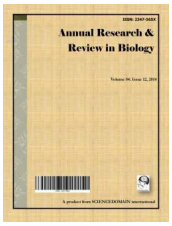

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A Study of the Early Disturbances in Vascular Hemostasis in Experimentally Induced Metabolic Syndrome

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Authors' contributions

This work was carried out in cooperation between both authors. Author IAS has developed the study, carried out the statistical analysis of the material and literature searches. Author SYZ wrote the minutes and the first draft of the manuscript. Both authors together carried out a set of material and conducted the analysis of the study. Both authors prepared the final version of the manuscript, read it and approved it.

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ABSTRACT

The unique characteristics of the early changes in vascular haemostasis during the development of metabolic syndrome are still unclear. This study aimed to examine the development of vascular dysfunction in experimentally induced metabolic syndrome. The study used 61 male Wistar rats aged 2.5-3 months. Thirty-two rats were given ad libitum access to 10% fructose dilution for drinking, while the remaining 29 control group rats were not given the fructose dilution. The study period was 8 weeks. We used biochemical, haematological, and statistical methods for investigation. The experimental rats received fructose, and we observed a deteriorating trend in their plasma lipid composition within 2 weeks. At the end of 4 weeks, it had further deteriorated, and it

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progressively worsened until the end of the experimental period. At the end of 2 weeks, there was significant reduction in the plasma antioxidant activity and rise in the levels of plasma lipid peroxidation products in the experimental rats. This effect persisted throughout the experimental period. At the end of 4 weeks, we observed imbalances in the metabolites; the plasma levels of arachidonic acid peaked by the 8th week; in addition, thromboxane B_2 levels rose by 37.3% and 6-keto-prostaglandin $F_{1\alpha}$ levels reduced by 21.8%. This was accompanied by an increase in endothelin-1 and decrease in the total nitric oxide metabolites by 20.2% in the experimental rats. At the end of 2 weeks, there was a reduction in the anticoagulant and fibrinolytic activities of the vessels of the experimental group rats; this effect increased with time. By 4 weeks, the vascular regulation of platelet aggregation in response to collagen, adenosine diphosphate and ristomicin had weakened in the experimental rats. Under experimental conditions of fructose ingestion, there was evident progressive weakening of antiaggregatory, anticoagulative, and fibrinolytic abilities of the vascular endothelium due to the inhibition of the production of prostacyclin, nitric oxide, antithrombin III, and tissue activator plasminogen in the vessels with a simultaneous increase in the body mass of the rats and the development of biochemical abnormalities that were characteristic of metabolic syndrome.

Keywords: Rats; fructose; metabolic syndrome; vessels; haemostasis.

1. INTRODUCTION

Optimum physiological vascular haemostasis maintains the homeostasis of the whole body in mammals [1,2]. The main contributor to vascular haemostasis is the vascular endothelium that produces large amounts of different biologically active substances. These determine the tone of the vessels, optimize their morphology, and regulate the processes involved in vascular haemostasis [3,4].

Previous researches on the initial haemostasis physiology in different directions have provided modern theories about the mechanisms underlying its regulation in several different pathologies [5,6] by explaining their dynamics in isolated arterial hypertension (AH) [7,8] and their interactions in different metabolic disturbances [9,10,11], especially in metabolic syndrome (MS) [12,13]. These findings revealed that the low production of haemostatically active substances (antithrombin III, prostacyclin, von Willebrand Factor, and tissue activators of plasminogen) in the endotheliocytes influenced AH and MS. This mainly contributes to frequent thrombotic episodes [14,15,16].

Some experimental and clinical researches were conducted with the aim of reducing the symptoms of angiopathy and minimizing the risk of thrombosis in patients with AH. These studies focused on assessing the individual mechanisms underlying the development of vessel wall dysfunctions and their roles in AH and MS pathogeneses [17]. However, to our knowledge, the distinct characteristics of the early changes in the vascular haemostasis in newly developed MS have not been clarified in any previous research. This physiological process cannot be tracked till completion in human beings owing to fall of persons with the first symptoms of metabolic syndrome out of clinicians' visual field, making it necessary to conduct this experiment on laboratory animals with experimentally induced MS [18]. These data can provide the basis for future clinical researches that aim to develop therapeutic strategies targeted at managing patients with early symptoms of MS. Considering this, we designed this research to examine the vascular dysfunction in experimentally induced MS in rats.

