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# Aging changes' inhibition of hemostasis and blood rheological features on the background of antioxidant liposomal preparation "Lipovitam-Beta" application

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## ABSTRACT

**Background:** One of geroprotectors for mammals are still polyvitaminic preparations, one of which is Lipovitam-beta. Purpose of research: to estimate Lipovitam-beta impact on the indices of hemostasis and blood rheology systems of aging rats.

**Methods:** We examined 193 healthy outbred male-rats at the age of 24 months being kept in conditions of vivarium and having traditional ration. In experimental group (98 rats) we investigated the impact of Lipovitam-beta feeding on the basis of 5.5 mg on 100 gr of body mass once in 5 days during 6 months on relevant indices. Control group was composed of 95 healthy male-rats. We estimated the basic indices of hemostasis, blood viscosity, aggregation and deformability of erythrocytes at the beginning and in 6 months of investigation.

**Results:** Lipovitam-beta application has led in case of rats from experimental group to reliable lowering of spontaneous and stimulated platelets' aggregation and activity weakening of plasma hemostasis. On the background of Lipovitam-beta feeding to rats we found lowering of blood viscosity and erythrocytes' aggregation index what was accompanied by increase of erythrocytes' deformability index.

**Conclusion:** Application of Lipovitam-beta to aging rats led to activity lowering of plasma hemostasis and platelets, improving rheological features what can positively influence microcirculation, the level of vital activity and forthcoming life duration.

**Keywords:** rats, lactation, Lipovitam-beta, hemocoagulation, platelets, blood rheology

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## INTRODUCTION

A living organism while its ontogenesis is in constant interaction with environment which including food composition, can influence its state defining the course of many physiological processes.<sup>1,2</sup> Aging processes affect all levels of a living being's organization negatively, influencing the structure and functions of the whole organism.<sup>3</sup> Gradual wilting inevitably causes increase of different pathologic burden, lowering vital activity and advancing lethal outcome.<sup>4</sup> Gradually, science comes to understand the great significance for mammals' vital activity provision to the state of one of its integrating systems, which is blood.<sup>5</sup>

Its hemostatic and rheological features mostly define the degree of tissues' perfusion and, consequently, anabolism level in an animal's organism and its characteristics at any age.<sup>6</sup> Because of great physiological significance and vulnerability of hemostasis and blood rheology, they are started to be investigated more and more actively.<sup>7</sup>

One of the valid ways causing intensification of anabolic processes in an organism and, thereby, increase of phenotypic manifestation of genetically

conditional features<sup>8,9</sup> is the application of different biologically significant impacts<sup>10,11</sup> and biologically active substances.<sup>12</sup> In their number, we include the rise of physical activity<sup>13</sup> and also application of vitamins. The need for some vitamins in the case of mammals is very high and with the help of ration can't sometimes be covered entirely.<sup>5</sup> One of modern vitamin sources for laboratory mammals is Lipovitam-beta which, being made on the basis of liposomes, can provide maximum vitamins' assimilation by an organism's cells.<sup>14</sup>

It is known that blood is the most labile indicator of an organism's state quickly reacting on different ingredients' inflow.<sup>15,16</sup> The more metabolism in an organism increases under their impact, the more evident will change in the blood.<sup>17,18</sup> Besides, blood changing its composition, hemostatic and rheological features, can itself influence the functional state of the whole organism.<sup>19,20</sup> In this connection we considered to be approved to fulfill estimation of Lipovitam-beta impact in case of aging laboratory rats on physiologically significant indices of hemostasis and blood rheology.

The aim of this study is to estimate Lipovitam-beta impact on the indices of hemostasis system and blood rheology of aging rats.

## MATERIALS AND METHODS

Research was conducted in a strict manner accordance to ethical principles established by the European Convent on protection of the vertebrate used for experimental and other scientific purposes (adopted in Strasbourg March 18, 1986, and confirmed in Strasbourg June 15, 2006) and approved by the local ethic committee of Federal State Budgetary Educational Institution of Higher Education "Samara State Agricultural Academy" (Record №12 dated December 3, 2015) and the local ethic committee of Samara National Research University (Record №11, dated December 4, 2015).

