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### ВЛИЯНИЕ ДОДЕЦИЛСУЛЬФАТА НАТРИЯ НА ФИЗИОЛОГО-БИОХИМИЧЕСКИЕ И ЦИТО-МОРФОЛОГИЧЕСКИЕ СВОЙСТВА ДРОЖЖЕЙ РОДА *CANDIDA* И *SACCHAROMYCES*

*Сравнены физиолого-биохимические и цито-морфологические свойства исходных штаммов Candida albicans ATCC 10331, Saccharomyces sp. KHY 1 и их вариантов, которые культивировали на среде Сабуро с анионным поверхностно-активным веществом (ПАВ) додецилсульфатом натрия (ДСН). Показано, что контакт с ДСН сопровождался исчезновением у дрожжей способности к ассимиляции ряда субстратов, но не влиял на чувствительность к антибиотикам. После первого пассажа изменялась морфология клеток, уменьшалось количество волутина, появлялись жировые включения. После четвертого пассажа цито-морфологические особенности клеток частично восстанавливались.*

*Ключевые слова: додецилсульфат натрия, биологические свойства, дрожжи.*

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### EFFECTS OF SODIUM DODECYLSULFATE ON PHYSIOLOGICAL, BIOCHEMICAL AND CYTOMORPHOLOGICAL PROPERTIES OF *CANDIDA* AND *SACCHAROMYCES* GENERA

*Physiological, biochemical, cyto-morphological properties of initial strain Candida albicans ATCC 10331, Saccharomyces sp. KHY 1 and their variants, which were cultivated in medium Saburo with anionic surfactant (SAS) sodium dodecyl sulfate (SDS) have been compared. It was shown that the effect of SDS was accompanied by disappearance of possibility to assimilate a number of substrates, but did not affect antibiotics sensitivity. They changed its morphology after 1 passage, diminution quantity of volutin, appearance of fat inclusion. Morphology of cells partially restored after 4-th passage.*

*Key words: sodium dodecyl sulfate, biological properties, yeasts.*

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### EFFECT OF DIFFERENT ORAL DOSES OF GLUCOSE ON THE BLOOD SERUM CONTENT OF SEROTONIN IN RATS

*The analysis of the effect of different doses of oral glucose content of serotonin in blood serum of rats. The increasing content of serotonin in blood serum of rats with diabetes and with the administration of glucose. The increase in the studied parameters in the serum of the control group of animals under conditions of a glucose. It is concluded that glucose has a direct positive effect on the endogenous flow of serotonin into the bloodstream.*

*Key words: glucose, serotonin, rat.*

**Introduction.** Ukraine has a population of about 45.7 million and the official data state that the prevalence of diabetes in Ukraine is 2.5% (1,133,922 people are registered with diagnosed diabetes). The Diabetes Atlas indicates for Ukraine an estimated prevalence of 9.6% [for the population between 20 to 79 years old] which is in great discrepancy with the figures registered by the health system (2.5%) but is closer to the results of local studies (8.7%).

Diabetes begins with a loss of insulin sensitivity in white adipose tissue and skeletal muscle. Initially, the body compensates for the decrease in insulin-mediated signaling by enlarging the beta cells (found in the Islets of Langerhans in the pancreas), resulting in increased insulin release to maintain euglycemia (2). Eventually, however, the beta cells begin to fail, leading to a loss of insulin production. The lack of insulin results in elevated plasma glucose concentrations, which if sustained, leads to

damage of the microvasculature of various internal organs (e.g., kidneys and eyes) and the peripheral aspects of the limbs, including the feet.

Current therapies for diabetes include agents that enhance insulin sensitivity, elevators of insulin release and inhibitors of carbohydrate absorption (3). More recently characterized agents mimic the role (and enhance the activity) of the incretin hormone glucagon-like peptide-1 (GLP-1) (Box 1). Such mimetics include the dipeptidylpeptidase inhibitor sitagliptin, which prolongs the half-life of endogenous GLP-1, and the non-hydrolyzable GLP-1 analog exendin-4. GLP-1 is released in a glucose-dependent manner from the L cells of the gut, enters the circulation, evokes GLP-1 receptor-mediated release of insulin from beta cells, inhibits glucagon release, and reduces gastric motility (4).

