

Functional Features of Hemocoagulation in Rats with Experimentally Formed Arterial Hypertension in Conditions of Increased Motor Activity

Makurina ON^{1*}, Vorobyeva NV¹, Mal GS², Skripleva EV³ and Skoblikova TV³

¹Department of Biochemistry and Biotechnology, Samara National Research University, Samara, Russia

²Department of Pharmacology, Kursk State Medical University, Kursk, Russia

³Department of Physical Education, South-West State University, Kursk, Russia

Abstract

In rats with experimentally formed arterial hypertension, lipid peroxidation in the plasma, amplification of blood clotting mechanisms with a decrease in anticoagulation and fibrinolysis was noted. Regular forced jogging provided the experimental rats with a positive dynamic of all the indicators considered. Thus, with increased muscular activity, the level of acyl hydro-peroxides of plasma decreased in rats with arterial hypertension formed due to the enhancement of its antioxidant activity. In addition, with the increase in muscle activity in experimental rats, normalization of clotting factor activity, indices of general coagulation tests, antithrombin III activity and protein C was achieved. This was accompanied by a normalization of the level of plasminogen, α 2-antiplasmin and spontaneous euglobulin lysis time. In rats with formed arterial hypertension with standard physical activity, the initial violations of the measured parameters were completely preserved.

Keywords: Rats; Experiment; Arterial hypertension; Blood coagulation; Physical activity

*Correspondence to: Makurina ON, Department of Biochemistry and Biotechnology, Samara National Research University, Samara, Russia, E-mail: ilmedv1@yandex.ru

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Introduction

One of the most important elements of providing homeostasis in the body is the hemocoagulation system. Its activity is of great importance at any age in living organisms in normal and pathological conditions [1]. The activity of the coagulation system strongly determines the fluid properties of the blood, thereby creating the necessary conditions for the development of the body's genetic program [2]. Despite the great advances in medicine, arterial hypertension (AH) is still a very common pathology [3]. Its presence can significantly weaken the body, promote frequent onset of temporary disability and increase the risk of thrombosis [4,5]. At the same time, AH remains an insufficiently studied condition with respect to its effect on blood parameters and especially on its coagulation system [6]. It remains unclear the effect on hemocoagulation in patients with developing hypertension increasing muscle activity. In view of the frequent loss of sight from patients with AH formed in them, it is rational to conduct such studies under experimental conditions. In this connection, the goal is to clarify the dynamics of coagulation hemostasis parameters in laboratory rats with experimentally generated AH on the background of different levels of physical activity.

Materials and Methods

The study was conducted in strict accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific

purposes (adopted in Strasbourg on March, 18th, 1986, and confirmed in Strasbourg on June, 15th, 2006), approved by the local Ethics Committee of Samara National Research University (record No. 12, dated December, 3rd, 2016), the local Ethics Committee of the South-West State University (record No. 11, December, 4th, 2016).

96 non-native male rats aged 2.5-3 months were taken from the healthy females with a second-third litter. The body weight of animals at the time of taking into the study was 211.2 ± 0.47 g, the circumference of their abdomen was 13.5 ± 0.26 cm. All rats were not involved in any experiments and were completely healthy before taking the study. Of these, 31 rats were not exposed to any influences and formed a control group. They were examined two times: at the beginning of observation and after 2 months at the age of 5-5.5 months. The second study was carried out simultaneously with the end of the observation of experimental rats. In view of the absence of statistically significant differences between the results of both studies of control rats, the survey results are represented by a single digit - their arithmetic mean.

According to the known technique [7], arterial hypertension was experimentally caused in 65 rats. To do this, they were given a cardiovascular diphtheria semisynthetic diet enriched with cholesterol, disodium phosphate salts and potassium and magnesium deficiency for 2 weeks. In addition, rats were daily intramuscularly injected with a suspension of hydrocortisone acetate 1.5 mg per 100 g of body weight of the animal and replaced drinking water with a 1% solution of common salt. At the end, the rats were cold-affected - 4 °C for 4 hours. In



a subsequent random manner, these rats were divided into test group 1 (32 rats) and test group 2 (33 rats). The rats of test group 1 were no longer subjected to any influences and were kept in standard vivarium conditions. Rats of test group 2 experienced daily physical loads on the horizontal TORNEO treadmill of KETLER Company, moving at a speed of 5 m / min for 60 consecutive days. Animals were placed in one of the sections mounted on the treadmill of a special wooden frame of rectangular shape, divided by partitions into 3 parts for the individual placement of rats. On the first day, the duration of the load was 1 min. Then it increased by 1 min. Per day and was brought up to 25 minutes. A day and then remained unchanged for a day until the end of the observation [8].

