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DETECTION OF EARLY DEMONSTRATIONS OF ERYTHROCYTES' AND THROMBOCYTES' AGGREGATION IN CASE OF DEVELOPMENT OF ARTERIAL HYPERTENSION AND DISLIPIDEMIA WITH THE HELP OF MICE IN THE MODEL OF THESE PATHOLOGIES' CONSECUTIVE FORMATION

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ABSTRACT

In this work we investigated early pathology demonstrations in mice' plasma, erythrocytes and thrombocytes in conditions of experimental consecutive formation of arterial hypertension and dislipidemia. We took into investigation 68 male-mice of Vistar line at the age of 2,5-3 months.33 animals of them had never received any impact and composed control group. Mice included into experimental group (35 animals) were consecutively formed to have arterial hypertention, and then - dislipidemia. During the experiment these animals were investigated 5 times. We applied biochemical, hematological and statistical methods of investigation towards experimental and control mice. At once after the formation of arterial hypertension and dislipidemia mice were noted to have quick increase of lipids' peroxidation processes in plasma, early number rise of reversibly and irreversibly modified erythrocytes and rapid increase of thrombocytes' intravascular activity. While mice were being formed to have arterial hypertension and dislipidemia they were noticed to have gradual increase of lipids' peroxidation in erythrocytes and thrombocytes at the rise of their aggregation. Control mice were noted to have stable normal level of investigated biochemical and hematological characteristics. The results of the fulfilled investigation can serve the basis for understanding of the earliest changes in erythrocytes' microrheological features and thrombocytes' activity at the debut of arterial hypertension development and start of dislipidemia formation on its background. Referring to the received in the present work results we consider the following factors to be quite possible: effectiveness rise in search of prophylaxis varients of erythrocytes' microrheological features' worsening and increase of thrombocytes' activity at the start of arterial hypertension development and especially at the addition of dislipidemia to it.

KEY WORDS: ***a model, arterial hypertension, dislipidemia, mice, erythrocytes, thrombocytes, aggregation, surface geometry.***

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INTRODUCTION

Nowadays medical science keeps in the focus of its rapt attention the investigation of the early stages of different pathologies development[1-3], primary mechanisms of their realization[4-5] and their social aspects and consequences[6]. Great interest os shown by investigators to functional and rheological peculiarities of regular blood elements in the norm[7-8] and pathology[9-10] and especially - to erythrocytes[11-12] and thrombocytes[13-14] at rather wide-spread nowadays cardiovascular and metabolic pathologies[15-17]. Among them one of the leading positions in the whole civilized world is occupied by arterial hypertension (AH) leading to wide-scale invalidization of population and contributing greatly to mortality figures of working population[18-20]. In industrially developed countries we often meet dislipidemia formed on the basis of AH what rather negatively influences the common prognosis[21-22]. It was noted that at AH large-scale clinical picture especially burdened by metabolic disturbances they have high thrombocytes' activity[23-24] and decrease of erythrocytes' microrheological features[25-26] with the weakening of vascular control over them[27-28]. It significantly reduces the efficiency of microcirculation and intensity of metabolism in all the tissues[29-30]. The state of erythrocytes' microrheological characteristics and thrombocytes' activity is now actively investigated at already formed cardiovascular and metabolic pathology[31-32] whereas their peculiarities at the early stages of AH development in combination with dislipidemia are not adequately explored. It is impossible to watch to the end the earliest development stages of erythrocytes' microrheological disturbances and thrombocytes' haemostatic features in case of a man because persons with first AH signs and dislipidemia developed on its basis[33] are out of clinicians' view. That's why there exists the demand to make experimental investigations with the help of laboratory animals[34] with modelling of AH and then - dislipidemia in them. So the aim of our work was as follows: to watch early pathology signs in mice' plasma, erythrocytes and thrombocytes in conditions of experimental consecutive formation of arterial hypertension and dislipidemia.