2. MATERIALS AND METHODS

2.1 Materials

All experiments in the present study were conducted as per the ethical norms and recommendations on the humanization of work with laboratory animals according to the "The European Convent on the protection of vertebrate animals used for experiments or in other scientific purposes" (Strasbourg, 1986) and approved by the local Ethics Committee of the Kursk Institute of Social Education, a branch of the Russian State Social University (Record №12, dated December 3, 2015) and the local Ethics Committee of the All-Russian Research Institute of Physiology, Biochemistry and Animals' Feeding (Record №11, dated December 4, 2015).

The study used 61 male Wistar rats aged 2.5-3 months that belonged to the first or second litter of healthy female rats. The average body mass of the rats at the time of enrolment was 261.1 ± 1.18 g, and their mean abdominal circumference was 14.7 ± 0.26 cm. None of the rats had been used for any experiment previously and did not have any illnesses. The animals were randomly divided into two groups; 32 rats were allocated to the experimental group and were given ad libitum access to 10% fructose dilution for drinking. This solution was made from crystallized fructose (Novaprodukt, Russia) [19]. The control group comprised 29 rats. The experimental period was 8 weeks. Blood samples were drawn from the caudal vein of the experimental rats at 2, 4, 6, and 8 weeks of fructose ingestion. The control group animals were examined twice, once at the beginning of the experiment and then at the age of 4.5-5 months (i.e., at the end of the study period). There were no statistically significant differences between these values in the control group rats. The data are presented as mean and standard deviation values.

2.2 Methods

The animals' body masses were measured using laboratory weighing scales and expressed in grams. For their abdominal circumferences, the diameter at the mid-body level was measured and expressed in centimetres.

Plasma concentrations of lipids, including total cholesterol and triglycerides were determined with the enzymatic colorimetric method using a diagnostic kit ("Vital Diagnostikum"). The plasma concentration of high-density lipoproteins was determined using the enzymatic colorimetric method with a diagnostic kit ("Olvex Diagnostikum").

The plasma concentration of low-density lipoprotein cholesterol was calculated according to the formula given by W. Friedwald et al., (1972), and the concentration of very-low-density lipoprotein cholesterol was calculated according to the following formula: concentration of triglycerides/2.2.

The degree of lipid peroxidation in the liquid part of the blood was determined according to the quantity of thiobarbituric acid-active products in it using a kit ("Agat-Med") and according to their acyl hydroperoxidase content [20]. We also determined the degree of blood antioxidant activity [21]. We determined the content of endothelin-1 in the plasma of experimental rats using the radio immunological method with the help of reagents manufactured by "DRG" (USA). Further, the levels of thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$ were determined using enzyme immunoassay with the help of kits developed by "Enzo Life science" (USA). We also determined the total nitric oxide metabolites in the blood of experimental rats [22].

Moreover, we determined the antithrombin III activity in the blood of the experimental rats [23] before and after the test with temporary venous occlusion and calculated the index value of the vessel wall anticoagulant activity (IAAVW). We divided antithrombin-III activity in the test during the venous occlusion by the basal activity of antithrombin-III.

In order to determine the vascular regulation of fibrinolytic ability, we registered the period of spontaneous euglobuliniclysis before and after the temporary ischemia of the venous wall [23]. We also performed consequent index calculation of the vessel wall fibrinolytic activity (IFAVW) by dividing the basal time of euglobuliniclysis by its value during venous occlusion.

Antiaggregation activity of a vascular wall was determined in the test with temporary venous occlusion (which aimed to weaken the platelet aggregation parameters) by calculating the index of platelet aggregation degree (IDAP). Therefore, we divided the aggregation degree without the cuff by the degree with it. Calculating the index of platelet aggregation sign (ISAP), we divided the aggregation sign without the imposition of a cuff by the aggregation sign with a cuff. Estimation of platelet aggregation was conducted using a two-channel laser analyser ALAT 2-"BIOLA" (LA230-2, Russia) with adenosine diphosphate (ADP) (0.5×10^{-4} M), collagen (dilution 1:2 of basic suspension), and ristomicin (0.8 mg/mL). Statistical analyses of the collected data were conducted using the programs: “Statistics for Windows v. 6.0” and “Microsoft Excel”. Significances of the differences were assessed using Student's t test. P values < 0.05 were considered statistically significant.

