Impact of Experimental Development of Arterial Hypertension and Dyslipidemia on Intravascular Activity of Rats' Platelets

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ABSTRACT

Great interest is shown by researchers to functional and rheological features of basic regular blood elements. Platelets are among them and take the most active part in hemostasis at rather wide-spread nowadays cardio-vascular and metabolic diseases. The aim is to analyze dynamics' strengthening of platelets' intravascular activity of rats in conditions of experimental consequent development of arterial hypertension and dyslipidemia. The study used 68 male-rats of Vistar line at the age of 2.5-3 months. Control group was composed of 33 animals. Experimental animals (35 rats) were developed at first – arterial hypertension (usage of cardioangiol pathogenic diet for 2 weeks and impact of cold at the end) and then - dyslipidemia (application of rich in calories diet at

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lowering of motor activity). The rats from experimental group were examined 5 times during the research. The rats from control group were examined twice - at the beginning and at the end of the experiment. While examining experimental and control rats we applied biochemical, hematological and statistical methods of investigation. At consequent arterial hypertension and dyslipidemia development experimental rats had gradual strengthening of lipids' peroxidation processes in plasma (acylhydroperoxides increased in 2.1 times) and platelets (acyl hydroperoxides increased in 1.4 times). Already at arterial hypertension development rats' blood was noted to have lowering of discocytes' quantity on 5.9%, deepening during the further dyslipidemia development on 7.4% more, and reaching 24.6±0.13%. This process was accompanied by gradual increase of activated platelets' sum on 75.7% during the whole period of investigation. The number of small, middle and large platelet aggregates, freely circulating in blood during modeling of double pathology, gradually increased in 2.8 times and in 10.3 times, respectively. Control rats had stable normal level of relevant biochemical and hematological characteristics. Subsequent development of at first arterial hypertension and then – dyslipidemia in rats gradually weakened their antioxidant protection of blood plasma and platelets and strengthened POL processes in them. It also strengthened lipids' peroxidation in them. Developing abnormalities gradually strengthened intravascular platelets' activity and their aggregative ability in experimental animals. The created model allowed tracking the earliest symptoms of strengthening of platelets' intravascular activity against the background of AH and dyslipidemia development.

1. INTRODUCTION

At present medicine devotes special attention to early stages of pathology development and mechanisms providing this development [1,2]. Great interest is shown by researchers to functional and rheological features of basic regular blood elements [3,4,5]. Platelets are among them and take the most active part in hemostasis at rather wide-spread cardio-vascular and metabolic diseases [6,7]. One of the leading positions among them in the whole civilized world is occupied by arterial hypertension (AH) leading to wide incapacitation of population and significantly contributing mortality of persons able to work [8,9]. Different metabolic abnormalities are developed more and more often against the background of AH. One of leading places among them belongs to dyslipidemia. It rather negatively influences the common prognosis [10,11]. It was noticed earlier that at long AH clinical course, especially loaded by metabolic abnormalities, patients had rising platelets aggregative activity [12] and lowering dis aggregative vessels' activity [13]. It essentially activated hemostasis and additionally worsened microcirculation and metabolic processes in all the tissues [14,15]. At the same time, platelets' intravascular activity at initial stages of AH development in combination with dyslipidemia has not yet been fully studied.

It is rather difficult to track on a human being the earliest stages of intravascular platelets' activity rise at the first AH manifestations and developing against its background dyslipidemia because such patients very rarely turn for medical treatment. It dictated the necessity of investigations on laboratory animals [16] with developing of at first AH and then – dyslipidemia in them. The researches, which were conducted earlier, studied development of AH [17,18] and dyslipidemia [19,20] on the models of animals. The researchers estimated different aspects of their pathogenesis [21,22]. At the same time, estimation of the earliest manifestations of platelets' intravascular activity increase in the model of consequent development of AH and dyslipidemia, hasn't yet been studied. In this connection we put the aim: to estimate the dynamics of strengthening of intravascular platelets' activity of rats in conditions of experimental consequent arterial hypertension and dyslipidemia development.

2. MATERIALS AND METHODS

2.1 Materials

Our research was conducted in accordance with ethical principles established by the European Convent on protection of vertebrates which are used for experimental and other scientific purposes (adopted in Strasbourg 18.03.1986 and ratified in Strasbourg 15.06.2006). The research was approved by the Ethics Committee of Kursk Institute of Social Education (a branch of Russian State Social University) (record №5 from 12.05.2014) and All-Russian Research Institute

of Physiology, Biochemistry and Nutrition of Animals (record №6 from 05.06.2014). Ethics Committees ratified the need to use animals for the study, sufficiency of animals' number in the study and humanity and minimum of impact on animals during the experiment.

