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CARBOHYDRATE METABOLISM AND THE STATE OF THE PRO-ANTIOXIDANT SYSTEM IN THE PANCREAS OF RATS WITH EXPERIMENTALLY INDUCED DIABETES AND THE RELEASE OF VANADIUM CITRATE

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ABSTRACT: We investigated the effect of vanadium citrate in the amounts of 0.125, 0.5, and 2.0 µg/mL of water on the enzymatic activity of carbohydrate metabolism, antioxidant system, and the level of lipid peroxide oxidation products in the pancreas of rats with alloxan-induced diabetes. Diabetes was detected at a glucose level of 15.14 mmol/L by measuring glucose level in the blood collected from the tail vein. In the pancreas of rats with experimentally induced diabetes, the levels of lipid hydroperoxides and TBA-positive substances increased significantly, while the level of reduced glutathione and the activity of SOD, CAT, GPx, and GR as well as carbohydrate metabolism enzymes LDH and G-6-PDH decreased as compared to the animals from the control group. With the exposure to vanadium citrate in the pancreas of rats for a month, the level of LPO products decreased and the activity of antioxidant and carbohydrate metabolism enzymes increased as compared to the diabetic animals and dose-dependently reached the level in the animals from the control group. The results obtained from the studies may indicate that the administration of vanadium citrate into the drinking water of rats during a one-month period restores the activity of carbohydrate metabolism enzymes and antioxidant defense enzymes in the pancreas of rats with alloxan-induced diabetes to the normal. Thus, vanadium citrate may be the basis for creating the means for the prevention and treatment of diabetes.

INTRODUCTION: Diabetes mellitus (DM) is a group of heterogeneous, hormonal, and metabolic disorders characterized by hyperglycemia and glucosuria [1]. DM remains a major health issue, despite the availability of insulin and a multitude of oral hypoglycemic agents [2]. As of 2015, 415 million people worldwide were suffering from type 2 diabetes [3], and this number may double by 2025 [4].

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Twenty years ago, an *in-vivo* discovery showed the effects of vanadium, namely the enhancement and imitation of the physiological effects of insulin. Vanadium is one of the trace elements that can be used as an alternative in diabetes mellitus therapy. It is an effective means for lowering blood glucose levels and leads to normoglycemia [5]. Vanadium influences various aspects of carbohydrate metabolism, including glucose transportation, glycolysis, glucose oxidation, and glycogen synthesis [6]. Vanadium also has an insulin-like effect on the metabolic pathways of lipid and protein metabolism [7]. Free radicals of oxygen are essential for cellular functions but, at the same time, highly toxic to cellular homeostasis.

Increased levels of free-radical oxidation processes lead to pathological changes in the body, oxidative stress being one of such changes. The magnitude of oxidative stress is significantly influenced by acute glucose fluctuations. It is important to note that oxidative stress has been postulated as a possible mechanism associated with tissue damage and other systemic complications [8]. Therefore, the purpose of the research was to find out the effect of various amounts of vanadium citrate on the carbohydrate metabolism and the state of the antioxidant system in the pancreas of rats with experimental diabetes mellitus.

MATERIALS AND METHODS: The research was conducted on 40 white laboratory rats kept in the vivarium of the Institute of Animal Biology of the National Academy of Sciences (12-h cycle of light/darkness). All animals were clinically healthy, received a standard granular feed for laboratory rats, and had free access to water.

Rats weighing 100-120 g were divided into 5 groups: I – the control group, II – the control group with diabetes, III, IV, and V – experimental groups. Rats from groups I and II were given pure water without any additives; animals from groups III, IV, and V were given water with the solution of vanadium citrate in the amounts of 0.125, 0.5, and 2.0 μg/mL of water during one month. Experimental diabetes mellitus (ECD) was induced in the animals from groups II, III, IV, and V after a 24-h fasting period by intraperitoneal administration of 5% solution of alloxan monohydrate ("Synbios") in the amount of 150 mg/kg of body weight. In order to detect hyperglycemia, we collected blood from the tail vein and measured glucose level in the collected blood using a portable glucose meter (Gamma-M). Glucose level in the blood of diabetic animals was 15.14 mmol/L.

On day 40 of the study, the animals were withdrawn from the experiment and decapitated under light anesthesia. The experiment was conducted according to the provisions of the "European Convention for the Protection of Vertebrate Animals used for Experiments and Other Scientific Purposes", European Treaty Series - No. 123 (Strasbourg, 1985) and "General Ethical Principles of Animal Experiments" adopted by the First National Congress on Bioethics (Kyiv, 2001). Protocol of the meeting of the Bioethics Committee of the Institute of Animal Biology no. 71 dated June 12, 2018.

