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GABA-ERGIC SYSTEM IN THE EXPERIMENTAL DIABETES

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γ-Aminobutyric acid (GABA) is a non-proteinogenic amino acid, neurotransmitter and concurrently trophic factor in the non-neuronal peripheral tissues. GABA is involved in the pathophysiology of endocrine disorders, in particular, diabetes mellitus (DM). This review summarizes the effects of GABA-ergic system components on the development of experimental diabetes induced in laboratory animals. The beneficial effect of GABA-associated amino acids mixtures in the DM treatment is discussed.

K e y w o r d s: GABA, diabetes experimental models, GABA-ergic system, ethanolamine-O-sulfate, GABA-supporting complex.

Diabetes mellitus (DM) is the most common metabolic disorder in humans and is expected to become one of the major public health problems. DM is an endocrine disorder with the risk of such complications as blindness, renal failure, cardiac and peripheral vascular disease, neuropathy, foot ulcers and limb amputation. DM occurs due to an absolute or relative deficiency of insulin, resulting in hyperglycemia, a persistently elevated glucose level in the blood. Insulin is a peptide hormone, produced by the β-cells of the islets of Langerhans in the pancreas. It activates the synthesis of proteins and amino acids in the liver, stimulates the absorption of amino acids into cells, promotes protein and fatty acids synthesis, increases the uptake of potassium, magnesium, and phosphorus ions into cells, facilitates the conversion of glucose into free fatty acids and triglycerides in the liver [1]. The secretion of insulin and glucagon by the pancreas preserves glucose homeostasis; together with insulin secretion, it is sustained by hormones released after nutrition and regulated by amino acids produced during protein digestion [2]. Insufficient endocrine function of the pancreas can cause disruption of glucose homeostasis, leading to long-term hyperglycemia and diabetes mellitus.

DM is characterized by chronic hyperglycemia due to insulin deficiency in type 1 diabetes (T1DM) or insulin resistance in type 2 diabetes (T2DM). The loss of pancreatic β-cells in the case of T1DM can be caused by infection or autoimmunity. Obesity, a disorder of energy homeostasis, is mainly associated with risk for T2DM, among many other diseases. DM is characterized by disturbances in all types of metabolism and the functions of vital enzymes of the body [3, 4]. It leads to disturbances in carbohydrate, fat and protein metabolism, vascular damage (angiopathies), neuropathies and pathological changes in various organs and tissues [5]. Non-invasive brain imaging techniques, including computed tomography and magnetic resonance imaging, have shown a relationship between DM and cerebral atrophy and lacunar infarcts [6]. Cerebral edema, cerebral hemorrhage, or intracranial thrombosis has been observed in children with T1DM and diabetic ketoacidosis [7]. The white matter hyperintensities are detectable in patients with T2DM [8]. These observations suggest that diabetes has a strong effect on the function of the brain, and the influence on this system may positively improve the expectancy and quality of life for diabetic patients [9].

GABA in Brain and Alternative Pathway of GABA Synthesis

γ-Aminobutyric acid (GABA) is a non-proteinogenic amino acid, the main inhibitory neurotransmitter or neuromodulator in the central nervous system of humans and other mammals [10]. GABA also serves as a hormone or trophic factor in non-neuronal peripheral tissues: it is widely distributed

in the pituitary, pancreas, adrenal glands, uterus, ovaries, placenta and testis. GABA is involved in the pathophysiology of endocrine disorders such as DM, diseases of the adrenal glands and reproductive tracts [11]. Glutaminase (GLS, EC 3.5.1.2) and glutamate decarboxylase (GAD, EC 4.1.1.15) are the enzymes involved in the formation of GABA. GLS deaminates glutamine (Gln), transforming it into glutamate (Glu), a precursor of GABA. GAD catalyzes the removal of the α-carboxyl group from Glu to produce GABA by liberating CO_2 (Fig. 1, solid arrows). GAD, a pyridoxal-dependent enzyme, is considered to be a key enzyme in the production and conservation of GABA. In humans, GAD is expressed in the brain and β-cells of the pancreas as isoenzymes GAD65 and GAD67, respectively. GAD67 isoform is one of the strongest autoantigens in the human pancreas that triggers T-cell-mediated autoimmune T1DM [12]. GAD, involved in the synthesis of GABA, is an antigenic target for T cells during the pathophysiology of T1DM. Destruction of GAD results in reduction of β-cells GABA through the induction of inflammatory reactions and β-cell apoptosis. Therefore, vaccination to protect β-cells GAD is considered a promising immunotherapy approach in the prevention of T1DM [13].