MATERIALS AND METHODS

Ethical clearance

Fulfilled work was made in accordance with ethical principles established by the European convention on vertebrates' protection which are used for experimental and other scientific purposes (adopted in Strasbourg 18.03.1986 and ratified in Strasbourg 15.06.2006). The work was approved by ethic Committee of the Kursk Institute of social education (branch) of Russian state social University (Moscow) (Protocol №5 from 20.05.2015) and ethics Committee of the all-Russian scientific research Institute of physiology, biochemistry and nutrition, Borovsk (Kaluga region, Russia) (Protocol №4 from 21.04.2015).

Experimental design

In our investigation we took 68 male-mice of Vistar line at the age of 2,5-3 months got from healthy females by first or second brood. 33 animals of them received combined feed by "Laboratorkorm" production (Russia) in corpore, were exposed to nothing and composed control group. They were investigated twice: at the beginning and at the age of 4-4,5 months, i.e. simultaneously with the completion of observation after experimental mice. Because of the absence of statistically significant differences between the results of both investigations received data are presented by one figure - their arithmetic average. 35 mice were formed to have arterial hypertension with the help of giving them of cardiovasonephopathogenic semisynthetic diet during 2 weeks. This diet was enriched by cholesterin, filled by salts of twice-substituted phosphate aqueous natrium and scarce in potassium and magnesium suspension of hydrocortisone acetate. It was injected intramuscularly daily by 1,5mg on each 100gr of animal's body mass. Water for drinking was changed into 1% solution of common salt. The animals were also impacted by cold - at the end of the given 2weeks' impact - 4ºC during 4 hours[35]. Three days later after AH formation these mice were put into small cages in 1 mouse for 30 days. They began to receive high-calorific diet consisting of combined feed (47%), sweet condensed milk (44%), vegetable oil (8%) and vegetable starch (1%). It provided the following composition of their ration: lipids 29,6%, proteins 14,8%, carbohydrates 55,6%[36]. Experimental mice were investigated five times - at the beginning, at the end of AH formation, in 3 days after AH modelling (at the beginning of additional dislipidemia formation0, in 15 days after the beginning of dislipidemia formation and at the end of its experimental formation. Measurements of animals' arterial pressure (AP) were fulfilled noninvasively with the help of the device MLU/4c501 by tail cuff superposition method (MedLab, China).

Observation of biochemical parameters

The level of lipids' peroxidation (POL) in animals' plasma was found according to the quantity of existing in it thiobarbituric acid (TBA)-active products with the help of the set "Agat-Med" (Russia) and according to the contents of acylhydroperoxides (AHP)[37] taking into consideration the level of antioxidant activity (AOA) of the blood liquid part[38]. In erythrocytes and thrombocytes we defined the concentration of malonic dialdehyde (MDA) and AHP and also the activity of catalase and superoxide dismutase (SOD)[39]. In erythrocytes and thrombocytes we appreciated enzymatically the level of cholesterol (CS) with the help of the set "Vitaldiagnosticum" (Russia) and found out the concentration of common phospholipids (CPL) by ratio calculation CS/CPL[40]. Citoarchitecture of red blood platelets was defined with the help of light phase-contrast microscopy with their subdivision into discocytes of reversibly deformed and irreversibly modified forms[41]. Erythrocytes' aggregation activity was defined with the help of light microscope in Gorjaev's box by the quantity of their aggregates, by the quantity of aggregated and nonaggregated erythrocytes in the suspension of washed erythrocytes[42]. The quantity of thrombocytes in blood was calculated in Gorjaev's box. Thrombocytes' aggregation activity was investigated by visual micromethod with the usage of inductors ADP ($0,5\times10^{-4}$M), collagen (dilution 1:2 of the main suspension), thrombine (0,125 units/ml), rhystomisin

(0,8mg/ml), adrenalin ($5,0\times10^{-6}$ M) and hydrogen peroxide ($7,3\times10^{-3}$ M) with standardized thrombocytes' quantity in investigated plasma - 200×10^{9} thrombocytes[42]. The morphology of intravascular thrombocytes' activity (IAT) was defined with the usage of phase-contrast microscope[42].

Statistical analysis

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

RESULTS

Experimental mice after AH formation were noted to have stable level increase of systolic and diastolic AT. It was still kept on the background of dislipidemia development till the end of investigation (table 1).