3. RESULTS AND DISCUSSION

There was an increasing trend in the body mass of animals at the end of the first 2 weeks of the experiment. From the 4th week onward, this increase reached statistical significance. At the end of 6 weeks of fructose ingestion, the mean

body mass of the experimental rats reached 283.4 ± 1.27 g and their mean abdominal circumference was 16.4 ± 0.19 cm; this indicated an increase in the animals' visceral adipose tissue volume. By the end of the study period, the experimental rats had a total increase of 4.6% in body mass and 4.9% in abdominal circumference (Table 1).

The experimental rats received fructose, and their plasma lipid composition started deteriorating at the end of the first 2 weeks of the study period. At the end of 4 weeks, it had worsened significantly, and it progressively worsened until the end of the study. At the same time, there was a significant reduction in the plasma antioxidant activity and increase in acyl hydroperoxides and thiobarbituric acid-active products in the experimental rats; these changes persisted during the entire study period (Table 1).

Initially, the optimal concentration of arachidonic acid metabolites in the plasma of the experimental rats was immediately altered. This imbalance was observed at the end of 4 weeks and peaked by the 8th week; the total increase in thromboxane B_2 was 37.3%, and the total reduction in 6-keto-prostaglandin $F_{1\alpha}$ was 21.8%. There was simultaneous rise in the endothelin-1 level to 12.5 ± 0.36 pg/mL (mean ± standard deviation) and a reduction in the total nitric oxide metabolites by 20.2% in the experimental rats (Table 1).

At the end of 2 weeks, the experimental rats demonstrated a significant reduction in the IAAVW that reduced further as the experiment progressed, with a total reduction of 20.8% at the end of 8 weeks. We assessed the unique characteristics of blood fibrinolytic activity with the help of dosated venous occlusion and found a gradual reduction in the vascular stimulus for fibrinolysis in the experimental rats, indicated by the 16% reduction in the IFAVW during the experimental period (Table 1).

The values of IDAP and ISAP reduced significantly at the end of 4 weeks in all the experimental rats; the reductions were 9.7% and 10.5% for collagen, 18.2% and 17.2% for ADP, and 11.2% and 15.0% for ristomicin, respectively (Table 1).

Currently, there are several theories describing the different functions of the vascular wall [24,25], including the development of cordial pathology [26,27]. In developed countries, MS is an important cause of compromised quality of life and mortality [12]. Previous researches have shown that both, high arterial pressure and metabolic disturbances contribute to the development of cardiovascular complications that are often a part of MS [28]. Therefore, the study of the initial stages of angiopathy remains crucial for both, scientists [29,30]and practicing medical professionals [31,32].

Chronic, high-dose fructose ingestion causes complex metabolic disturbances, encouraging the development of MS. Therefore, a fructose model seems to be most suitable for studying the early vascular dysfunctions occurring during the development of MS [19].

The experimental rats who were given free access to the fructose dilution exhibited a rapid increase in body mass owing to the accumulation of adipose tissues in the abdominal region. Simultaneously, there were abnormalities in the plasma lipid composition and in the activation of lipid peroxidation in the blood (common for MS). These findings are in keeping with previous reports [13,33] and indicate that enhancing lipid peroxidation in the blood damages the endotheliocytes in rats, enabling the inflow of cholesterol into the vessel wall, initiating atherosclerosis and increasing the risk of thrombosis [34].

During the period of fructose ingestion, the experimental rats had a gradual reduction in the rate of antithrombin-III formation in the vessels. This was accompanied by a steady suppression of the fibrinolytic activity of the vascular wall in the experimental animals, possibly due to the impact of high arterial pressure on the vessels, active lipid peroxidation, dyslipidaemia, and the resultant thrombocytopathy that led to morphological and functional abnormalities of the endotheliocytes [35,36].

During the development of MS, the experimental rats had an increased production of thromboxane A_2 and endothelin-1 and decreased production of the antiaggregants: prostacyclin and nitric oxide. This leads to a reduction in vascular wall regulation of adhesion and platelet aggregation. At the same time, the formation of hyper-normal plasma thromboplastin on the platelet membranes in these conditions accelerated thrombin formation, leading to a further increase in the number of blood platelets and acceleration in the formation of fibrin fibres on them. It also gradually accelerated haemostasis [23].