A tryptophan derivative, neurotransmitter and tissue hormone serotonin is a biologically active substance, characterized by a wide range of effects on the body [1-3]. Central nervous system saves about 2% of the body's serotonin. Serotonin affects food intake, sleep, anxiety, sexual behavior, mood, involved in the formation of pain and also plays an important role in the regulation of emotional behavior [4-9]. On the other side, in the peripheral system where about 98% of the body's serotonin is synthesized and stored, serotonin acts as a peripheral hormone affecting vasoconstriction, intestinal motility, primary hemostasis and is involved in the regulation of vasoconstriction [10-15].

Serotonin (5-HT)-mediated neural networks—and the 5-HT<sub>2C</sub> receptor (5-HT<sub>2CR</sub>) in particular—have long been implicated in the control of food intake and energy homeostasis. Evidence for this comes from both pharmacological and genetic experiments. Fenfluramine, a stimulator of serotonin release and an inhibitor of serotonin reuptake, was marketed as a weight loss agent from 1973 until 1997 (5), when it and its more potent enantiomer dexfenfluramine were removed from the market because of their cardiac side effects, which were likely due to activity at the 5-HT<sub>2BR</sub> (6). These weight loss effects are 5-HT<sub>2CR</sub>-mediated, as is demonstrated by the reduction in efficacy of m-chlorophenylpiperazine (mCPP) and fenfluramine when administered to 5-HT<sub>2C</sub> knockout (KO) mice (7, 8). Thus, highly selective 5-HT<sub>2C</sub> receptor agonists have been extensively studied over the last decade as a drug development target for obesity and more recently as a possible treatment for schizophrenia. Two compounds, lorcaserin and vabicaserin, developed for the treatment of obesity and schizophrenia, respectively, have entered late-stage trials and might reach the marketplace in the next two to five years. New research by Zhou et al. implies that these and other 5-HT<sub>2CR</sub> agonists may have utility in the treatment of type II diabetes (9). If true, these findings would indicate that a distinctly neuronal mechanism may be an effective treatment option for regulating plasma glucose concentrations.

The first step in the synthesis of serotonin from tryptophan is an enzyme tryptophan hydroxylase (TRH), which is also an enzyme that limits the rate of biosynthesis. TRH is known to have two isoforms that are identical by about 70%. They are called TrH1 and TrH2 [16]. TrH1 mainly present in the pineal gland, thymus, spleen and enterochromaffin cells of the gastrointestinal tract. TrH2 is only in nerve cells, such as brain stem nuclei seam. Mice lacking TrH1 practically did not contain serotonin in the blood and gastrointestinal tract while maintaining normal levels in the brain. Peripheral serotonin in mice deprived TrH1 cannot be substituted for the central nervous system serotonin synthesized TrH2 [17]. Moreover, as known from the literature, serotonin does not cross the blood-brain barrier. Serotonin wasn't found in the brains of animals treated with serotonin (50 mg/kg, intraperitoneally) [18, 19]. Thus, there are two serotonin systems: one in the central nervous system and one on the periphery, with independent functions and biosynthesis pathways.

Current published data show that the increase of the concentration of circulating serotonin lowers blood glucose levels by inducing insulin secretion in mice [20, 21]. In contrast, serotonin causes hyperglycemia by adrenaline

release from the adrenal glands of rats, which operates indirectly through 5HT<sub>1A</sub>, 5HT<sub>2A</sub> or 5HT<sub>7</sub> receptors [22-24]. In addition, serotonin enhances the absorption of glucose by the liver under conditions of hyperglycemia and hyperinsulinemia [25] and stimulates the synthesis of glycogen in nanomolar concentrations, but inhibits it at micromolar concentrations via serotonergic mechanisms in hepatocytes [26]. These results suggest that peripheral serotonin plays an important role in the metabolism of glucose. Thus, the aim of our work was to study the effect of different doses of oral glucose on the content of serotonin in serum of control rats.