The study used 68 healthy male-rats of Vistar line at the age of 2.5-3 months got from healthy females by first or second brood. 33 animals of them were fed with combined feed by "Laboratorkorm" production (Russia) in corpore, were exposed to nothing and composed control group. They were examined twice: At the beginning and at the age of 4-4.5 months, i.e. simultaneously with the completion of experimental rats' observation. There were no statistically significant differences between the results of both studies. That's why, received data are presented by one figure - their arithmetic average. 35 rats were to have arterial hypertension after feeding with cardio angionepho-pathogenic semi synthetic diet for 2 weeks. This diet was enriched by cholesterol, filled by salts of twice-substituted phosphate aqueous natrium and scarce in potassium and magnesium suspension of hydrocortisone acetate. This preparation was injected intramuscularly daily by 1.5 mg on each 100 gr of animal's body mass. Water for drinking was substituted by 1% dilution of common salt. The animals were also exposed to cold - at the end of the given 2weeks' impact - 4ºC for 4 hours [23]. In three days after AH development these rats were put into small cages (a rat in a cage) for 30 days. They began to be fed with high-calorific diet consisting of combined feed (47%), sweet condensed milk (44%), vegetable oil (8%) and vegetable starch (1%). So, they got lipids-29.6%, proteins- 14.8%, carbohydrates- 55.6% [24] in their ration.

Experimental rats were examined five times - at the beginning, at the end of AH formation, in 3 days after AH modeling (at the beginning of additional dyslipidemia development), in 15 days after the beginning of dyslipidemia development and at the end of its experimental development.

2.2 Methods

Measurements of animals' arterial pressure (AP) were carried out noninvasively with the help of the device MLU/4c501 by the method of tail cuff superposition (MedLab, China). The level of lipids' peroxidation (POL) in animals' plasma was determined according to the quantity of existing

thiobarbituric acid (TBA)-active products in it with the help of the set "Agat-Med" (Russia) and according to the contents of acylhydroperoxides (AHP), taking into consideration the level of antioxidant activity of the blood liquid part [25].

Concentrations of common cholesterol (CCS) and triglycerides (TG) in animals' blood were determined by enzymatic colorimetric method with application of a set produced by "Vital Diagnostikum". The content of high-density lipoproteins (HDLP) in plasma CS was determined by a set produced by "Olveks Diagnostikum," again by enzymatic colorimetric method. The CS content of low-density lipoproteins (LDLP) was determined using the formula reported by W. Friedwald et al. (1972). Concentration of CS in very low-density lipoproteins (VLDLP) was calculated according to the formula: CS VLDLP = concentration TG/2.2.

We determined the concentration of malondialdehyde (MDA) and AHP and also the activity of catalase and superoxide dismutase (SOD) in platelets [19]. We also estimated enzymatically the level of cholesterol in platelets with the help of the set "Vital Diagnostikum" (Russia) and found the concentration of common phospholipids (CPL) [25]. We carried out washing platelets off plasma for estimation of POL products' content in platelets, level of lipids and antioxidant activity of enzymes. It was done according to the following method. Blood, mixed with 5% ethylene-diamine-tetra-acetic acid, was centrifuged at 1000 turns a minute during 10 minutes. Supernatant layer was put into clean dry test tube and centrifuged at 1500 turns a minute for 6 minutes. Then, the same layer was put into new clean dry test tube and centrifuged at 2200 turns a minute for 15 minutes. In the result, we got precipitation which was composed only of platelets. Then, supernatant liquid was removed, and there was added 1/3 of the volume of initial blood of 0.85% sodium chloride solution to the platelets' precipitation. It was prepared on 2.7% solution of ethylene-diamine-tetra-acetic acid. The precipitation was mixed carefully and centrifuged at 2200 turns a minute for 10 minutes. After that, the supernatant was removed, and there was again added physiological solution to the precipitation which was prepared on the solution of ethylene-diamine-tetra-acetic acid. The described procedure was conducted three times [26].

Statistical processing of received data was made with the help of a programme package "Statistics for Windows v. 6.0", "Microsoft Excel". Differences in data were considered reliable in case of p<0.05.

The quantity of platelets in blood was calculated in Gorjaev's box. The morphology of intravascular platelets' activity was determined with the help of phase-contrast microscope [27]. The results were processed by Student's criterion (t).

3. RESULTS AND DISCUSSION

Experimental rats had stable increase of systolic and diastolic AP levels after AH development. They still had it against the background of dyslipidemia development till the end of investigation (Table 1).

Rats with AH were noted to have increased AHP and TBA-active products' quantity in plasma. At dyslipidemia development AHP and TBA-active products' concentrations in plasma additionally increased in these animals, becoming essentially higher than control figures. Found POL strengthening at consequent modeling of AH and dyslipidemia in rats was possible because of gradual weakening of antioxidant plasma activity in them summarily on 43.8% (Table 1).

At AH development the quantity of cholesterol rose a bit in rats' platelets while the content of common phospholipids in their membranes stayed stable at the given stage. During dyslipidemia development cholesterol rose in them, but common phospholipids lowered (Table 2).