The rats of both experimental groups were examined twice - at the time of the completion of their AH formation and at the age of 5-5.5 months, that is, at the same time as the repeated examination of control rats.

The measurement of blood pressure in rats in the study was performed non-invasively on the MLU/4c501 instrument by the method of applying the tail cuff (MedLab, China).

In all rats, the activity of peroxide oxidation of plasma lipids was determined by the number of acyl hydroperoxides (AGP) [9] and thiobarbituric acid (TBA) -active products in it using the Agat-Med (Russia) kit. In all rats, the antioxidant activity of plasma was determined [10]. The functional activity of the hemocoagulation system was evaluated in general coagulation tests (activated partial thromboplastin time, prothrombin and thrombin time), and also detecting the activity of coagulation factors (I, II, V, VII, VIII, IX, X, XI, XII) [11]. The anticoagulant potential of plasma in rats was elucidated by the level of antithrombin III and protein C [11]. The fibrinolytic properties of plasma in rats were assessed by the time of spontaneous euglobulin lysis, the level of plasminogen and the activity of α 2-antiplasmin [11].

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, Microsoft-Excel. Differences in data were considered reliable in case of $p < 0.05$.

Results

In the plasma of the rats of both test groups, a steady increase in systolic and diastolic arterial pressure was noted immediately after the formation of hypertension in them. This was accompanied by a stable increase in plasma AGP and TBA-active products in 2.46 times and 1.63 times, respectively. The initial activation of lipid peroxidation in rat plasma was caused by the weakening of their antioxidant activity of their plasma by almost 35.0% (Table 1).

In both groups of experimental rats, the time of general coagulation tests was comparatively accelerated. The duration of activated partial thromboplastin time in them was reduced by an average of 32.5%, prothrombin time on average by 18.5%, thrombin time on average by 13.8%. This was accompanied in the outcome in experimental rats by increased activity of I, II, V, VII, VIII, IX, X and XI plasma coagulation factors with an unchanged level of XII factor activity.

In the end, the activity of antithrombin III and protein C in both experimental groups of rats after the formation of hypertension was reduced in comparison with the control group by an average of 15.9% and 21.5%, respectively. In all experimental rats at the beginning of the observation, the time of spontaneous euglobulin lysis was increased by an average of 26.5%, plasminogen activity was reduced by an average

of 30.0%, and α 2-antiplasmin was increased by an average of 11.0% (Table 1).

Regular physical activity in rats with hypertension caused a decrease in the level of blood pressure and positive dynamics of all the indicators taken into account. By the end of the observation, in both experimental groups of rats, all the animals remained alive. At the same time, in the second experimental group of rats there was a decrease in the level of arterial pressure to the level of control. Also, in these rats, the levels of AGP and TBA-active compounds in the plasma decreased by the end of the observation ($p < 0.01$) and reached the control level. This was possible as a result of the normalization in them of the state of antioxidant protection of the plasma of these rats (Table 1).

The time of coagulation tests in rats of the second experimental group as a result of physical exertion reached the level of control values: the activated partial thromboplastin time increased by 32.9% ($p < 0.01$), the prothrombin time increased by 19.1% ($p < 0.01$) and thrombin time was extended by 14.4% ($p < 0.01$).

The results obtained in the rats of the second test group were based on complete normalization of the activity of all excessively enhanced clotting factors (I, II, V, VII, VIII, IX, X and IX) while maintaining the optimal activity of the XII factor (Table 1).

Against the background of regular exercise in rats of the second test group, the activity of antithrombin III and protein C increased by 14.9% ($p < 0.05$) and by 20.3% ($p < 0.01$), respectively, to the normal level. Also, as a result of physical exertion, the activity of α 2-antiplasmin decreased by 12.1% ($p < 0.01$) and the activity of plasminogen increased by 30.5% ($p < 0.01$), ensuring the achievement of these levels of control. This was accompanied by the acceleration of spontaneous euglobulin lysis to a level of control.

In the rats of test group 1, under standard conditions of maintenance, all the initial pathological manifestations of the AH were preserved until the end of the observation.

Discussion

Already at the very beginning of the development of hypertension in the animal's body, adverse changes are noted. Their presence can greatly weaken the body and often leads to its death [12,13]. In the study, a significant weakening of the antioxidant protection of plasma was registered in rats immediately after the formation of hypertension when the level of LPO products was increased in it. The emerging situation naturally caused in these rats increased aggregation of blood cells [14,15], damage to the walls of blood vessels and liver cells [16]. This strongly violated the balance between pro- and anticoagulants in their plasma [17]. In all experimental animals with the formed hypertension, acceleration of hemocoagulation along the external and internal pathways was noted. This increased hypoxia in the experimental rats and formed the risk of microcirculation disorders [18,19].