We used homogenates of pancreatic tissue as the material for the study. The homogenate was prepared using 0.05 M Tris-HCl buffer, pH of 7.8 (1 g of tissue and 10 ml of buffer). The concentration of protein in the homogenates of the pancreatic tissue was determined by Lowry's method [9]. The content of lipid hydroperoxides (LPO) in the homogenates was determined by the method the principle of which is based on the precipitation of protein with a solution of trichloroacetic acid, followed by the introduction of ammonium thiocyanate [10]. The concentration of TBA-positive substance was measured using the color reaction of malonic dialdehyde with thiobarbituric acid [11].

Superoxide dismutase (SOD) activity was determined by the method the principle of which consists in the restoration of nitrotetrazolium by superoxide radicals [12]. Glutathione peroxidase activity (GPx) was determined using the rate of oxidation of reduced glutathione [13]. Catalase activity (CAT) was determined by the ability of hydrogen peroxide to produce a stable stained complex with molybdenum salts [14]. Glutathione reductase activity (GR) was determined by the rate of glutathione recovery in the presence of NADPH [15]. The content of reduced glutathione (GSH) was determined by the level of formation of thionitrophenyl anion as a result of the interaction of the SH group of glutathione with 5.5-dithiobium, 2-nitrobenzoic acid [9]. The activity of glucose-6-phosphate dehydrogenase and lactate dehydrogenase was measured using the spectrophotometric method that is based on the oxidation-reduction of NAD^+-coenzymes [9]. The obtained digital data was processed statistically using the Microsoft Excel 2016 package. We determined arithmetic mean, mean square deviation, and the standard error of the arithmetic mean. To determine the probable differences between the statistical groups the Student's criterion was used.

RESULTS AND DISCUSSION: Alloxan (a thiol reagent) is used to model diabetes in experimental animals. Glucose transporters GLUT2 deliver

alloxan into pancreatic β-cells through the ROS mechanism. This leads to the accumulation of alloxan in the cells and their subsequent destruction, which causes hyperglycemia and oxidative stress [16]. The increase of oxidative stress in the tissues of animals with experimentally induced diabetes may cause changes in the state of the antioxidant system. Pancreatic cells are very susceptible to oxidative stress, probably due to the extremely low level of antioxidant enzymes. Oxidative stress plays an essential role in diabetes mellitus, and control over this process can be important in the fight against this disease.

Oxidative stress in tissues leads to an increase in the level of lipid peroxidation products. In particular, the levels of lipid hydroperoxides and TBK-positive substances are significantly higher in the pancreas of rats from group II as compared to the control group: lipid hydroperoxides - higher by 194%, TBK-positive substances - higher by 65.8%. Lipid peroxidation products can form compounds with proteins and phospholipids, which leads to lower membrane permeability and a decrease in the activity of membrane enzymes. Under normal conditions, the amount of lipid peroxidation products is at a constant level. An increased amount of lipid peroxidation products can disrupt the body's protective system. The obtained results are confirmed by the data from some other authors: the increased formation of TBK-positive substances is observed during E-avitaminosis, tumor diseases, iron deficiency anemia, diabetes mellitus, and physical activity, as well as in old animals and under ionizing radiation [9]. The administration of vanadium citrate into the drinking water of rats from groups III, IV, and V led to a decrease in the level of LPO products as compared to the rats from group II, indicating the positive effect of vanadium.

TABLE 1: INDICATORS OF LIPID PEROXIDATION PRODUCTS AND ANTIOXIDANT DEFENSE SYSTEMS IN RATS PANCREAS DURING EXPERIMENTALLY INDUCED DIABETES UNDER THE INFLUENCE OF VANADIUM CITRATE IN THE AMOUNTS OF 0.125, 0.5, AND 2.0 µg/mL OF WATER