Dynamics of plasma biochemical parameters

Mice after AH formation were noted to have increase in plasma of AHP and TBA-active products quantities. When these animals happened to have dislipidemia the concentration of AHP and TBA-active products in plasma additionally increased becoming significantly higher control figures. Found POL increase at consecutive modelling of AH and dislipidemia turned out to be possible because of gradual weakening of plasma AOA summarily on 43,8% (table 1).

Changes in biochemical characteristics of red blood cells

After AH formation cholesterine quantity in mice' erythrocytes increased to some extent while CPL content in their membranes had the tendency to decrease. Given changes were additionally intensified at dislipidemia development and it led to the increase of CS/CPL gradient on 43,1%. During AH formation we noticed in mice' erythrocytes POL activation due to weakening of their antioxidant protection activity. Given changes were reliably strengthened during subsequent dislipidemia development causing AHP and MDA growth in erythrocytes to 3,02±0,020 $D_{233}/10^{12}$ ar. and 1,67±0,014 nmol/10^{12} ar. POL activation in model animals' erythrocytes at AH and then - dislipidemia formation turned out to be possible as the result of their catalase and superoxidismutase depression summarily on 24,8% and 22,6%, correspondingly (table 2).

Dynamics microrheological properties of erythrocytes

At AH formation and then - dislipidemia mice' blood was noted to have decrease of erythrocytes-discocytes quantity and increase of erythrocytes modified both reversibly and irreversibly. When mice got the development of a full picture of double pathology we found the increase of erythrocytes' sum in aggregate and these aggregates' quantity at simultaneous decrease of free erythrocytes' number on 35,0%, 73,2% and 19,7%, correspondingly (table 2).

Changes of biochemical indicators of platelets

As a result of AH development mice' thrombocytes were noticed to have some increase of cholesterine quantity while CPL content in their membranes stayed at this stage still permanent. On the background of second pathology development in thrombocytes' membranes of experimental animals we noticed increase of the first and decrease of the second indices what led finally to the increase of CS/CPL gradient on 25,9%. Already during AH formation POL activated in mice' thrombocytes due to weakening of their antioxidant protection. Given changes were reliably strengthened during following dislipidemia development providing AHP and MDA summarized growth in thrombocytes on 36,8% and 54,3%, correspondingly. Found changes of POL activity in model animals' thrombocytes at AH and dislipidemia formation turned out to be possible as the result of summarized depression of their catalase and superoxidismutase on 27,2% and 13,0%, correspondingly (table 3).

Dynamics of platelet activity

At AH formation and then- dislipidemia in mice' blood thrombocytes' quantity stayed permanent. Creation of double pathology model made observed animals decrease AT development time with all the used inductors (table 3). So, to the end of model realization the time of AT attack in response to collagen impact reduced on 33,8%, with ADP - on 41,6%, with rhystomisin - on 36,8%, with H_2O_2 - on35,4%, with thrombine - on 32,1%, with adrenalin - on 24,6%. Already at AH development in mice' blood we noticed decrease of discocytes' quantity on 5,9% what deepened on the background of following dislipidemia formation additionally decreasing on 7,4%. It was combined during the whole period of observation with gradual increase of activated thrombocytes' sum on 75,7% due to smooth increase of all their varieties (disco-echinocytes, spherocytes, sphero-echinocytes and bipolar forms). The number of freely circulating in blood little, medium and large thrombocyte aggregates while double pathology modelling gradually increased in 2,8 times and in 10,3 times, correspondingly (table 3).

