0.01	1.16±0.024 p<0.01	1.07±0.021 p<0.01	1.00±0.020 p<0.05	0.92±0.019	1.17±0.040 p<0.01	0.91±0.018
Catalase of erythrocytes, ME/10 ¹² erythrocytes	9920.0±12.5	8700.0±16.5 p<0.01	8720.0±21.3 p<0.01	9010.0±19.5 p<0.01	9400.0±17.3 p<0.05	9920.0±15.1	8735.0±18.4 p<0.01	9880.0±11.9
Superoxidismutase of erythrocytes, ME/10 ¹² erythrocytes	1835.0±2.87	1610.0±4.12 p<0.01	1600.0±4.92 p<0.01	1680.0±4.52 p<0.01	1770.0±3.84 p<0.05	1810.0±4.02	1590.0±7.10 p<0.01	1830.0±4.05
Erythrocytes-discocytes,%	84.4±0.39	71.0±0.42 p<0.01	72.0±0.36 p<0.01	75.0±0.45 p<0.01	78.1±0.39 p<0.05	83.2±0.32	70.5±0.54 p<0.01	84.0±0.34
Reversibly modified erythrocytes,%	9.5±0.32	17.8±0.41 p<0.01	17.2±0.46 p<0.01	14.7±0.35 p<0.01	12.9±0.29 p<0.05	10.3±0.27	17.5±0.49 p<0.01	9.5±0.29
Irreversibly modified erythrocytes,%	6.1±0.27	11.2±0.32 p<0.01	10.8±0.30 p<0.01	10.3±0.26 p<0.01	9.0±0.25 p<0.01	6.5±0.29	12.0±0.38 p<0.01	6.5±0.25
Sum of all the erythrocytes in an aggregate, units	37.2±0.09	46.0±0.12 p<0.01	46.1±0.09 p<0.01	43.2±0.07 p<0.01	40.6±0.06 p<0.05	37.9±0.04	46.7±0.14 p<0.01	37.3±0.07
Quantity of aggregates, units	8.6±0.08	12.2±0.12 p<0.01	12.3±0.08 p<0.01	10.8±0.06 p<0.01	9.2±0.08 p<0.05	8.5±0.10	12.4±0.10 p<0.01	8.8±0.04
Quantity of free erythrocytes, units	247.5±0.43	225.4±0.55 p<0.01	229.6±0.59 p<0.01	231.8±0.52 p<0.01	242.0±0.47	248.7±0.41	227.3±0.65 p<0.01	249.2±0.52

*Conventional signs: p - found reliability of indices' differences with control group of healthy animals.

levels of these antioxidant features in erythrocytes of experimental rats were decreased during the OB development and reached the values nearly

the same with one in the control group of healthy rats owing to their activation on 13.7% and 13.1%, correspondingly (p<0.01) (table 1).

In the OB groups, we found a decrease in the erythrocytes-discocytes quantity in the blood which was returning to control the level of healthy rats during the 60 days of observations. A similar pattern was also found in the blood of experimental animals by corresponding quantity dynamics of changed reversibly and irreversibly erythrocytes, which was increased at OB development and decreased to the control level of healthy rats ($10.3 \pm 0.27\%$ and $6.5 \pm 0.29\%$, correspondingly). At the OB development in rats, we found a total increase of red corpuscles in aggregate and quantity of these aggregates at simultaneous number lowering of free red corpuscles having returned to control values of healthy animals to the end of 60 days of observations (table 1).

The absence of meldonium use in the control group of sick rats was accompanied with the biochemical and hematological abnormalities, inherent for invariably high OB level.

DISCUSSION

The applied model helps to trace the early disorders arising in the body associated with OB, which is very difficult to do in clinical practice.^{44,45}

The experiment of developing OB in rats has resulted in the creation of a pathological state nearly identical to the genetically determined OB.^{46,47} During this time, the AOA level of blood weakens which is followed by an increase in the AHP and TBA-products and negatively influencing metabolism in tissues. Moreover, the activation of LPO processes in the liquid part of blood causes an alteration of the vascular endothelium of the regular blood elements' outer structures which is including the most abundant component of their population – erythrocytes and negatively affecting their function.^{10,11,48-51} The burdened from hypoxia in the rats with OB affects the erythrocytes and disrupting its membrane.

The erythrocyte loses their usual biconcave form and affects their circulation in the capillaries.¹⁹ The change in the erythrocytes leads to an increase in the quantity of the reversible and irreversible forms of erythrocytes.⁵² In our experiment, the rats with OB show a change in the number of erythrocytes at the beginning of the OB development. The transition of erythrocytes from a discoid foma to an echinocyte, and then to a stomatocyte or sphere significantly worsens the rheological properties of a significant part of red blood cells. This transformation inevitably proceeds into the forming of spherocinocyt, spherostomatocyt and, the final form, spherocyte, which will eventually be destroyed.¹⁰

The increase in the erythrocytes aggregation in the OB rats group was caused by the changes in

their membrane's polarity due to the degradation of the glycoproteins. In the normal condition, the erythrocytes have a negative charge when the LPO was active.⁵³ The oxidative stress of the membrane structures and the damage to the plasma globular proteins formed a "bridge" between the erythrocytes and promoted their aggregations. Moreover, the LPO products gradually increase the erythrocytes disaggregation threshold resulting in the strengthening of erythrocytes aggregation, supporting the aggregation process between itself and platelets on the presence of the oxidative damages to their lipid membrane.^{54,55}

