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Diagnostics of early dysfunctions of anticoagulant and fibrinolytic features of rats' vessels in the course of metabolic syndrome formation with the help of fructose model

Boris Veniaminovich Usha,[1] Svetlana Yurevna Zavalishina,[2*] Yuri Anatolyevich Vatnikov,[3] Evgeniy Vladimirovich Kulikov,[3] Vladimir Ivanovich Kuznetsov,[3] Nikolay Vladimirovich Sturov,[3] Margarita Vasilievna Kochneva,[3] Anton Alexandrovich Poddubsky,[3] Alina Vadimovna Petryaeva,[3] Tatyana Ivanovna Glagoleva[4]

ABSTRACT

The optimal feature of anticoagulant and fibrinolytic of the vascular wall provides the major homeostasis process in the whole body of a mammal. It is impossible to track in clinic peculiarities of the earliest change in vascular hemostasis in a debut of metabolic syndrome formation. Thus, it dictates the necessity of conducting experimental researches on laboratory animals with modeling of metabolic syndrome within them. The aim of the research is to examine early stages of vascular hemocoagulation weakening control in conditions such as the formation of metabolic syndrome. The study used 61 male-rats of Wister line at the age of 2.5-3 months. The animals were subdivided into two groups: 32 rats received 10% fructose dilution with free access for drinking, and 29 rats to the control group. Biochemical, hematological and statistical methods of investigation were applied. We found that in high fructose level, there is a fast evident of a weakening of the anticoagulant and fibrinolytic activities of vascular endothelium as well as the body mass gain and development of biochemical abnormalities, which is typical for metabolic syndrome. The early weakening of vascular control over hemocoagulation turns metabolic syndrome into a very dangerous state because of thromboses, which may take place even at the very beginning of its development.

Key words: rats, fructose, metabolic syndrome, blood vessels, hemostasis.
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[1]Moscow state University of food production, Volokolamskoe Highway 11, Moscow, 125080, Russian Federation
[2]Russian State Social University, st. V. Pika, 4, Moscow, 129226, Russian Federation
[3]Peoples Friendship University of Russia (RUDN University), 6 Miklukho-Maklaya Street, Moscow, 117198, Russian Federation
[4]All-Russian Research Institute of Physiology, Biochemistry and Nutrition of Animals, Institute of village, Borovsk, Russian Federation

*Corresponding to:
Svetlana Yurevna Zavalishina, Russian State Social University, st. V. Pika, 4, Moscow, 129226, Russian Federation
svetlanazsyu@mail.ru

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INTRODUCTION

Vascular endothelium leads an important role in providing the optimal homeostasis in the whole body of a mammal.[1,2,3,4] The output of biologically active substances[8,9] mostly depending on genome activity and protein synthesis apparatus[5,6,7] in vascular endothelium. They determine blood vessels' activity over hemocoagulation,[10,11] platelets' activity[12,13] and whole hemostasis process.[15,16]

Research conducted earlier on different aspects of hemostasis physiology had formed modern ideas about mechanisms of its regulation at different somatic pathology.[15,16,17] Studies showed that age-specific dynamics[18,19] at development of cardio-vascular pathology[20,21] were often combined with metabolic disturbances,[22,23,24] especially with metabolic syndrome (MS).[25,26] It became clear that arterial hypertension (AH) at MS is characterized by low level of hemostatic active substances' formation in endotheliocytes, providing most of the high-frequency thrombotic episodes[27,28] at this state.

For reducing the chance of angiopathy and minimizing thromboses' risk at AH, there were several serious experimental and clinical observations had been conducted, which were aimed to estimate separation mechanisms of vascular wall dysfunctions development and their role in AH and MS pathogenesis.[29] Variants of dyslipidemia correction worked out as it is the leading element of angiopathy at MS.[30,31,32] At the same time, peculiarities of early changes in vascular hemostasis in a debut of MS formation cannot be fully studied yet. Due to the impossibility of tracking this process (MS signs often cannot be seen clearly by clinicians), dictates the necessity of conducting of experimental researches on laboratory animals with MS modeling within them. These data can serve as basis for clinical research, aiming to pathogenically clarify the moment of the beginning of correction impacts at early symptoms of MS. Taking the given circumstances into consideration, the author formulated the aim of our research: to examine early stages

of vascular control weakening over hemocoagulation in conditions of an experimental metabolic syndrome.

MATERIALS AND METHODS

All the investigations in the study were conducted in full correspondence with ethical norms and recommendations on humanization of work with laboratory animals containing "The European Convent on the protection of vertebrate animals used for experiments or in other scientific purposes" (Strasbourg, 1986).