**Materials and methods.** Experiments were carried out on the white nonlinear rats of both sexes in compliance with the standards of the Convention of Bioethics of the Council of Europe in 1997, European Convention for the protection of vertebrate animals that used for experimental and other scientific purposes, the general ethical principles of animal experiments approved by first National Congress of Bioethics of Ukraine (September 2001) and other international agreements and national legislation in this field.

Male Wistar rats aged 180 days and weighing 240–290 g were used (n = 90). They were maintained under controlled temperature conditions (22–24°C) and lighting (lights on from 05.00 to 19.00 h). All tests were conducted under the light cycle. Standard rat chow and water were freely available. The experimental diabetes mellitus type 2 is caused by disposable intraperitoneal introduction of streptozotocin solution to 1-2 diurnal neonatal rats at the rate of 80 mg per 1 kg of body weight (Hemmings, 2000). The control group included rats, which were injected intraperitoneally with 10 mM citrate buffer (pH 4.5) at the same age, which was used for breeding streptozotocin. To confirm the development of insulin resistance in experimental animals the sensitivity of peripheral tissues to insulin was determined through insulin-glucose test (Zhang, 2003) conducted with our own modifications. 180 days after the STZ injection, blood glucose level was measured by using a portable glucometer (Gluco-Plus Inc., Kiev, Ukraine) in the blood collected from tail vein. Animals with non-fasting blood glucose (NFBG) level >7 mmol/l were considered as diabetic.

Glucose in a dose of 2, 4 and 6 g/kg of body weight was administered per os. Control group of rats received an equal amount of 0,9% NaCl, which was used as a vehicle. 1 hour after the procedure serotonin was extracted from serum using ion-exchange chromatography and was determined by spectrophotometrical methods.

Statistical analysis was performed using statistical analysis applications of Microsoft® Excel. To assess inter-group differences the parametric Student test was used. The difference between the parameters was considered statistically significant at p<0,05.

#### **Results and discussion.**

Whereas peripheral serotonergic system is involved mainly in the regulation cardiovascular and digestive systems, serotonin serves as a tissue hormone on the outskirts and involved in the regulation of blood glucose so it was advisable to establish the content of serotonin in blood serum of rats under conditions of experimental type 2 diabetes. The results show the increase of serotonin content in blood serum of diabetic animals in 3.2 times compared of the control group (Fig.1).

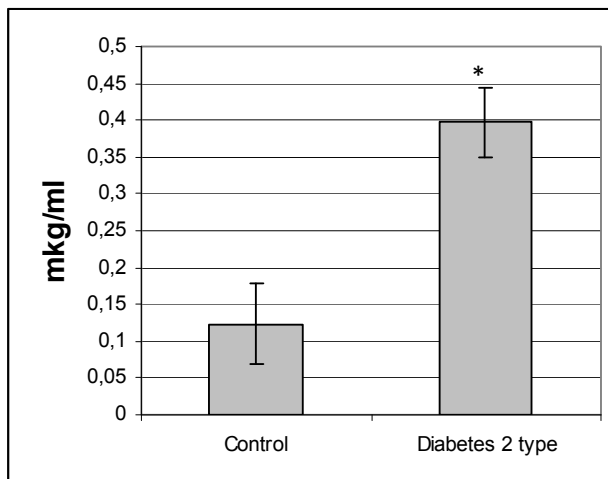


Fig. 1. Serotonin level in the blood of rats of the control and experimental group