Developing in the experimental rats, excessive thrombin formation was less inhibited by weakened by their natural anticoagulants - antithrombin III and protein C [20,21]. Active lipid peroxidation, which damaged the endothelium, significantly contributed to the disruption of binding of antithrombin III to heparin sulfate and glucosaminoglycans on the surface of the vessels, which greatly reduced their level of thrombore resistance [22,23]. The attenuation of the plasma activity of protein C found in experimental rats with AH indicated depression of inhibitory control over the activity of V and VIII factors [24]. This was accompanied in all experimental rats by the



Table 1. Dynamics of hematological parameters in newborn calves with dyspepsia who received gamavit.

Indicators	initial state, M ± m, n=65	Experienced group 1, M ± m		Experienced group 2, M ± m		Control, M ± m, n=31
		Start of observation, n=32	End of observation, n=32	Start of observation, n=33	End of observation, n=33	
Acylhydroperoxides of plasma, D233/1 ml	1.33 ± 0.14	3.11 ± 0.17 p<0.01	1.66 ± 0.12 p ₁ <0.01	3.14 ± 0.16 p<0.01	1.32 ± 0.12 p ₁ <0.01 p ₂ <0.01	1.33 ± 0.14
Thiobarbituric acid-products of plasma, μmol / l	3.02 ± 0.16	4.99 ± 0.09 p<0.01	3.55 ± 0.08 p ₁ <0.01	4.95 ± 0.11 p<0.01	3.03 ± 0.09 p ₁ <0.01	3.02 ± 0.16
Antioxidant activity of plasma, %	37.0 ± 0.10	28.3 ± 0.08 p<0.01	34.0 ± 0.14 p ₁ <0.01	27.5 ± 0.18 p<0.01	36.9 ± 0.19 p ₁ <0.01 p ₂ <0.05	37.0 ± 0.10
Activated partial thromboplastin time, s	36.1 ± 0.18	27.4 ± 0.25 p<0.05	32.0 ± 0.20 p ₁ <0.05	27.8 ± 0.16 p<0.05	36.2 ± 0.12 p ₁ <0.05 p ₂ <0.05	36.1 ± 0.18
Prothrombin time, s	16.0 ± 0.15	13.4 ± 0.21 p<0.05	15.0 ± 0.25 p ₁ <0.05	13.5 ± 0.22 p<0.05	16.1 ± 0.38 p ₁ <0.05	16.0 ± 0.15
Thrombin time, s	17.3 ± 0.12	15.6 ± 0.26 p<0.05	16.8 ± 0.15	15.4 ± 0.18 p<0.05	17.4 ± 0.29 p ₁ <0.05	17.3 ± 0.12
Factor I, g/l	1.4 ± 0.08	2.1 ± 0.15 p<0.01	1.7 ± 0.17 p ₁ <0.01	2.0 ± 0.08 p<0.01	1.4 ± 0.18 p ₁ <0.01 p ₂ <0.05	1.4 ± 0.08
Factor II, %	64.1 ± 0.15	67.4 ± 0.20 p<0.05	65.2 ± 0.26 p ₁ <0.05	67.2 ± 0.25 p<0.05	64.2 ± 0.32 p ₁ <0.05	64.1 ± 0.15
Factor V, %	89.2 ± 0.12	120.1 ± 0.29 p<0.01	99.2 ± 0.45 p ₁ <0.01	119.6 ± 0.38 p<0.01	89.4 ± 0.42 p ₁ <0.01 p ₂ <0.01	89.2 ± 0.12
Factor VII, %	72.3 ± 0.08	78.7 ± 0.32 p<0.05	78.3 ± 0.26 p ₁ <0.05	78.9 ± 0.37 p<0.05	72.4 ± 0.46 p ₁ <0.05 p ₂ <0.01	72.3 ± 0.08
Factor VIII, %	97.6 ± 0.12	132.8 ± 0.40 p<0.01	111.2 ± 0.33 p ₁ <0.01	133.2 ± 0.25 p<0.01	97.7 ± 0.37 p ₁ <0.01 p ₂ <0.01	97.6 ± 0.12
Factor IX, %	88.7 ± 0.15	97.6 ± 0.41 p<0.05	92.4 ± 0.29 p ₁ <0.05	96.9 ± 0.38 p<0.05	88.8 ± 0.30 p ₁ <0.05 p ₂ <0.05	88.7 ± 0.15
Factor X, %	62.1 ± 0.14	65.5 ± 0.35 p<0.05	63.0 ± 0.18 p ₁ <0.05	65.8 ± 0.26 p<0.05	61.2 ± 0.28 p ₁ <0.05 p ₂ <0.05	62.1 ± 0.14
Factor XI, %	90.2 ± 0.12	94.7 ± 0.30 p<0.05	92.1 ± 0.25 p ₁ <0.05	95.2 ± 0.28 p<0.05	89.9 ± 0.36 p ₁ <0.05 p ₂ <0.05	90.2 ± 0.12
Factor XII, %	91.3 ± 0.20	91.0 ± 0.32	90.9 ± 0.16	90.1 ± 0.25	91.2 ± 0.17	91.3 ± 0.20
Activity of antithrombin III in plasma, %	92.0 ± 0.16	81.2 ± 0.12 p<0.05	88.7 ± 0.21 p ₁ <0.05	81.6 ± 0.23 p<0.05	92.3 ± 0.30 p ₁ <0.05	92.0 ± 0.16
Protein C, %	50.3 ± 0.18	42.7 ± 0.09 p<0.05	47.2 ± 0.14 p ₁ <0.05	43.1 ± 0.12 p<0.05	50.1 ± 0.22 p ₁ <0.01 p ₂ <0.05	50.3 ± 0.18
Time of spontaneous euglobulin lysis, min	188.5 ± 0.38	242.6 ± 0.52 p<0.01	201.2 ± 0.34 p ₁ <0.01	239.8 ± 0.42 p<0.01	188.4 ± 0.46 p ₁ <0.01 p ₂ <0.05	188.5 ± 0.38
Plasminogen, %	110.2 ± 0.24	84.0 ± 0.26 p<0.01	101.3 ± 0.37 p ₁ <0.01	84.4 ± 0.32 p<0.01	110.5 ± 0.27 p ₁ <0.01 p ₂ <0.05	110.2 ± 0.24
α2 antiplasmin, %	128.1 ± 0.29	143.4 ± 0.33 p<0.01	132.1 ± 0.21 p ₁ <0.05	143.9 ± 0.15 p<0.01	128.2 ± 0.24 p ₁ <0.01 p ₂ <0.05	128.1 ± 0.29