Table 1
Dynamics of arterial pressure and biochemical plasma indices of experimental mice

Registrated parameters	Experimental formation of AH, M±m, n=35		Experimental formation of dislipidemia on the background of AH, M±m, n=35			Control, M±m, n=33
	initial state	end of AH formation	initial state	intermediate stage	end of dislipidemia formation on the background of AH	
systolic blood pressure, mm et.al. Hg.	110,4±0,23	152,6±0,41 p<0,01	152,0±0,39 p<0,01	149,9±0,51 p<0,01	152,4±0,51 p<0,01	110,5±0,33
diastolic blood pressure, mm et.al. Hg.	74,2±0,32	94,8±0,33 p<0,01	95,1±0,28 p<0,01	94,6±0,39 p<0,01	95,2±0,42 p<0,01	73,6±0,40
Total cholesterol, mmol / l	2,18±0,007	2,20±0,009	2,21±0,01	2,50±0,010 p<0,01	2,82±0,011 p<0,01	2,19±0,008
HDL cholesterol, mmol / l	1,14±0,009	1,13±0,011	1,16±0,012	1,00±0,010	0,89±0,016	1,17±0,005

				p<0,05	p<0,01	
LDL cholesterol, mmol /l	0,56±0,008	0,58±0,007	0,57±0,005	0,88±0,009 p<0,01	1,12±0,011 p<0,01	0,55±0,002
VLDL, mmol /l	0,48±0,006	0,49±0,009	0,48±0,005	0,62±0,008 p<0,01	0,81±0,006 p<0,01	0,47±0,005
TG, mmol /l	1,06±0,009	1,08±0,009	1,07±0,004	1,38±0,009 p<0,01	1,79±0,010 p<0,01	1,05±0,004
total lipids, mmol /l	3,02±0,012	3,05±0,008	3,06±0,009	4,28±0,010 p<0,01	5,20±0,12 p<0,01	3,04±0,007
AHP, D_{233} /1ml	1,35±0,007	1,74±0,006 p<0,01	1,78±0,005 p<0,01	2,36±0,009 p<0,01	2,85±0,012 p<0,01	1,38±0,004
TBA-compounds, mcmol / l	2,15±0,009	2,91±0,007 p<0,01	2,94±0,008 p<0,01	3,41±0,016 p<0,01	4,20±0,014 p<0,01	2,12±0,008
AOA, %	28,9±0,15	24,7±0,09 p<0,05	24,8±0,13 p<0,05	22,3±0,10 p<0,01	20,1±0,09 p<0,01	29,0±0,10

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

Table 2
Dynamics of taken into account erythrocyte indices of experimental mice

Registrated parameters	**Experimental formation of AH, M±m, n=35**		**Experimental formation of dislipidemia on the background of AH, M±m, n=35**			**Control, M±m, n=33**
	initial state	**end of AH formation**	**initial state**	**intermediate stage**	**end of dislipidemia formation on the background of AH**	
cholesterol of erythrocytes, mkmol/10^{12} erythrocytes	0,92±0,004	0,94±0,006	0,94±0,007	1,09±0,005 p<0,01	1,16±0,009 p<0,01	0,93±0,005
common phospholipids of erythrocytes, mkmol/10^{12} erythrocytes	0,49±0,003	0,47±0,004	0,47±0,006	0,45±0,005 p<0,05	0,43±0,009 p<0,01	0,49±0,003
cholesterol/common phospholipids of erythrocytes	1,88±0,003	2,00±0,007 p<0,05	2,00±0,005 p<0,05	2,42±0,009 p<0,01	2,69±0,010 p<0,01	1,89±0,004
acylhydroperoxides of erythrocytes, D_{233}/10^{12} erythrocytes	2,04±0,012	2,39±0,010 p<0,01	2,41±0,015 p<0,01	2,88±0,018 p<0,01	3,02±0,020 p<0,01	2,05±0,010
malonic dialdehyde of erythrocytes, nmol/10^{12} erythrocytes	1,11±0,006	1,26±0,007 p<0,01	1,25±0,009 p<0,01	1,39±0,012 p<0,01	1,67±0,014 p<0,01	1,10±0,006
catalase of erythrocytes, ME/10^{12} erythrocytes	9274,1±10,60	8400,0±9,80 p<0,01	8410,0±11,50 p<0,01	7900,0±12,30 p<0,01	7430,0±13,10 p<0,01	9300,0±19,40
superoxidismutase of erythrocytes, ME/10^{12} erythrocytes	1815,0±1,02	1700,0±2,10 p<0,05	1705,0±3,05 p<0,05	1660,0±2,72 p<0,01	1480,0±2,84 p<0,01	1820,0±7,54
erythrocytes-discocytes,%	86,1±0,08	77,5±0,05 p<0,01	77,8±0,07 p<0,01	70,6±0,09 p<0,01	65,0±0,13 p<0,01	85,8±0,07
reversibly modified erythrocytes,%	7,7±0,14	15,2±0,15 p<0,01	14,8±0,12 p<0,01	20,6±0,16 p<0,01	25,6±0,11 p<0,01	8,1±0,14
irreversibly modified erythrocytes,%	6,2±0,12	7,3±0,14 p<0,01	7,4±0,10 p<0,01	8,8±0,15 p<0,01	9,4±0,16 p<0,01	6,1±0,09
sum of all the erythrocytes in an aggregate	38,0±0,08	45,2±0,05 p<0,01	45,0±0,06 p<0,015	48,8±0,09 p<0,05	51,3±0,10 p<0,01	37,9±0,11
quantity of aggregates	8,6±0,10	10,7±0,09 p<0,01	10,8±0,11 p<0,01	12,6±0,10 p<0,01	14,9±0,13 p<0,01	8,5±0,07
quantity of free erythrocytes	251,6±0,32	232,6±0,40 p<0,05	233,0±0,48 p<0,05	227,5±0,52 p<0,05	210,1±0,50 p<0,01	249,6±0,17