The study showed that some new GABA-amides (the storage form of GABA) provide moderate activation of GABA-A receptor channels, making them promising molecular tools for the functional analysis of GABA-A receptors [14]. The presence of GABA-amide in the brain and its alternative generation from glutamine (Gln) may provide additional flexibility to the amino acid transmitter system. The metabolisms of GABA and GABA amide under normal conditions and after aluminum neuro-intoxication (an experimental model that mimics neurodegenerative syndrome specific for Alzheimer's disease) were examined [15]. Gln utilization and GABA formation in the brain mitochondria of aluminum-intoxicated rats were shown to be independent of activation or inhibition of phosphate-activated GLS. Intoxication increased both the Gln utilization and formation of GABA and its amide. ATP and ammonium sulphate intensified GABA utilization in mitochondria. These data support the hypothesis of an alternative pathway for GABA formation directly from Gln via GABA-amide.

An alternative pathway for the direct synthesis of GABA from Gln, bypassing the formation of excitotoxic Glu, has been proposed by R. G. Kamalyan [16]. In this way, Gln is decarboxylated by the enzyme GAD with the formation of GABA-amide, which is followed by spontaneous deamidation, resulting in GABA (Fig. 1).

GABA in the Pancreas

In addition to the nervous system, GABA is also synthesized in relatively high levels in the insulin-producing β-cells of the islets of Langerhans of the pancreas. GABA promotes survival of β-cells and conversion of α-cells to β-cells [17-19]. Moreo-

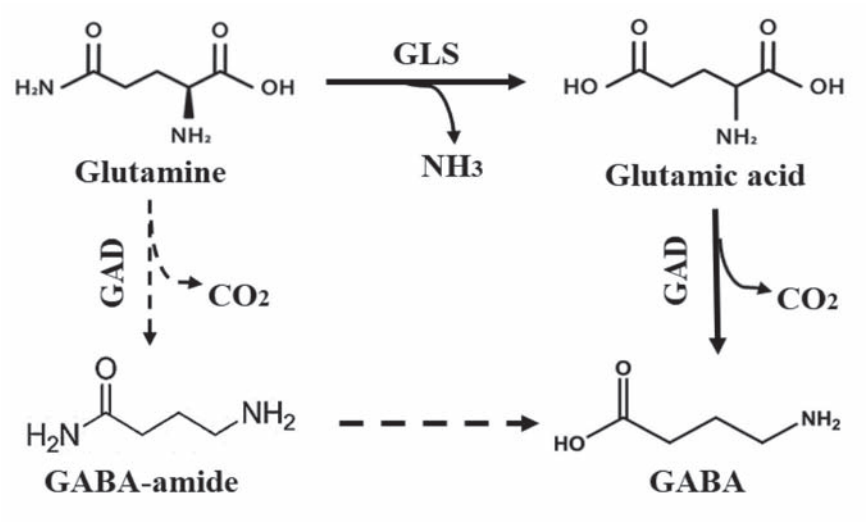

Fig. 1. Pathways for GABA synthesis from Gln: solid arrows represent the known classical pathway, dotted arrows represent the alternative pathway proposed by Professor R. G. Kamalyan. (GLS – glutaminase, GAD – glutamate decarboxylase)

ver, GABA inhibits immune activation and attenuates inflammation in DM that results in the regulation of glucose homeostasis and the reduction of diabetic complications [20]. Therefore, GABA is considered one of the approaches in the treatment of DM [21]. It should be noted that, according to the data available in the literature, GABA and baclofen (a GABA-like compound that stimulates GABA-B receptors) suppress insulin secretion by β-cells while maintaining pancreatic microcirculation [22]. The authors attributed this effect to the activation of the GABA receptors.

The levels of neuro-active amino acids Asp, Glu, GABA, and their precursor Gln were estimated in the rat pancreas. The addition of phosphate (NaH_2PO_4 or ATP) to the mitochondrial fraction from rat pancreas containing Gln stimulated the breakdown of Gln, accompanied by the increase of the Glu, Asp and ammonia levels. The addition of Glu suppressed the utilization of Gln and increased the content of Asp, GABA and ammonia. These data proved the presence of phosphate-activated GLS in mitochondria of rat pancreas [23]. The results of incubation of pancreas homogenate with the addition of Asn, a-ketoglutarate, or ATP confirmed the similarity of metabolism of the neuro-active amino acids in the pancreas to the one described in the brain [24].