p-reliability of differences in the initial indices in the experimental groups and in the control, p₁-reliability of the dynamics of the indices in the experimental groups, p₂ - reliability of the differences in the indices in the experimental groups at the end of the observation.

excessive activity of α₂-antiplasmin and a decrease in the functionality of plasminogen, leading to a depression of the fibrinolytic properties of their blood.

Detected in experimental rats, coagulopathy needed an effective correction capable of eliminating hemocoagulation disorders [25,26]. To this end, it was decided to apply the metered exercise load.

Regular physical exertion had a positive effect in the experimental

rats of group 2 on the level of plasma lipid peroxidation, metabolism in the liver and bone marrow. It became clear that an increase in their motor activity stimulates metabolic and enzymatic processes, weakens the manifestations of hypertension and ensures the maximum possible activation of antioxidant defense of the body. The normalization of hemocoagulation results achieved at the same time was due to a reduction in the level of activity norm of all clotting factors. The dynamics of their activity against the background of regular runs



in rats with hypertension can be considered a consequence of the increase to the level of the norm of hepatic metabolism [27]. Their use was accompanied in experimental group 2 by an increase in anticoagulant plasma activity. Apparently, only against the background of the increase in muscle activity, the most pronounced increase in antithrombin III activity, lower in AH, is possible. It was as a result of this that it was possible to control the level of activation of II, VII, IX, X, XI and XII coagulation factors in rats with developed AH [28,29]. In addition, high muscular activity led to normalization in the blood of experimental rats with AH protein C activity, thereby inhibiting the activation of V and VIII clotting factors in their plasma [30,31]. In rats with hypertension on a background of regular physical exertion, the intensity of synthesis of plasminogen was strengthened to normal [32], which was accompanied by the suppression of an excess level of antiplasmin in plasma [33,34]. The obtained results on the possibility of weakening the manifestations of hypertension on the background of moderate muscular activity have been confirmed in the literature. The results obtained in the study confirm the point of view about the possibility of stimulation of the mammalian organism with the help of muscle activity. In particular, physical activity increases the vital processes in the body of mammals increase its resistance [35]. The study showed that high muscular activity in rats with hypertension leads to complete normalization of the hemocoagulation system in them, optimizing the liquid properties of their blood and thereby creating functionally favorable conditions for microcirculation [36].

Conclusion

When AH is formed in rats, the coagulation activity of the plasma is increased and its anticoagulant and fibrinolytic properties are weakened. In the case of early onset of regular physical activity in rats after 2 months, the coagulation activity of the plasma and its anticoagulation and fibrinolysis mechanisms are normalized. In rats with the formed pathology, which are in standard conditions of the vivarium, all disorders in their body, related to the presence of AH, persisted.

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