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

Table 3
Dynamics of taken into account thrombocyte indices of experimental mice

Registrated parameters	**Experimental formation of AH, M±m, n=35**		**Experimental formation of dislipidemia on the background of AH, M±m, n=35**			**Control, M±m, n=33**
	initial state	**end of AH formation**	**initial state**	**intermediate stage**	**end of dislipidemia formation on the background of AH**	
cholesterol of thrombocytes, mkmol/10^{9} thrombocytes	0,65±0,005	0,67±0,004	0,67±0,006	0,71±0,008 p<0,05	0,75±0,009 p<0,01	0,66±0,004
common phospholipids of thrombocytes, mkmol/10^{9} thrombocytes	0,48±0,003	0,48±0,005	0,48±0,005	0,46±0,008 p<0,05	0,44±0,010 p<0,05	0,49±0,006
cholesterol/common phospholipids of thrombocytes	1,35±0,004	1,39±0,007 p<0,05	1,39±0,005 p<0,05	1,54±0,007 p<0,01	1,70±0,008 p<0,01	1,35±0,007
acylhydroperoxides of thrombocytes, D_{233}/10^{9} thrombocytes	1,82±0,007	2,02±0,008 p<0,05	2,03±0,009 p<0,05	2,32±0,005 p<0,01	2,49±0,009 p<0,01	1,83±0,006

malonic dialdehyde of thrombocytes, nmol/10^9 thrombocytes	0,70±0,008	0,83±0,009 p<0,01	0,82±0,009 p<0,01	0,95±0,013 p<0,01	1,08±0,015 p<0,01	0,69±0,007
catalase of thrombocytes, ME/10^9 thrombocytes	8910,0±10,03	8100,0±12,11 p<0,01	8050,0±15,24 p<0,05	7520,0±13,02 p<0,01	7002,0±17,22 p<0,01	8890,0±16,18
superoxidismutase of thrombocytes, ME/10^9 thrombocytes	1650,0±5,28	1560,0±6,03 p<0,05	1570,0±6,36 p<0,05	1500,0±6,61 p<0,01	1460,0±6,92 p<0,01	1650,0±4,65
AT with ADP, s	45,6±0,06	40,5±0,06 p<0,05	40,8±0,08 p<0,05	36,5±0,09 p<0,01	32,2±0,07 p<0,01	45,0±0,10
AT with collagen, s	36,8±0,10	33,0±0,12 p<0,05	33,1±0,09 p<0,05	30,1±0,14 p<0,01	27,5±0,12 p<0,01	36,5±0,09
AT with thrombin, s	57,6±0,07	52,1±0,10 p<0,05	52,3±0,08 p<0,05	47,3±0,14 p<0,01	43,6±0,13 p<0,01	57,7±0,06
AT with ristomycin, s	47,9±0,05	43,6±0,08 p<0,05	43,2±0,09 p<0,05	39,4±0,09 p<0,01	35,0±0,10 p<0,01	47,5±0,07
AT with H_2O_2, s	50,1±0,04	46,2±0,07 p<0,05	46,4±0,08 p<0,05	40,2±0,10 p<0,01	37,0±0,12 p<0,01	49,9±0,08
AT with epinephrine, s	99,2±0,12	91,2±0,14 p<0,05	91,4±0,10 p<0,05	85,6±0,13 p<0,01	79,6±0,15 p<0,01	98,8±0,05
Thrombocytes-discocytes, %	86,0±0,10	81,2±0,12 p<0,05	81,0±0,16 p<0,05	78,2±0,19 p<0,05	75,4±0,23 p<0,01	85,6±0,12
Sum of thrombocytes' active forms, %	14,0±0,08	18,8±0,09 p<0,05	19,0±0,12 p<0,05	21,8±0,15 p<0,01	24,6±0,13 p<0,01	14,4±0,12
Number of little aggregates (in 100 free thrombocytes)	3,0±0,08	5,6±0,09 p<0,01	5,7±0,05 p<0,01	6,9±0,06 p<0,01	8,5±0,09 p<0,01	3,1±0,09
Number of medium and large aggregates (in 100 free thrombocytes)	0,18±0,005	0,49±0,007 p<0,01	0,51±0,09 p<0,01	1,22±0,011 p<0,01	1,86±0,010 p<0,01	0,16±0,004