Experimental Models of Diabetes Mellitus

In experimental studies of DM, the diabetogenic chemicals, such as streptozotocin (STZ), alloxan, etc, damage β-cells in laboratory animals, leading to the development of DM models. The chemicals accumulate in β-cells via GLUT2 transporters as glucose analogs and exert cytotoxic effects, causing diabetes by inducing β-cell death. The harmfulness of alloxan lies in the generation of superoxide anions in both β-cells and the extracellular environment. STZ, absorbed by β-cells, is broken down to glucose and methyl nitro-urea and exhibits a cytotoxic effect on β-cells, causing modification of biological macromolecules, fragmentation of DNA, etc. [25-27].

In experimental models of DM, induced by alloxan and STZ in laboratory animals, hyperglycemia developed with blood glucose levels of 25 versus 6.5 mmol/l, and 24 versus 7 mmol/l, respectively. In the alloxan model, the contents of neuroactive amino acids Gln, Glu and Asp in the pancreas increased compared to those in the pancreas of native rats by 35.5%, 31% and 16.5%, respectively. In these experiments, GABA content did not change significantly (1.6 versus 1.9 μmol/g of tissue). Probably, alloxan suppressed the oxidation of excitatory amino acids in the pancreas and did not affect GABA utilization. Since alloxan does not cross the blood-brain barrier, no changes were detected in the levels of the amino acids studied in the brain for this diabetes model. The shifts in the contents of the amino acids in the pancreas, registered in the STZ model, were opposite to those in the alloxan model: the contents of Gln, Glu, Asp and GABA dropped by 55, 58, 11 and 69%, respectively. Decreases in the levels of these compounds were recorded in the brain as well: by 49, 22, 36 and 56%, respectively. These results confirmed different mechanisms underlying the development of experimental DM models induced by two diabetogenic chemicals [28].

Effect of Ethanolamine-O-sulfate on Alloxan- and Streptozotocin-induced Diabetes Mellitus

Ethanolamine-O-sulfate (EOS) is an inhibitor of GABA transaminase (GABA-T), the enzyme responsible for the breakdown of GABA, a key inhibitory neurotransmitter in the brain. EOS increases GABA level by inhibiting GABA transaminase (GABA-T), preventing GABA metabolism and causing multiple effects on neuronal activity. The ability of EOS to elevate GABA level and modulate GABA receptor density [29] suggests potential therapeutic applications, especially in conditions of deficiency of GABA-ergic activity, as in epilepsy and some neuronal degeneration [30]. EOS has been investigated for its potential role in managing T2DM, particularly through its effects on the level of hepatic GABA. The study revealed that glucose homeostasis in obese mice can be improved by inhibiting GABA-T activity with EOS. EOS treatment led to a decrease in serum insulin and glucose concentrations, as well as to an increase in insulin sensitivity and reduced body weight [31].

Alloxan induced an increase in blood glucose level in rats up to 25 mmol/l vs 7 mmol/l in control. This hyperglycemia was accompanied by an ncrease in the levels of both Gln (1.8-fold) and Glu (1.5-fold) in the pancreas, without significantly affecting the amount of GABA. A 3-day preliminary administration of EOS to rats prevented the hyperglycemic effect of alloxan administered intravenously on the 4th day. Besides, in the EOS-received animals, the increase of Gln and Glu levels in the pancreas was prevented, but the GABA levels in both of these tissues

doubled, due to inhibition of GABA-T by EOS. Obviously, the increase in the GABA level in the pancreas protected against alloxan-induced destruction of β-cells, affirming the important role of GABA in diabetes protection [32].

The DM induction in rats by intraperitoneal injection of STZ significantly decreased the levels of neuroactive amino acids in the brain and pancreas. In the mitochondria from the brain and pancreas of STZ-diabetes rats, the utilization of Glu and GABA was inhibited. That may be a cause of impeding in the endocrine function of the pancreas [33]. Oxaloacetic acid and ATP relieved the observed inhibition of Glu utilization in the studied preparations, due to mitochondrial GLS activation [34]. The administration to rats with montmorillonite (a food additive), β-Ala (an amino acid) and EOS (an inhibitor of GABA-T) prevented the hyperglycemic effect of STZ and hindered the inhibition of Glu utilization in the homogenates of brain and pancreas, proving the mitigation of diabetes induced by STZ [35].