During AH development POL activated in rats' platelets on behalf of activity weakening of their antioxidant protection. Given changes were evidently strengthened during consequent dyslipidemia development. It provided summary growth of AHP and MDA in platelets on 36.8% and 54.3%, respectively. Observed changes of POL activity in platelets of model animals at AH and dyslipidemia development were possible as the result of their catalase and superoxide dismutase summary depression on 27.2% and 13.0%, respectively (Table 2).

There was reached lowering of discocytes' quantity in rats' blood on 6.2% already at AH development. It deepened on 7.4% against the background of further dyslipidemia development. It was accompanied by gradual rise of activated platelets' sum on 75.7% on behalf of smooth increase of all their varieties (disco-echinocytes, spherocytes, sphero-echinocytes and bipolar forms) during the whole period of investigation. The number of small, middle and large platelet aggregates freely circulating in blood, while modeling of double pathology, gradually increased in 2.8 times and in 10.3 times, respectively (Table 2).

In conducted experiment on consequent AH and then - dyslipidemia development in rats we observed rather relevant for a human being [28] weakening of antioxidant plasma potential which led to gradual increase of AHP and TBA-active compounds' quantity in it. Developing activation of POL processes in plasma caused surface structures' alteration of regular blood elements [29] in animals, including platelets. It promoted early increase of their activity [30].

Forming changes in model rats in ratio between lipids' fractions of platelets' membranes and POL activation in them early damaged receptor and post-receptor mechanisms of their functioning. Observed lipid membrane imbalance led to abnormal dynamics of platelet ion and antioxidant regulation [31]. It provided negative changes in their metabolism and activity rise in vessels' lumen what was rather relevant for patients with AH [32].

Observed increase of intravascular platelets' activity in experimental rats pointed indirectly at the rise of inductors' aggregation level (thrombin, ADF, adrenaline) in their blood while AH and then - dyslipidemia development. At the same time, platelets' sensitivity to them increased [33]. On this reason there began to develop reliable lowering of discoid platelets' quantity in blood of experimental rats. It supported activity increase of their receptors [34]. Number increase of platelets' active forms in these animals' blood during the experiment coincided with the increase of their aggregative activity and was connected, first of all, with expression strengthening of fibrinogenic receptors (GP IIb - IIIa) on their membranes [35]. It's evident that in experimental rats it was accompanied by gradual density increase of platelet glycoproteins Ia-IIa, Ib and VI, availability rise of vascular wall's collagen and level increase of von Willebrand Factor in plasma [36].

Table 1. Dynamics of blood pressure and biochemical plasma parameters in experimental rats

Registered parameters	Experimental formation of AH, M±m, n=35		Experimental formation of dyslipidemia against the background of AH, M±m, n=35			Control, M±m, n=33
	Initial stage	End of AH formation	Initial stage	Intermediate stage	End of dislipidemia formation against 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 p<0.05	0.89±0.016 p<0.01	1.17±0.005
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
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, umol/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
antioxidant activity, %	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 – reliability of distinctions of experimental and control values;
Symbols are the same in the next table

Table 2. Dynamics of platelets' biochemical indices and their intravascular activity in experimental rats

Registered parameters	Experimental formation of AH, M±m, n=35		Experimental formation of dyslipidemia against the background of AH, M±m, n=35			Control, M±m, n=33
	Initial stage	End of AH formation	Initial stage	Intermediate stage	End of dislipidemia formation against the background of AH	
cholesterol of platelets, mkmol/10^9 platelets	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 platelets, umol/l /10^9 platelets	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
acylhydroperoxides of platelets, D_{233}/10^9 platelets	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
malondialdehyde of platelets, nmol/10^9 platelets	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 platelets, ME/10^9 platelets	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
Superoxide dismutase of platelets, ME/10^9 platelets	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
Platelets-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 platelets' 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 platelets)	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 platelets)	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

Increase of platelets' activity in the given model should be connected not only with rise of quantity and activity of receptors on their surface [37]. The following factors are also of great significance: activation of phospholipase A_2 and C, intensity of thromboxane A_2 synthesis and factor of platelets' activation, and secretion increase of biologically active substances out of platelets. Besides, while conducting the model of double pathology in platelets, the yield of Ca^{2+} out of the depo was activated what rose actomyosin readiness to fast reduction [38].

4. CONCLUSION

Subsequent development of at first AH and then dyslipidemia in rats quickly weakened antioxidant protection of blood plasma and platelets and strengthened POL processes in them. Developing abnormalities gradually strengthened intravascular platelets' activity and their aggregative ability in experimental animals. The created model allowed tracking the earliest manifestations of strengthening of intravascular activity of platelets against the background of AH development at the beginning and then dyslipidemiya. Such situation is rather common for human beings.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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