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

DISCUSSION

Although AH and dislipidemia development in human population has in most cases genetic causes[43-46], formed in this investigation model can be considered to be quite correct in the sense of possibility to watch initial pathological changes in plasma, erythrocytes and thrombocytes as at pathology formation the main moments of AH and dislipidemia pathogenesis are reproduced[47]. During consecutive AH and then-dislipidemia development mice were noted to have quite common for a human being weakening of plasma antioxidant potential[48-49]. It quickly led to the rise of AHP and TBA-active compounds in it what worsened metabolism in tissues[18]. Besides, activation of POL processes in plasma inevitably caused alteration of surface structures of regular blood elements including erythrocytes and thrombocytes rather negatively influencing their morphology and functions[50-51].Forming in the experiment changes in the proportion of CS and CPL membranes of erythrocytes and thrombocytes and activation of POL in them rather quickly disturbed model mice' receptor and postreceptor mechanisms of their functioning. Appeared lipid disbalance in membranes led also to negative dynamics in regulation of ion andantioxidant status in erythrocytes and thrombocytes what provided negative changes of their metabolism and structure-functional features in vessels and regular blood elements. A human being has similar signs at a rather early stage of AH development[52] or sometimes while ageing[53]. Appearing in model mice' organisms' changes led to quantity decrease of negative charges exhibited to the surface of erythrocytes responsible for their support шт disaggregated state[22]. It was provided by degradation of having negative charges glycoproteins on their membranes. In the basis of this phenomenon also lay the decrease of sialic acids' quantity in erythrocytes' membranes on the background of POL activation. It led to the evident growth of erythrocytes' ability to aggregation. Strengthening of active oxygen forms' generation in these conditions provided in a being formed model oxidative alteration of membrane's structures at simultaneous damage of plasma globular proteins able to join in the form of "bridges" between separate erythrocytes and realize the process of their aggregation what is rather typical for the patients with AH and dislipidemia[54]. We have some ground to suppose that found increase of erythrocytes' aggregation in case of experimental mice is also connected with the impact of catecholamines' surplus which concentration at different disturbances in an organism, and especially AH in combination with dislipidemia can significantly increase[55]. Such increase in the given case can have compensatory meaning as it is directed at the intensification of metabolism in experiencing metabolic difficulties organs and tissues. Catecholamines acting through specific α-adrenoreceptors: α_1, α_2a, α_2b and α_2c involve as mediators of their impact the system Ca^{2+}-calmodulin, cascade of intracellular reactions of phosphatidyl inositol on the background of adenylate cyclase suppression and decrease of quantity with AMP in erythrocytes[11]. Formed situation greatly favoured the fact that significant part of erythrocytes lost their biconcave form which caused difficulties when they were moving along vessels in microcirculation basin. Changes appearing in erythrocytes worsened their citoarchitecture leading to the increase of their reversibly and irreversibly modified varieties in blood[54]. Increase of experimental mice' thrombocyte sensitivity to aggregation inductors evidently also took place through activation of some mechanisms. So, on their thrombocytes' surface we determined gradually increasing density of glycoproteids Ia - IIa and VI participating in blood platelets' adherence[56]. We judged it by AT intensification in response to collagen. Strengthening of experimental