Effect of [Gln+EOS] on Experimental Diabetes

Glutamine (Gln), one of the neuroactive amino acids, is the most abundant naturally occurring, non-essential amino acid in the human body. Gln is a very important source of energy in the human immune system. It plays a key role in the restoration of damaged tissues. Gln is quantitatively predominant in both the brain and peripheral organs. Gln serves as a key source of amides and is involved in the transport, supply and removal of amino groups to/from amino acids. Gln is transported across biological membranes by specific transporters, including those in the SLC38 family. These transporters facilitate the movement of Gln into and out of cells, contributing to its role in various physiological processes. Gln plays a significant role in various metabolic processes, including those related to diabetes mellitus [36]. Research indicated that glutamine supplementation may influence glycemic control and insulin sensitivity in individuals with diabetes. A systematic review [37] examined 19 studies involving 1,482 participants and found that Gln supplementation improved glycemic control in DM. Specifically, nine studies reported a significant increase in serum GLP-1 levels, an incretin hormone that enhances insulin secretion. Additionally, eight studies observed reductions in fasting blood sugar levels, and four noted decreases in postprandial blood sugar and triglyceride levels after Gln supplementation. However, the findings on glycated hemoglobin (HbA1c) levels were inconclusive, and more precise clinical trials are needed to obtain more convincing results. Although Gln supplements show promising results, they should be used with caution. A pilot study published in Diabetes Care [38] found that Gln increased the cumulative probability of post-exercise overnight hypoglycemia in adolescents with T1DM. This suggests that Gln supplementation may affect blood glucose levels during and after exercise, potentially leading to hypoglycemia.

The study of the separate and combined action of Gln and EOS on the levels of Gln family amino acids (Asp, GABA, Gln, Glu) in the brain, liver and pancreas of native rats demonstrated an effective GABA-enhancing in these tissues, more pronounced in the case of the combined [Gln+EOS] action. STZ-induced hyperglycemia (24 mmol/l compared to the normal level of 7 mmol/l) was accompanied by a decrease of Glu and GABA levels by 1.3 and 2.6-fold, respectively, in the rat brain. In the pancreas, the levels of Gln, Glu and GABA decreased by 1.5, 2 and 1.4-fold, respectively.

The 3-5-day intra-peritoneal pre-injection of combined [Gln+EOS], followed by STZ-diabetes induction, resulted in a decreased level of glucose compared with the STZ-control diabetic animals (17 against 24 mmol/l). Simultaneously, in the STZ-diabetic animals pre-treated with [Gln+EOS], the levels of amino acids were protected in the brain, liver and pancreas [39]. Interestingly, the level of ethanolamine (EA), which was suggested as a carrier and transporter of glucose via biological membranes [40], was increased toward that in the control STZ-diabetic animals.

In two series of cultures of β-cells from native and STZ-treated animals, insulin-producing cells were labeled with an insulin-specific fluorescent dye, FITC [41]. The individual compounds (EOS, GABA, Gln and Glu) were added to both of these series. Comparison of the resulting images revealed a sharp bleached FITC fluorescence in the culture of β-cells from STZ-treated animals, as compared to the culture from native animals (Fig. 2, control and STZ). This phenomenon reflected the decrease in the number of insulin-producing cells by STZ treatment. The additions boosted the levels of insulin-producing β-cells in cultures from both native and STZ-treated animals by EOS, GABA, Gln and Glu (Fig. 2), confirming their antidiabetic ac-

tivity. Hence, the levels of antidiabetic GABA and its precursor Gln are maintained in the STZ-induced pancreatic β-cell damaging conditions, if animals have been pre-injected with [Gln+EOS]. Therefore, it was suggested that the combined [Gln+EOS] supported glucose utilization, as well as insulin synthesis and secretion. These results can be considered as evidence for the possibility of GABA synthesis via GABA-amide by direct decarboxylation of glutamine, bypassing the formation of neurotoxic Glu [15].

Effect of GABA Supporting Complex on Experimental Diabetes

Then, Professor R. G. Kamalyan proposed and successfully tested a "GABA-supporting complex" (GSC), consisting of GABA, β-Ala, Gln and EOS, all the components, which promote GABA level in the body. The research has shown that this GABA-supporting complex had a therapeutic effect on the function of the pancreas. A five-day intraperitoneal injection of GSC followed by alloxan prevented the high blood glucose levels observed in animals receiving alloxan alone. The complex also normalized the alloxan-caused shifts of the levels of Gln family neuroactive amino acids (Asp, Gln, Glu, GABA) in the brain and pancreas of rats. The studied GSC may be recommended for a clinical trial in the DM cases [42].