The rise of the erythrocytes aggregation in rats with developed OB is mostly associated with the effect of catecholamines which is increased during the first development stages of cardiovascular pathology and OB.⁵⁶ The result of α_1 -receptors' activation in these conditions was resulting in the cascade of phosphatidyl inositol's intracellular reactions which was mediated with the Ca^{2+} -calmodulin system. On the other hand, the activation of α_2 -adrenoreceptors takes place by adenylate cyclase suppression owing to the impact of a receptor-agonist on Gi-proteins leading to the reduction in the quantity of cAMF in a cell and stimulating Ca^{2+} inflow into a cell that additionally increase the erythrocytes' aggregation.^{57,58} The rise in the number of freely moving aggregates in the blood of rats with OB leads to the damage of endothelial bed in the vessels. The damage promotes the exposure of subendothelial structures and induces the hemostasis processes which is worsening the process of blood rheology.^{54,59} The rise of the circulating aggregates can block the vasa vasorum and significantly weaken the vascular metabolism, promoting a depression of deaggregates output in endothelial cells.^{60,61}

The use of meldonium results in the antioxidant protection of blood plasma and erythrocytes with the reduced level of LPO.^{62,63} In the experiment, the antioxidant plasma activity caused the reduced level of AHP and TBA products in the rats with developed OB. The reduced level of LPO lowering in the blood promotes stabilization in the endothelium and receptors on the outer membranes of normal blood elements including erythrocytes. Simultaneously, with the increase in the antioxidant protection of erythrocytes, it inhibits the lipid peroxidation process.¹⁰ The use of meldonium was able to quickly change and positively affecting the structural-functional features of red corpuscles' membranes and their protein cytoskeleton. In the presence of the weakened LPO, the ATF synthesis in erythrocytes and other regular blood elements, lead to the increase in the activity of the ion pumps which are providing optimum content of Ca^{2+} ,

Na⁺ and K⁺ in erythrocytes.^{9,22,64} It is possible that the cytoarchitectonics' stabilization provides an optimum provision of spectrin net structure with the provision of necessary distance between spectrin molecules. A 60-days observation of rats with modeled OB showed that the use of meldonium leads to the normalization of the erythrocytes' cytoarchitectonics with the lower content of their activated forms to the level of the control groups. In rats, a decrease in the number of altered forms of red blood cells was observed in the blood. In rats with OB who received meldonium, there is a significantly reduced quantity of erythrocytes that proceed into the process of echinocytosis to the state of spheres, and particularly, with the appearance of acanthas of different forms on their membranes. The process of erythrocytes' transformation through stomatocytosis to unilaterally arched disk are minimized in these conditions. These conditions promote a better circulation along the vessels, especially of the least caliber.²⁷

The aggregation of erythrocytes was observed to be gradually normalized at the end of 60 days observation period in the OB developed rats groups. This is mostly affected by the changes in their membranes polarity because of the optimization of glycoproteins in the presence of weakened LPO. The plasma globular proteins can be connected as "bridges" between erythrocytes to minimized the damage from their aggregation. Moreover, the reduced level of LPO-products in plasma and erythrocytes lowers their deaggregation threshold because of the weakening of erythrocytes' adhesion in aggregates.¹² It is proposed that the use of meldonium in rats reduce the aggregation of erythrocytes by minimizing the effect of catecholamines.⁵⁶ The presence of α_1 -receptors activity decreases the functional readiness of the Ca²⁺-calmodulin system and phosphatidylinositol's intracellular reactions. The diminishing activity of α_2 -adrenoreceptors leads to the activation of adenylate cyclase during physiological impact from receptors on Gi-proteins which is causing the rise of cAMP level in a cell, blocking Ca²⁺ inflow and reducing the erythrocytes aggregation.^{19,65}

The lowering level of aggregation in the experimental rats' blood after the use of meldonium stabilize the endothelial bed, which leads to a minimum exposition of subendothelial structures and prevents the stimulation of hemostasis processes and subsequently promotes the processes of blood rheology.^{20,66} It is especially important for hemocirculation in vasa vasorum, which plays a great role in supporting the vascular wall's tropism and physiological level by providing its aggregative effect on erythrocytes through optimizing the output of nitric oxide and prostacyclin in endothelium.^{31,39,63}

CONCLUSION

During the experimental OB modeling in rats' blood, we noticed a very early decline in the erythrocytes-discocytes content, rise in the level of their reversible and irreversible variants with the increase in their aggregative ability. These were supported with the diminished antioxidant protection of erythrocytes and the activation of lipids' peroxidation in them. The use of meldonium eliminates pre-existing abnormalities of the erythrocytes microrheological features in rats with experimentally developed OB. Thus, it controls the level of aggregates in experimental rats blood and prevents the hemostasis process. These data provide physicians and cardiologists a reason to focus on the potential of meldonium in developing OB treatment.

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ETHICAL CLEARANCE

This study has obtained ethics approval prior to the study conducted.

CONFLICT OF INTERESTS

The authors declare that there were no conflicts of interest in the process of this study.

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AUTHOR CONTRIBUTION

All of the authors are equally contributed to the study from the study framework, data gathering, data analysis, until reporting the result of study.

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