Note. \* –  $P \leq 0,05$  compared to the control group

It was shown morphological changes enterochromaffin cells of the gastrointestinal tract in diabetic rats, particularly the occurrence of large serotonin-positive cells in areas of the mucosa, which was absent in animals of the control group. Also known that diabetic animals have an increase content of serotonin in the gastrointestinal tract. Shown to increase serotonin content in enterochromaffin cells duodenum in rats with diabetes caused by streptozotocin administration, improve the content shown, also shown abuse activity of type 3 serotonin receptor. So, the increase in content of peripheral serotonin may be due to hyperfunction of enterochromaffin cells in diabetic animals and/or malfunction of vascular-platelet hemostasis system level. The imbalance in the hemostatic system associated with platelet hyperfunction, determined by pathogenetic peculiarities of type 2 diabetes. Given that platelets are a place of storage and transportation of peripheral serotonin it may be the cause of its increase in serum.

These data correlate with the results which obtained in the study of the blood of patients with diabetes. Was found increased of serotonin content in blood plasma these patients, and this increase is associated with platelet hyperfunction. Serum serotonin content also increased in patients with diabetes. Also in patients with type 2 diabetes with high content in plasma 5-hydroxyindoleacetic acid concentration of this metabolite positively correlated with the release of albumin in the urine, so, it may indicate increased susceptibility to the development of diabetic neuropathy.

As can be seen from Table 1, observed an increase of serotonin content in blood serum of rats under conditions of glucose to control group and in group of animals with type 2 diabetes. Serotonin content increased in 2 times in control animals and in 1.2 times in animals with type 2 diabetes have been injected glucose (Tab.1).

Table 1. Serotonin content in control group and in group of animals with type 2 diabetes have been injected glucose

	Control	Control GI	DM 2	DM 2 GI
Serotonin	0,123±0,0554	0,249±0,0522*	0,397±0,0467*	0,461±0,0634*

Note. \* –  $P \leq 0,05$  compared to the control group

Not only hyperinsulinemia is caused by serotonin, but hyperglycemia either, without any changes in the concentration of glycogen in the liver and skeletal muscle. It is believed that the reason for this is inhibition of tissues glucose capture from the blood. Researches of Hajduch E. et al. (1999) and Moor M. et al. (2004, 2005) were show that serotonin directly inhibits peripheral tissues glucose capture, including hepatocytes and skeletal muscle cells. However, in experiments Watanabe et al. (2011) showed that serotonin has no effect on glucose uptake neither in the liver nor in the skeletal muscles, while plasma insulin concentrations is increased after administration of serotonin. This indicates that hyperinsulinemia and hyperglycemia caused by serotonin have different independent mechanisms. These hypotheses are confirmed in experiments using antagonists to serotonin receptors: ketanseryn (antagonist of 5-NT2A receptor), SB-269970 (antagonist of 5-NT7 receptor) and metyserhid (5-NT1 antagonist, 5-HT 2, 5-receptor NT7) – in all cases there was an increase of glucose in the blood plasma. This increase in insulin levels was observed only when metyserhid was

administered. Thus, it was shown that there are two different mechanisms of action of serotonin on glucose metabolism: one that directly affects the secretion of insulin by beta cells of the pancreas, and another that inhibits glucose uptake by cells of the liver and skeletal muscle.

Serotonin in plasma may be free or bound to the 14-3-3 protein. In addition, the capture of serotonin from plasma to platelets occurs quickly, by the mechanism of saturation that makes platelets a fundamental regulator of serotonin concentration in plasma. The capture of serotonin from plasma by platelets is dependent on the serotonin transporter (SERT) mechanism, the operation of which is usually regarded as a transporter reuptake of neurotransmitters in the central nervous system, but it is also present in the plasma membrane of platelets. It was shown that administration of serotonin affects SERT plasma membrane density. Recently, the analysis of the effect of extracellular serotonin at different concentrations (0-2.5nM) on SERT expression on the platelets cell surface was found that this phenomenon is biphasic. Specifically, the level of platelet membrane SERT and serotonin capture