The study used 61 healthy male-rats of Wister line at the age of 2.5-3 months. Animals' body mass at the beginning of the experiment was ranging between 261.1±1.18 gr, abdominal circumference – 14.7±0.26 cm. All the rats have not participated in any experiments before the research. All the animals were casually subdivided into two groups: 32 rats were taken into the experiment and received 10% fructose dilution for drinking in free access. The dilution was made with (or using) crystallized fructose ("Novaprodukt", Russia),[33] while the other rats composed control group. The experiment lasted for 8 weeks. Experimental animals' blood was taken from the caudal vein at 2, 4, 6 and 8 weeks of fructose ingestion. The animals from the control group were examined twice: at the beginning and at the age of 4.5-5 months, i.e. simultaneously with the end of experimental rats' observation. Because of the absence of statistically significant differences between the results of two control rats' examinations, received data are presented by one figure - their average.

Animals' body mass weighed by using laboratory scales and was expressed in grams. Abdominal circumference was determined by measuring the circumference at the middle part of the body and expressed in centimeters. Concentration of the common cholesterol (CCS) and triglycerides (TG) was calculated by an enzymatic colorimetric method with the help of sets, produced by the firm "Vital Diagnostikum" (Russia). The content of high-density lipoproteins (HDL) in cholesterol plasma was found by the enzymatic colorimetric way with the help of a set produced by "Olvex Diagnostikum". The concentration of cholesterol of low-density lipoproteins (LDL) was calculated according to the formula of W. Friedwald et al., (1972). CS concentration of very-low-density lipoproteins (VLDL) was calculated according to the formula: cholesterol of VLDL=concentration of triglycerides/2.2.

The level of lipids' peroxidation (LPO) in the liquid part of blood was found according to the quantity of thiobarbituric acid-active products (TBA-compounds) in it by a set called "Agat-Med" (Russia) and according to the content of acylhydroperoxides (AHP). The author also determined the level of blood plasma antioxidant activity.[34]

Furthermore, the author determined antithrombin III[35] activity in experimental animals' blood before and after the test with temporary venous occlusion using the calculation of the index value of vessels' wall anticoagulant activity (IAAVW). We divided antithrombin-III activity in the test with venous occlusion on basal activity of antithrombin-III.

In order to determine vascular control over blood fibrinolytic ability, the author registered the period of spontaneous euglobulinic lysis before and after temporary ischemia of a venous wall[35] with consequent index calculation of fibrinolytic activity of vascular wall (IFAVW) by dividing the basal period of euglobulinic lysis on its value against the background of venous occlusion. The results were statistically processed by Student's t-criterion.

RESULTS

Initially, there is an increase growth trend of animals' body mass within 2 weeks of the experiment. In the 4th week, the body mass reached the level of reliability. In the 6th week (or within 6 weeks) of fructose ingestion with drinking water, the body mass of experimental rats reached 283.4±1.27gr and the value of abdominal circumference 16.4±0.19cm. By the end of the experiment, observed rats were found to have an additional increase of body mass by 4.6%, abdominal circumference - by 4.9% (table 1).

Within 2 weeks, the experimental rats were noted to have a declining/deterioration trend of plasma lipid composition. At the same time, the experimental rats had lower antioxidant plasma activity and increase of acylhydroperoxides and thiobarbituric acid-active products, which lasted during the whole period of fructose ingestion (table). In 4-week it reached the level of reliability and then progressively worsened till the end of the experiment.

In fructose-modeled rats, within 2 weeks, there were lowered anticoagulant activity of vascular wall, deepening in the course of the experiment and composing 20.8% in 8 weeks. Estimating peculiarities of blood fibrinolytic features of experimental rats with the help of dosated venous occlusion, there was a gradual lowering of vascular stimulus on fibrinolysis. This became clear due to index lowering of fibrinolytic activity of vascular wall, which was 16.8% in the course of the experiment (table).