This study involved a total of 193 healthy outbred male-rats of 24 months of age being kept in conditions of specially equipped for rats' keeping vivarium. All the animals were healthy during the time preceded the moment of taking them into the investigation. The animals were casually subdivided into experimental and control groups. The experimental group was composed of 98 rats having additionally received Lipovitam-beta ("Biodom", Russia) on the basis of 5.5 mg on 100 gram of an animal's body mass by its solution in water forcibly being given to drink. The preparation was given twice in seven days during six months of investigation. Control group was composed of 95 male-rats of the same age being kept in the same conditions and receiving the same ration. The examination of animals in both groups was conducted twice, at the beginning and in six months of investigation (at the age of 30 months).

All the rats were examined with the object to the content of fibrinogen in blood by Klause' modified method.<sup>21</sup> Estimation of plasminogen level was defined by a kinetic method with the help of the device FP-901 ("LabSystems", Finland) with chromogen substrates ("Dade Behring", Germany). The concentration of soluble fibrin-monomeric complexes (SFMC) was defined by a visual method with the help of reagents by the firm "Technology-standard", Russia.<sup>21</sup> Activated partial thromboplastin time (APTT) was examined with the help of coagulometer "HumaClot" ("HUMAN GmbH", Germany) with a set of reagents HemoStat aPTT-EL. The measurement of international normalized relation (INR) was made by Quick's method.<sup>21</sup> Platelets' aggregative ability was examined with the help of two-channel laser analyzer of platelets' aggregation ("Biola", Russia) by the turbo-dymetric method. As inductor, we applied 0,5mkM ADP.<sup>22</sup>

Registration of blood viscosity was fulfilled by rotary viscosimeter AKP-2 ("Melt", Russia) at shift speeds 200 sec<sup>-1</sup> and 20 sec<sup>-1</sup> with the consequent calculation of erythrocytes' aggregation index and deformability index.<sup>22</sup> Statistical processing of the received results was made with the help of Student's t-criterion. Statistical processing of received information was made with the help of a programme package "Statistics for Windows v. 6.0", "MicrosoftExcel". Differences in data were considered reliable in case of p<0.05.

## RESULTS

Estimation of hemostasis state on in the end of both groups rats didn't find significant differences in values of defined indices of coagulant and anti-coagulative systems (table 1). Platelets' functional activity before the start of investigation also had no differences in both groups.

At the beginning of the investigation, we also didn't find any significant differences between both groups of animals as far as indices of blood rheological features are concerned. Blood viscosity at shift speed 200 sec<sup>-1</sup> in the group which later began to receive Lipovitam-beta was 4.20 ± 0.12 centipoise, while in the control group was 4.22 ± 0.17 centipoise. At shift speed 20 sec<sup>-1</sup> the values of blood viscosity were also comparable composing 6.34 ± 0.34 and 6.29 ± 0.32 centipoise, respectively. Initially indices' values of erythrocytes' deformability and erythrocytes' aggregation of animals in both groups statistically didn't differ from each other.

To the end of the study period, the rats receiving Lipovitam-beta were noted to have significant inhibition of APTT, the tendency for increase of INR and plasminogen indices, decrease of fibrinogen and SFMC concentrations. In the control group of rats in 6 months of the study, we noticed decrease of APTT, the tendency for decrease of INR and plasminogen activity, and increase of fibrinogen and SFMC.

After six months of investigation, rats from experimental group were noted to have a decrease of platelets' aggregation (spontaneous on 10.6% and stimulated on 11.1%). In the control group of aging rats, spontaneous and ADP-induced platelets' aggregation significant reliably increased, having exceeded initial values on 11.7% and 30.0%, respectively. At the same time, differences in platelets' aggregation in both groups to the end of investigation composed for spontaneous – 22.9% (p<0.01), for stimulated – 43.7% (p<0.01).

At repeated investigation of accountable indices of blood rheological features in 6 months, we noticed multidirectional tendency of blood