in the initial stage increases in response to the increase of serotonin levels, but the initial response is accompanied by a second phase – a reduction in the SERT levels to the initial values because the concentration of serotonin continues to grow. SERT gene polymorphism is associated with depression and other mood disorders, autism, and anxiety which often occurs in patients with diabetes. Usually the intensity of serotonin by platelets is proportional to the number of transporters in the plasma membrane. However, it was found that the number of SERT in the plasma membrane is regulated by extracellular concentration of serotonin. Platelets of rats which were knockout by SERT gene contain virtually no serotonin. Homberg J. et al. (2009) observed in animals,

which were knockout by SERT gene (Sert – / -) an increase in plasma glucose and an increase in visceral fat in females. It is shown that the bond of SERT with vimentin, a cytoskeletal protein, increases in serotonin concentrations higher than physiological.

Data on how a glucose effect on serotonin content in blood serum of rats are scarce. Therefore, on the first phase of the experiment rats were injected with glucose per os at a doses of 2, 4 and 6 g/kg of body weight. The control group received the same volume of fluid (0,9% NaCl) which was used to dissolve the glucose. The introduction of glucose at a dose of 2 g/kg showed an increase in this indicator in 1.6 times, the introduction at a doses of 4 and 6 g / kg – 4.2 and 4.8 times, respectively (Fig. 2).

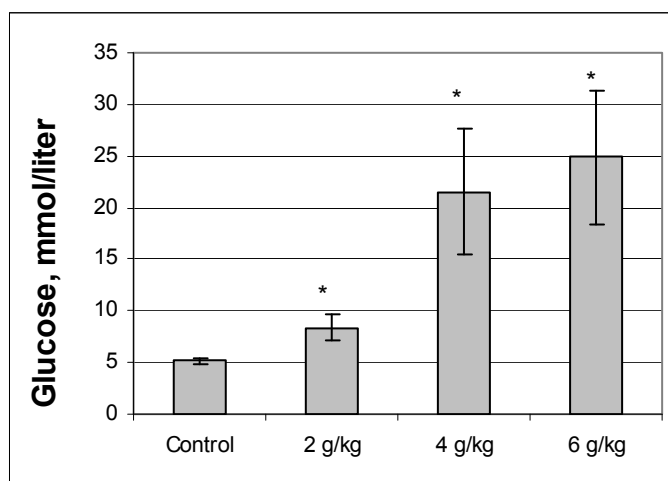


Fig. 2. Glucose level in the blood of rats of the control group after the oral administration of glucose at a dose of 2, 4 and 6 g/kg

Note. \* –  $P \leq 0,05$  compared to the control group

Serotonin levels in the rat serum were determined in 1 hour after glucose administration at a dose of 2, 4 and 6 g/kg by body weight. During the research it was found that

after oral administration of glucose, the content of serotonin in the blood of experimental animals increased by 11.8, 0.5 and almost 4 times according to the dose (Fig. 3).

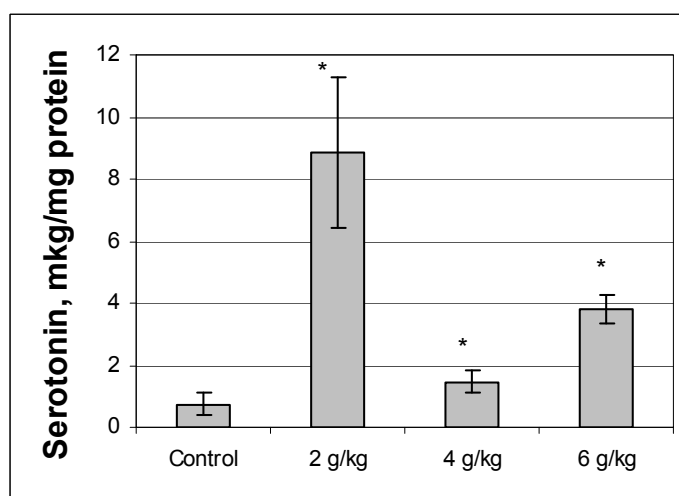


Fig. 3. Serotonin level in the blood of rats of the control group after the oral administration of glucose at a dose of 2, 4 and 6 g/kg