Indicators	Animal groups				
	I	II	III	IV	V
LPO OE/ml	0.05±0.002	0.147±0.009***	0.063±0.017$^{\#\#\#}$	0.065±0.012$^{\#\#\#}$	0.140±0.1***
TBA-positive substances, nmol/mL	2.204±0.235	4.025±0.453**	2.951±0.279	3.215±0.393*	3.687±0.223***
SOD, U/mg of protein	20.851±1.29	12.908±0.933***	17.075±1.178$^{*\#}$	10.638±0.604***	14.846±1.119**
CAT, µmol/min×mg of protein	5.981±0.747	3.232 ±0.242**	1.525±0.237$^{***\#\#\#}$	4,279±0,535	4.150±0.529
GSH mmol/L	0.431±0.029	0.335±0.034*	0,385±0,041	0.244±0.006$^{***\#}$	0.312±0.033*
GPx, µmol/min×mg of protein	47.095±1.912	37.830±0.935***	41.104±0.618$^{**\#}$	44.143±2.332$^{\#}$	43.275±2.399$^{\#}$
GR,µmol/min×mg of protein	0.761±0.112	0.488±0.035*	0.507±0.019*	0.546±0.028	0.605±0.1

Here and onward * (P < 0.05), ** (P <0.01), and *** (P < 0.001) significantly the indicators of groups II, III, IV, and V as compared to group I; $^{\#}$ (P < 0.05), $^{\#\#}$(P <0.01), and $^{\#\#\#}$ (P < 0.001) significantly the indicators of groups III, IV, and V as compared to group II

Superoxide dismutase (SOD) is an antioxidant enzyme that catalyzes the dismutation of superoxide anion (O^{2-}) into hydrogen peroxide and molecular oxygen. SOD plays an important protective role against cellular and histological lesions that arise from the activity of reactive forms of oxygen. SOD reduces superoxide to hydrogen peroxide, and GPx and CAT catalyze hydrogen peroxide to water [17].

The activity of this enzyme in the pancreas of rats is significantly reduced during experimental diabetes mellitus. In particular, the enzymatic activity decreased by 38.1% in the tissue of animals from group II as compared to the control group. The observed decrease may be the result of inactivation of H_2O_2 or the glycosylation of the enzyme, which has been reported to occur during diabetes [18]. When vanadium citrate is present in the diet, the activity of SOD grows in groups III and V as compared to group II and approaches the levels of the control group given the use of the compound at the concentration of 0.125 µg/mL.

Catalase is an important enzyme for removing the active forms of oxygen and regulates the level of hydrogen peroxide that is formed during metabolic processes. Excessive concentration of hydrogen peroxide can cause significant damage to proteins, DNA, RNA, and lipids [19]. Unlike many other cells, pancreatic β-cells have a low level of catalase activity and expression and, at the same time, high enzyme sensitivity to hydrogen peroxide [20]. The study revealed a significant 46% decrease of catalase activity in pancreatic homogenates of animals from group II during alloxan-induced

diabetes. The tissue of animals from study groups undergoes changes in catalase activity during the administration of vanadium citrate into the drinking water. In particular, in group III there was a significant decrease in the enzymatic activity, while in groups IV and V there was a tendency to increase in the enzymatic activity as compared to group II.

The level of glutathione peroxidase activity in pancreatic β-cells is not high, but the expression of activity provides an enhanced protection against oxidative stress. This suggests that GPx mimetics may represent a valuable auxiliary treatment that could add a new layer of β-cells protection. The study of pancreatic homogenates of the animals in group II with experimental diabetes revealed a significant 19.7% decrease in the activity of the enzyme. However, under the conditions of vanadium citrate consumption, the activity of the enzyme increases significantly in groups III, IV, and V groups as compared to group II.

Reduced glutathione can maintain protein SH-groups in the recovered state and is involved in the transport of amino acids and the detoxification of external radicals. This enzyme acts as a coenzyme in several enzymatic reactions and prevents tissue damage [21]. The obtained data shows a probable decrease in the level of GSH in the pancreas of diabetic rats in group II. This decrease can be one of the factors causing DNA damage in patients with type 2 diabetes [22, 23]. The administration of vanadium citrate into the drinking water led to an increase in the activity of the enzyme in group III and a significant decrease in group IV showed as compared to group II.

Glutathione reductase catalyzes the restoration of oxidized disulfide form of glutathione to the reduced sulfhydryl form owing to $NADFN^{+}H^{+}$, which is a proton donor. This glutathione regeneration reduces the need for its de novo synthesis. For experimental diabetes in the pancreas of rats from group II, the activity of GR decreased by 22.3% in the pancreas of diabetic rats from group II. At the same time, the study of vanadium citrate in the concentrations observed revealed a tendency towards increase in the level of the activity in animals from groups III, IV, and V as compared to group II.