**Table 1** Indices' dynamics of hemostasis and blood rheology

Indices	Lipovitam-beta, n=98		Control, n=95	
	Initial state	After 6 months	Initial state	After 6 months
<b>Indicators of hemostasis</b>				
INR	1.13 ± 0.12	1.22 ± 0.04	1.13 ± 0.17	1.10 ± 0.19
APTT, sec	27.8 ± 1.2	34.6 ± 0.5*	28.1 ± 0.9	26.0 ± 0.7*
Fibrinogen, g/l	3.3 ± 0.22	2.5 ± 0.18*	3.1 ± 0.23	3.7 ± 0.34*
SFMC, mg/decilitre	3.1 ± 0.35	2.5 ± 0.26*	3.0 ± 0.32	3.8 ± 0.20*
Plasminogen, %	84.7 ± 1.6	92.6 ± 1.3	85.3 ± 1.4	80.1 ± 1.8
Spontaneous platelets' aggregation, Units	1.22 ± 0.14	1.09 ± 0.09*	1.20 ± 0.13	1.34 ± 0.17*
Platelets' aggregation 0,5 mkM ADP, Units	2.34 ± 0.12	2.08 ± 0.18*	2.30 ± 0.15	2.99 ± 0.20**
<b>Indices of blood rheology</b>				
Index of erythrocytes' aggregation	1.26 ± 0.04	1.21 ± 0.09	1.27 ± 0.07	1.34 ± 0.12
Index of erythrocytes' deformability	1.11 ± 0.04	1.14 ± 0.07	1.10 ± 0.08	1.08 ± 0.10
Blood viscosity at 200 sec <sup>-1</sup> , centipoise	4.20 ± 0.12	4.02 ± 0.19	4.22 ± 0.17	4.46 ± 0.29
Blood viscosity at 20 sec <sup>-1</sup> , centipoise	6.34 ± 0.34	5.81 ± 0.42	6.29 ± 0.32	6.73 ± 0.49

Conventions: reliability of dynamics during six months of observation \* -  $p < 0.05$ , \*\* -  $p < 0.01$ .

viscosity common for animals of both groups. The rats from experimental group were noted to have the tendency to decrease of blood viscosity at shift speeds 20 sec<sup>-1</sup> and 200 sec<sup>-1</sup> on 8.4% and 4.3%, respectively. However, indices in control group showed a tendency to grow on 5.7% and 6.9% for blood viscosity at shift speeds of 200 sec<sup>-1</sup> and 20 sec<sup>-1</sup>, correspondingly. Experimental rats were also noted to have a tendency to value decrease of erythrocytes' aggregation index by 4.0%, while control animals were found to have a tendency to increase by 5.5%. At the same time index of erythrocytes' deformability of aging rats having received Lipovitam-beta had a tendency to increase and in the case of control animals had a tendency to decrease.

## DISCUSSION

Being clear genetically coded all the features of a living organism<sup>23,24</sup> can change the degree of their phenotypic survival depending on the environment.<sup>25</sup> In this connection, high urgency of profound investigation continuation of living organisms' physiology different aspects<sup>26</sup> and a human being is still kept, including negative environmental conditions<sup>27,28</sup> with obligatory registration of their social consequences.<sup>29</sup> In this connection, additional investigations devoted to mammals physiology can provide solid basis for further perfection of impedes the aging technologies.<sup>1,3</sup> As the result of summation of received during these investigations knowledge and their consequent practical application we can reach medical progress.<sup>2,5</sup>

In previous investigations they showed with the help of different biological objects that hemostasis<sup>30,31</sup> and hemorheology<sup>32,33</sup> rather keenly respond to environmental impacts including unfavorable factors<sup>34</sup> and development of different dysfunctions<sup>35</sup> and evident pathology<sup>15,16</sup> in an organism. It is also known that inhibition of lipid peroxidation and suppression of lack of vitamins can influence a living organism rather variously and favorably.<sup>38</sup> It was noted that on this background activity decrease of many components of hemostasis system<sup>39</sup> and improvement of blood rheological parameters on the whole and erythrocytes in particular<sup>40,41</sup> are developing. With these very changes of hematological indices, we connect improvement of microcirculation processes and intensification of metabolic processes on the background of different variants' impacts on an organism having in its basis antioxidant impact.<sup>42</sup>

As the result of fulfilled investigation on the background of Lipovitam-beta application, the aging rats were noted to have a weakening of hemostasis activity and improvement of blood rheology. At the same time control results showed reverse regularity having provided to the end of investigation reliability of different accountable indices in both groups of animals.

Received results allow us to consider that additional administration of balanced vitamin complex into an body of aging rats weakens the process of hemocoagulation along both ways of its realization.<sup>21</sup> It is evidently connected with decrease of most coagulation factors participating in it. Most probably that some decrease of

thromboplastin generation and weakening of XII factor's contact activation were also developing in these animals' blood. Lipovitam-beta addition into animals' feeding also led to decrease of fibrinogen and SFMC in blood what pointed at inhibition of its polymerization which was actively restrained by a physiologically activated system of fibrinolysis. Control aging rats were noted to have opposite phenomena promoting the increase of all the hemocoagulation stages and decrease of fibrinolysis activity.