Note. \* –  $P \leq 0,05$  compared to the control group

It has been reported that increasing circulating concentrations of 5-HT induces hyperglycemia through the release of adrenaline from the adrenal gland in rats via

action through the 5HTR1A, 2A or 7 [11]–[13]. Additionally, 5-HT stimulates glycogen synthesis at nanomolar concentrations but inhibits it at micromolar concentrations in

hepatocytes by serotonergic mechanisms [14], and 5-HT enhances net hepatic glucose uptake under hyperglycemic and hyperinsulinemic conditions [15]. On the other hand, we have previously reported that peripheral 5-HT decreases plasma lipid levels via action through several 5HTRs in mice [16]. These results suggest that peripheral serotonin plays an important role in glucose and lipid metabolism.

Thus, the highest content of serotonin was observed at the lowest concentration of administered glucose. The next

stage of our work was to study the glucose and serotonin levels 5 hours after oral administration of glucose at a dose of 2 g/kg. During the study it was found a gradual decrease in blood glucose levels in rats. The decrease in blood glucose at 3 hours was in 1.4 times and in 2 times at 5 hours after administration compared to the first hour. Thus at 5 hours after administration of glucose at a dose of 2 g/kg content of the studied parameters fell below the control value (Fig. 4).

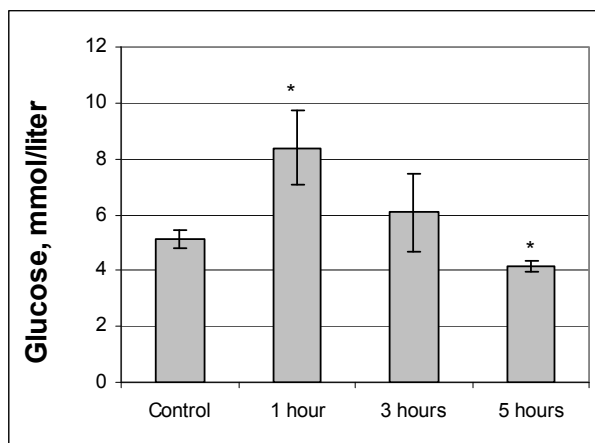


Fig. 4. Glucose level in the blood of rats of the control group in 1, 3 and 5 hours after oral glucose administration at a dose of 2 g/kg

Note. \* –  $P \leq 0,05$  compared to the control group

For the next 5 hours after administration of glucose at a dose of 2 g/kg by body weight content of serotonin in the blood of rats remained similarly high (Fig. 5). During the study

it was found that after 3 hours after the glucose administration the content of serotonin was in 9.2 times higher than the control values, and after 5 hours – in 6.9 times.

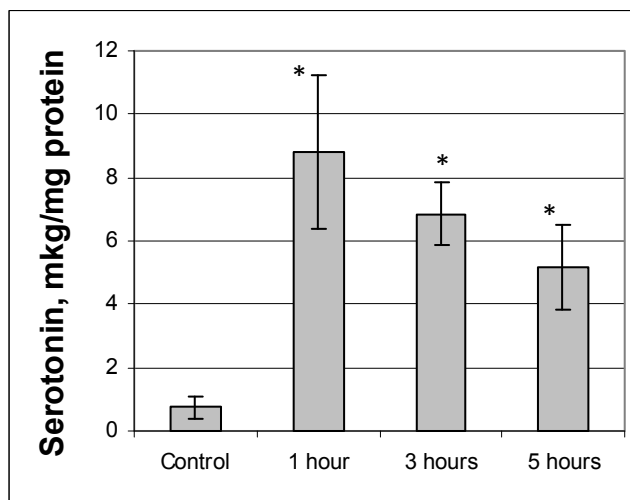


Fig. 5. Serotonin level in the blood of rats of the control group in 1, 3 and 5 hours after oral glucose administration at a dose of 2 g/kg