mice' blood platelets' adherence is also connected with increase of receptors' expression to Willybrand's factor on their surface. Given mechanism of thrombocytes' adhesive activity strengthening of these mice we managed to registrate with the help of gradual AT acceleration with rhystomisin influencing thrombocytes equally to vessels' subendothelial structures[57]. Taking into consideration that for rhystomisin AT coming we need Willybrand's factor fixing by one side of a molecule to rhystomisin and by the other one - to a thrombocyte through its receptor - Ic[58]. In case of experimental mice we could state strengthening of "adherence axis" forming: rhystomisin(collagen) - Willybrand's factor - GPIc. At the same time the very significant quantity increase of Willybrand's factor's binding points on blood platelets' membranes of model mice is an important initial mechanism of thrombocytes' adhesive ability increase. Rise of thrombocytes' sensitivity to collagen should be connected with quantity increase of receptors to it on the surface of blood platelets. It is inevitably accompanied by early phospholipase C activation, synthesis stimulation of diacilglycerol and protein kinase C with the following evident phospholirirovation of contractile system's proteins. In this connection in conditions of early AH and dislipidemia development inositolthreephosphat stimulates more and more active Ca^{2+} coming from the depo of blood platelets contributing to rapid actomнosin reduction and secretion process development[59]. ADP inductor being one of weak inductors of thrombocytes' aggregation more and more actively stimulated blood platelets while realizing models of double pathology. In case of experimental mice it was connected with the increasing quantity of receptors to it on thrombocyte membranes. Besides, activation of thrombocyte ADP-aggregation is always connected with strengthening of fibrinogenic receptors expression on thrombocytes' surface what is accompanied by activation of phospholipase A_2 providing detachment of arachidonic acid out of membrane phospholipids[60]. Found IAT increase of experimental mice indirectly pointed at the level rise of aggregation inductors (thrombin, ADP, adrenalin) in their blood while consecutive AH and dislipidemia formation. It happened at the growth of thrombocytes' basal sensitivity to them. In these conditions blood of experimental mice began to be early characterized by the quantity decrease of intact discoid formed thrombocytes what confirmed activity increase of their receptors. Increase of the number of disco-echinocytes and other active thrombocyte forms in their blood on the background of model formation coincides with the increase of thrombocytes' aggregation activity. It should be mostly connected with the increase of membranepathy evidence on the background of pathology development together with expression rise on thrombocyte surfaces of different receptors[61].

CONCLUSION

Formation of AH and then - dislipidemia in rats quickly weakens antioxidant protection of blood plasma, erythrocytes and thrombocytes strengthening in them POL processes. Developing abnormalities in experimental animals turned out to be able to early worsening erythrocytes' citoarchitecture and intravascular thrombocytes' activity rising their aggregative activity and making these indices comparable with the same ones of people with AH and dislipidemia. Formed model allowed to clear out the question about evidence of early disturbances in plasma, erythrocytes and thrombocytes during consecutive AH and dislipidemia development what is rather characteristic for the great part of population in industrially developed countries. The results of the fulfilled investigation can serve the basis for understanding of the earliest changes in erythrocytes' microrheological features and thrombocytes' activity at the debut of arterial hypertension development and start of dislipidemia formation on its background. Referring to the received in the present work results we consider the following factors to be quite possible: effectiveness rise in search of prophylaxis varients of erythrocytes' microrheological features' worsening and increase of thrombocytes' activity at the start of arterial hypertension development and especially at the addition of dislipidemia to it.

CONFLICT OF INTEREST

No Conflict of interest to declare.

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