The activity of glucose-6-phosphate dehydrogenase plays a central role in cellular oxidative-reduction processes [24, 25]. This enzyme plays a significant role in the regulation of oxidative stress through the initial regulation of NADPH as the main intracellular reductant. It was determined that the activity of G-6-PDH in the pancreas of rats from group II decreased by 46.13% as compared to the control group. High glucose level that accompanies diabetes stimulates the growth of cAMP level due to the increase in adenylate cyclase activity, which leads to the inhibition of G-6-PDH activity. In particular, cAMP is considered to cause most of its effects through cAMP-dependent protein kinase A.

Therefore, the activation of cAMP-dependent protein kinase A is accompanied by the inhibition of G-6-PDH activity [26]. In its turn, the decrease in the G-6-PDH activity and a high glucose level in the pancreas of animals from group II also lead to the decrease in the level of reduced glutathione [26].

When vanadium citrate was administered into the drinking water of rats, G-6-PDH activity increased as compared to the animals from group II, in particular: group III – by 59.96%, group IV – by 79.09%, and group V – by 100%. There is evidence that the interaction of vanadium compounds with the 6-hydroxyl group of the glucose molecule produces glucose-6-vanadate, which is a fairly good substrate for the glucose-6-phosphate dehydrogenase enzyme [27, 28].

TABLE 2: THE ACTIVITY OF CARBOHYDRATE METABOLISM ENZYMES IN THE PANCREAS OF RATS DURING EXPERIMENTALLY INDUCED DIABETES AND UNDER THE INFLUENCE OF VANADIUM CITRATE IN THE AMOUNTS OF 0.125, 0.5, AND 2.0 µg/mL OF WATER (M ± m, n = 8), µmol/min × mg OF PROTEIN

Indicators	Animal groups				
	I	II	III	IV	V
G-6-PDH	56.47±5.7	30.42±3.02***	48.66±3.2$^{\#\#}$	54.48±4.8$^{\#\#\#}$	59.56±5.1$^{\#\#\#}$
LDH	57.32±4.5	38.71±3.1**	38.92±3.16**	42.265±3.8**	51.88±4.9$^{\#}$

Lactate dehydrogenase is one of the enzymes that actively participates in the oxidation of glucose to lactate without oxygen. Changes in lactate dehydrogenase activity demonstrate the state of

inflammatory processes under diabetes [29]. LDH activity in the pancreas of diabetic rats from group II decreased by 32.46% as compared to group I. Alloxan-induced diabetes promotes the growth of free radicals, which attack the mitochondrial genome, thus triggering the destruction of β-islets of the pancreas (known to be sensitive to oxidative stress) [30], which results in disrupted insulin production and causes a decrease in the activity of enzymes, including LDH [31]. The decrease in LDH activity in the pancreas suggests a partial destruction of pancreatic cells and the release of the enzyme into the blood. Additionally, reduced LDH activity may be associated with the regulation by NAD^+ coenzyme required for enzyme activity or pyruvate, a substrate that is oxidized in a citric acid cycle [32].

When vanadium citrate was administered into the drinking water of rats, LDH activity increased in the pancreas of rats from group IV by 9.18% and rats from group V by 34% as compared to group II. Increased LDH activity may be mediated by the ability of vanadium to modify glucose and lipid homeostasis, reversing key glycolytic, gluconeo-genic, and lipogenic enzymes [33, 34]. Vanadium, as an insulin mimetic, is able to lower the level of glucose in the blood as a result of glucose transportation to the cells of the body's tissues, including pancreas, as well as the activation of glycolysis and the pentose phosphate pathway (PPP), which is confirmed by the growth of LDH and G-6-PDH activity.

This data indicates that vanadium compounds restore the depressed glycolysis and PPP in the pancreas of diabetic rats due to their ability to reduce oxidative stress by stimulating antioxidant enzymes. Administration of vanadium citrate restores the changes in the activity of enzymes of carbohydrate metabolism and antioxidant defense in the pancreas of rats with alloxan-induced diabetes, which indicates the insulin-like nature of vanadium citrate.

CONCLUSION: Compared to the rats from the control group, the study of the pancreas of rats with experimentally-induced diabetes has revealed significantly increased levels of lipid hydro-peroxides and TBA-positive substances. The study has also revealed decreased levels of reduced glutathione, reduced activity of SOD, CAT, GPx, and GR as well as the reduced activity of LDH and G-6-PDH carbohydrate metabolism enzymes. Compared to the rats from the control group, a one-month period of exposure to vanadium citrate dissolved in drinking water resulted in the following changes in the pancreas of diabetic rats: decreased levels of LPO products, an increase in the activity of antioxidant system enzymes, and an increase in the activity of carbohydrate metabolism. The changes were dose-dependent.

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