Relying on literature data we can consider that Lipovitam-beta application stimulates organism's antioxidant protection,<sup>12,14</sup> what, as it is known, decreases platelets' ability to both spontaneous and stimulated aggregation.<sup>43,44</sup> We have some basis to think that addition of the given preparation into animals' feeding rises their level of cyclic adenosine monophosphate in platelets and decreases thromboxane A<sub>2</sub> formation. Given situation blocks the formation of thrombocyte aggregates in the lumen of the vascular bed.<sup>45,46</sup> Noted in control rats aptitude to the growth of platelets' aggregative ability may be connected with the decrease of cyclic adenosine monophosphate<sup>47</sup> and increase of thromboxane A<sub>2</sub> synthesis in them,<sup>48,49</sup> naturally leading to increase of platelets' dynamic aggregates' number in these animals' blood.<sup>50,51,52</sup>

The increase of erythrocytes' aggregation which found in control rats can mostly be provided by coming changes of their membranes' charge because of degradation on their surface of some glycoproteins under the influence of always strengthening in conditions of low physical activity lipid peroxidation.<sup>35</sup> Intensification of oxygen active forms' generation in given conditions provides oxidative alteration of erythrocyte membranes' structures in these animals<sup>53</sup> at simultaneous damage of plasma globular proteins having the ability to be connected in the kind of "bridges" between erythrocytes and realize their aggregation.<sup>54</sup> Given situation promotes the growth of disaggregation threshold of control rats red platelets.<sup>55</sup>

It can be hypothesized that weakening of erythrocytes' aggregation which found in experimental rats is mostly provided by strengthening of antioxidant plasma activity as the result of Lipovitam-beta application. On this background we noticed decrease of  $\alpha_1$ -receptors activity, weakening of Ca<sup>2+</sup>-calmodulin system and cascade of phosphatidylinositol intracellular reactions.<sup>56</sup> Taking place at this time decrease of  $\alpha_2$ -adrenoreceptors' activity leads to strengthening of adenylate cyclase during physiological impacts from receptors on

Gi-proteins what causes rise of cyclic adenosine monophosphate quantity in erythrocytes, blocks Ca<sup>2+</sup> inflow into them, providing not high erythrocytes' aggregation.<sup>40,53</sup>

We can consider that erythrocytes of animals having received Lipovitam-beta are more able to deformation what is an important factor of maintenance in them of necessary microcirculatory bed's perfusion. It is possible that in these animals' erythrocytes there is the rise of ATP content what positively influences the interaction of spectrin, actin and other integral proteins of the erythrocyte membrane playing an important role in its features' maintenance. Besides, the rise of erythrocytes' deformability in experimental rats is mostly explained by lowering of unbounded ions Ca<sup>2+</sup> concentration what minimizes its interaction with membrane's proteins and makes it more deformed. At the same time, in erythrocytes of control animals, there is evidently lowering of ATP content what negatively changes the character of interaction of spectrin, actin and erythrocyte membrane's integral proteins. Erythrocytes' deformability lowering in control cows is evidently mostly caused by the rise of unbounded ions Ca<sup>2+</sup> level in them which interacting with membrane's proteins make it firmer and less deformed.<sup>40</sup>

In modern literature, the opinion is gradually forming about close connection of somatic status capacity with their hematological indices.<sup>3,57</sup> At the same time, in this investigation, we didn't trace the whole lactation and, that's why it's too early to make conclusions about the impact of Lipovitam-beta feeding on degree aging trying to explain the results from the position of hemostasis activity dynamics and state of blood rheology.

## CONCLUSION

From senescent rats older than two years get the tendency to hemostasis activation and worsening of blood rheological features which negatively influences microcirculation and can become one of the factors gradually limiting viability. Lipovitam-beta application to aging rats led to decrease of plasma hemostasis and platelets' functional activity, weakening of erythrocytes' aggregative ability, strengthening of their deformability, improvement of blood fluidity at different shift speeds what can positively influence microcirculation and level of dairy anabolism.

## CONFLICT OF INTEREST

No conflict of interest to declare.



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