Note. \* –  $P \leq 0,05$  compared to the control group

Thus, there are two systems of serotonin, one in the brain, the other on the periphery. They are self-regulated and have different functions. According to the literature, the intraperitoneal administration of serotonin affects the concentration of metabolites associated with glucose metabolism in peripheral blood and liver. Disorders of glucose metabolism in case of diabetes are accompanied by multiple pathological changes in the structural organization and functional activity of cells and leads to

dysregulation of processes that provide homeostasis in the body. Therefore it was interesting to us to investigate the effect of glucose on the content of serotonin. Our results indicate a correlation between the concentration of glucose and serotonin content.

**Conclusion.** There are two independent 5-HT systems, one in the brain and the other in the periphery. In humans and rodents, 5-HT regulates glucose and lipid metabolism through several 5HTRs and the 5-HT transporter (SERT).

5-HT is known to be associated with glucose metabolism, mainly because of its regulation of the secretion of insulin in pancreatic  $\beta$  cells. The insulin secretion induced by glucose is inhibited by 5-HT in rat islet of Langerhans incubations in vitro. Another report demonstrates that 5-HT regulates insulin secretion by serotonylation of GTPase within the pancreatic  $\beta$ -cells. Additionally, 5-HT directly controls the uptake of glucose into the peripheral tissues, including the liver and skeletal muscles. 5-HT enhances net hepatic glucose uptake under hyperglycemic and hyperinsulinemic conditions [15], and stimulates glycogen synthesis at nanomolar concentrations, but inhibits it at micromolar concentrations by serotonergic mechanisms in hepatocytes [14]. Moreover, we previously reported that 5-HT induced the elevation of plasma glucose and insulin concentrations through different 5HTRs in mice, and that hyperglycemia after the injection of 5-HT was induced by repressing glucose uptake into the tissues [16].

The study shows that glucose has a direct positive effect on endogenous serotonin outflow into the bloodstream. Our previous experiments showed that the content of serotonin is increased in the serum of rats with type 2 diabetes. Thus, a diet with extremely high glucose content can lead to increase of serotonin levels in serum and complications of type 2 diabetes. Furthermore, serotonin action may well offer new drug strategies for developing therapeutic drugs for the treatment of metabolic diseases such as hyperlipidemia, hypercholesterolemia, diabetes and obesity.

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### ВПЛИВ РІЗНИХ ПЕРОРАЛЬНИХ ДОЗ ГЛЮКОЗИ НА ВМІСТ СЕРТОНИНУ В СИРОВАТЦІ КРОВІ ЩУРІВ

Проведено аналіз впливу різних пероральних доз глюкози на вміст серотоніну в сироватці крові щурів. Встановлено підвищення вмісту серотоніну в сироватці крові щурів з цукровим діабетом та за умов введення глюкози. Встановлено зростання досліджуваного показника в сироватці крові контрольної групи тварин за умов введення глюкози. Зроблено висновок, що глюкоза має прямий позитивний вплив на ендогенний відтік серотоніну в кровотік.

Ключові слова: глюкоза, серотонін, щури, цукровий діабет 2 типу.

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### ВЛИЯНИЕ РАЗЛИЧНЫХ ПЕРОРАЛЬНЫХ ДОЗ ГЛЮКОЗЫ НА СОДЕРЖАНИЕ СЕРТОНИНА В СЫВОРОТКЕ КРОВИ КРЫС

Проведен анализ влияния различных пероральных доз глюкозы на содержание серотонина в сыворотке крови крыс. Установлено повышение содержания серотонина в сыворотке крови крыс с сахарным диабетом и при условии введения глюкозы. Установлен рост исследуемого показателя в сыворотке крови контрольной группы животных в условиях введения глюкозы. Сделан вывод, что глюкоза имеет прямое положительное влияние на эндогенный отток серотонина в кровотоке.

Ключевые слова: глюкоза, серотонин, крысы, сахарный диабет 2 типа.