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Table 1 **Dynamics of morphometric, biochemical and hematological indices of rats which freely received fructose dilution**

Registered parameters	initial state	Dynamics of parameters during the experiment, n=32, M±m				Control, n=29, M±m
		2 weeks of fructose load	4 weeks of fructose load	6 weeks of fructose load	8 weeks of fructose load	
Body weight, g	262.1±1.24	268.5±1.10	276.3±1.23 p<0.05	283.4±1.27 p<0.01	296.6±1.34 p<0.01	260.1±1.12
Abdominal circumference, cm	14.7±0.22	15.1±0.28	15.8±0.12 p<0.05	16.4±0.19 p<0.01	17.2±0.20 p<0.01	14.8±0.31
Total cholesterol, umol/l	2.19±0.06	2.30±0.09	2.54±0.07 p<0.01	2.79±0.05 p<0.01	2.92±0.03 p<0.01	2.22±0.06
HDL cholesterol, umol/l	1.12±0.05	1.06±0.04	1.01±0.003 p<0.05	0.96±0.004 p<0.01	0.94±0.005 p<0.01	1.10±0.004
LDL cholesterol, umol/l	0.59±0.04	0.67±0.05 p<0.05	0.82±0.07 p<0.01	1.09±0.08 p<0.01	1.15±0.04 p<0.01	0.63±0.02
VLDL, umol/l	0.48±0.003	0.57±0.06 p<0.05	0.71±0.05 p<0.01	0.78±0.006 p<0.01	0.83±0.002 p<0.01	0.49±0.004
TG, umol/l	1.05±0.05	1.26±0.06 p<0.05	1.56±0.04 p<0.01	1.72±0.03 p<0.01	1.83±0.02 p<0.01	1.08±0.04
AHP, D_{233}/1ml	1.37±0.12	1.64±0.06 p<0.05	1.97±0.07 p<0.01	2.50±0.05 p<0.01	2.85±0.04 p<0.01	1.41±0.03
TBA-compounds, umol/l	2.27±0.06	2.83±0.06 p<0.05	3.39±0.09 p<0.01	3.98±0.07 p<0.01	4.48±0.08 p<0.01	2.30±0.04
antioxidant activity plasma, %	29.2±0.05	27.6±0.08	26.0±0.08 p<0.05	24.6±0.06 p<0.01	22.4±0.05 p<0.01	29.7±0.04
IAAVW	1.45±0.03	1.37±0.06 p<0.05	1.31±0.06 p<0.01	1.26±0.07 p<0.01	1.20±0.08 p<0.01	1.44±0.03
IFAVW	1.46±0.12	1.41±0.10	1.32±0.08 p<0.01	1.27±0.11 p<0.01	1.25±0.09 p<0.01	1.45±0.15

Conventional signs: p - reliability of indices' differences of experimental rats from control values.

DISCUSSION

At present, there are rather full views about the participation of hemostasis and vascular wall in the different process, including the development of cordial pathology.[36] Its wide propagation in civilized countries leading to high incapacitation and mortality supports the interest of researchers to the problems and especially to MS as the most dangerous state in this context.[37] In several previous research, both high arterial pressure and metabolic disturbances[40] participated/contributed in the development of the majority of MS cardiovascular complications.[42,43] It makes the study of initial stages of angiopathy formation at MS really essential for both theoreticians[44,45] and experts in medicine.[46]

Taking into consideration the complexity of metabolic disturbances at long surplus fructose inflow into mammals' body and MS development against such background, fructose model seems to be the most approved one for observing the earliest stages of vascular dysfunctions in conditions of MS development.

In the course of the experiment, the observed rats were noted to have a quick increase of body mass on behalf of adipose tissue accumulation in the abdominal area. It happened alongside with abnormalities in lipid profile of animals' blood and activation of LPO (common for MS). Received results were fully adjusted with those of previous researches.[47,48] It became clear that strengthening of LPO in the blood caused damage of endotheliocytes in rats, making cholesterol inflow into a vascular wall easier and creating a condition for consequent thrombosis.[49]

As the period of fructose ingestion continued, the observed rats were noted to have a gradual decrease of antithrombin-III intensity formation within blood vessels.[50,51] It was accompanied by early diminishing/decreasing/weakening of fibrinolytic features of the vascular wall. It, evidently, happened because of the impact of high arterial pressure, active lipids' peroxidation, atherosclerosis on vessels and inevitably, thrombocytopathy.[52,53]

Such a complex leading to morphological[54,55] and functional abnormalities of endotheliocytes[56,57] and stable hemostasiopathy in animals' bodies.[58]

CONCLUSION

In an experimental condition of fructose ingestion, it was found out that weakening of anticoagulant and fibrinolytic abilities of vascular endothelium quickly developed and progressed simultaneously by gaining body mass and development of biochemical abnormalities relevant to MS. Depression of antithrombin-III product and tissue activator plasminogen in it, lay the basis of this process.

CONFLICT OF INTEREST

The authors declare that they don't have any competing interest regarding manuscript

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