Table 1. Morphometric, biochemical, and haematological indices of the rats in both the groups

Registered parameters	Dynamics of parameters during the experiment, n=32, M±m					Control, n=29, M±m
	Initial state	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, %	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
Thromboxane A_2, pg / ml	145.9±0.21	168.7±0.50	184.7±0.59 p<0.01	208.1±0.42 p<0.01	232.6±0.69 p<0.01	148.1±0.28
6-keto-prostaglandin $F_{1\alpha}$, pg / ml	75.9±0.20	72.4±0.26	69.6±0.32 p<0.05	65.4±0.38 p<0.01	62.3±0.44 p<0.01	76.5±0.22

Nitric oxide's metabolites, umol/l		27.9±0.28	27.1±0.16	26.4±0.09	24.7±0.19	23.2±0.06	28.5±0.29
				p<0.05	p<0.01	p<0.01	
Endothelin-1, pg / ml		6.9±0.18	8.2±0.23	10.1±0.27	11.4±0.29	12.5±0.36	6.8±0.16
			p<0.05	p<0.01	p<0.01	p<0.01	
IAAVW		1.45±0.03	1.37±0.06	1.31±0.06	1.26±0.07	1.20±0.08	1.44±0.03
			p<0.05	p<0.01	p<0.01	p<0.01	
IFAVW		1.46±0.12	1.41±0.10	1.32±0.08	1.27±0.11	1.25±0.09	1.45±0.15
				p<0.01	p<0.01	p<0.01	
Antiaggregative activity for collagen	IDAP	1.46±0.09	1.42±0.07	1.39±0.12	1.36±0.14	1.33±0.13	1.45±0.08
				p<0.05	p<0.01	p<0.01	
	ISAP	1.47±0.05	1.45±0.08	1.41±0.07	1.37±0.10	1.33±0.12	1.46±0.04
				p<0.05	p<0.01	p<0.01	
Antiaggregative activity for ADP	IDAP	1.49±0.03	1.45±0.04	1.39±0.07	1.32±0.06	1.26±0.07	1.48±0.02
				p<0.05	p<0.01	p<0.01	
	ISAP	1.50±0.06	1.46±0.05	1.40±0.07	1.34±0.06	1.28±0.08	1.49±0.05
				p<0.05	p<0.01	p<0.01	
Antiaggregative activity for ristomycin	IDAP	1.49±0.02	1.47±0.04	1.42±0.08	1.37±0.06	1.34±0.07	1.50±0.03
				p<0,05	p<0.01	p<0.01	
	ISAP	1.53±0.02	1.48±0.04	1.42±0.03	1.38±0.05	1,33±0,04	1.51±0.02
			p<0.05	p<0.01	p<0.01	p<0,01	

Conventional signs: p – significance of the differences in the indices of the rats in the experimental and control groups

The experimental rats showed a gradual reduction in the vessels' control over the response of the platelet receptors to collagen Ia - IIa and VI, clearly due to the reduction in the inhibition of platelet aggregation with collagen during temporary venous occlusion. This was accompanied by a rise in the activity of phospholipase C, synthesis stimulation of diacilglycerol and protein kinase C with consequent evident proteins' phospharylation of the contractile system in platelets [37]. Under these conditions, inositol triphosphate began to stimulate Ca^{2+} inflow out of the blood platelets more actively. It increasingly promoted actomyosin contraction. Moreover, the hyper-normal adhesion of the blood platelets in the experimental rats was also associated with the rise in the synthesis of von Willebrand Factor in their vessels and strengthening of its interaction with the receptors to it (Ic) on the platelet membranes [38,39].

In conditions involving substantial reduction of nitric oxide and prostacyclin formation in the vessels, ADP (which refers to the weak inductors of platelet aggregation) actively interacted with the receptors of their membranes. This encouraged strong expression of the fibrinogenic receptors on them, gradually strengthening the activation of phospholipase A_2, separating arachidonic acid from phospholipids [40] for greater synthesis of thromboxane A_2.

4. CONCLUSION

In experimental conditions of fructose ingestion, there was substantial inhibition of the antiaggregation, anticoagulative, and fibrinolitic abilities of the vascular endothelium with concurrent increase in the body mass and the development of biochemical abnormalities characteristic of MS. These changes were due to the inhibition of prostacyclin, nitric oxide, antithrombin-III, and tissue activator plasminogen production.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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