Then the same GSC showed a well-pronounced thrombolytic activity in healthy animals: its intravenous injection in doses of 5-10 mg/100 g increased blood fibrinolytic activity by ~36%. The alloxan-induced DM resulted in a 7% increase in fibrinolysis time, compared to healthy animals. Daily injection of GSC for five days into rats with alloxan-induced DM resulted in a decrease of blood glucose level to norm. Concurrently, positive changes in the hemostasis system were observed: on the fifth day after GSC injection to the alloxan diabetic rats, the recalcification period was extended by 35%, the prothrombin time decreased by 20%, the thrombin time decreased by 42%, and the concentration of fibrinogen decreased by 15%, as compared to non-injected animals. Consequently, it can be concluded that the GSC, in addition to neutralizing the hyperglycemic effect of alloxan, possesses an anti-coagulant activity and can be recommended for regulation of the blood clotting system [43]. Moreover, the study of the effect of GSC on the hemostasis system in normal blood plasma has shown that GSC has anticoagulant features and can find its application in the alternative treatment of diseases caused by a lack of anticoagulants [44]. The beneficial effects of GSC on the blood hemostasis were registered in the experiments with cadmium intoxication of rats. The morphological study revealed that chronic cadmium intoxica-

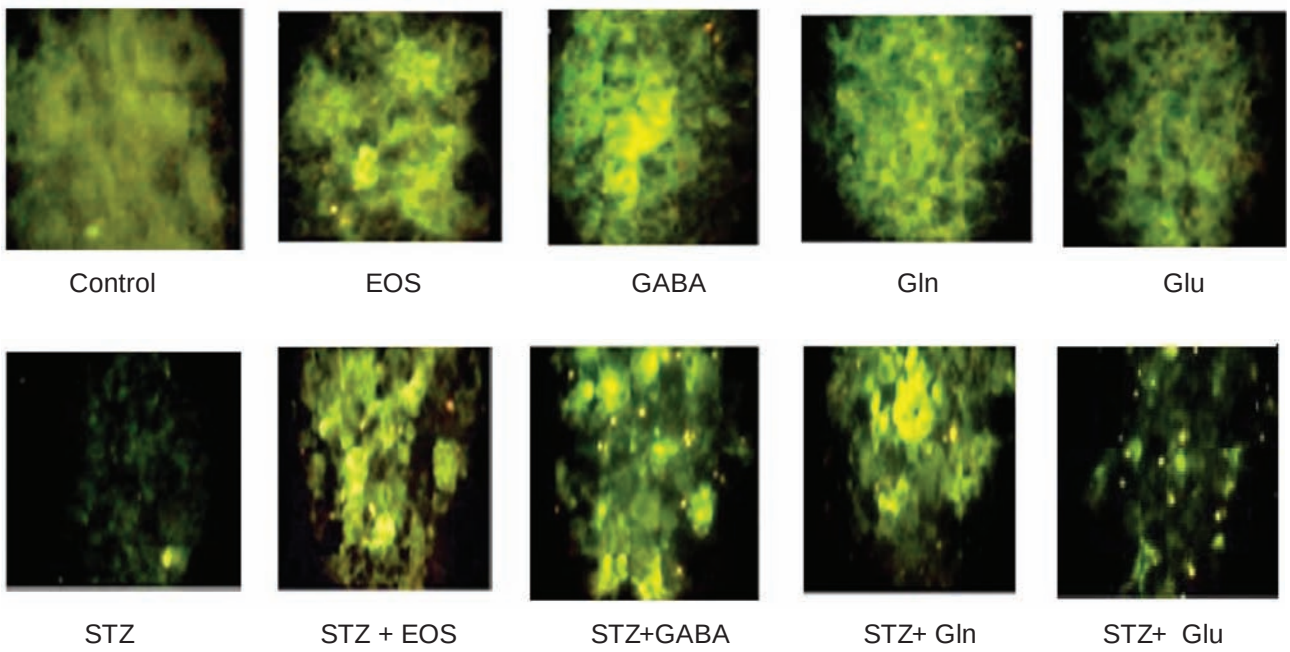

Fig. 2. FITC fluorescence images of insulin production in cultures of β-cells from native (upper line) and STZ-treated (bottom line) animals [41]

tion altered several blood coagulation parameters, suggesting a predisposition to hypercoagulation: the morphology of red blood cells and leukocytes was transformed, clustered or grouped platelets appeared. Conversely, the administration of GSC to cadmium-poisoned rats normalized the erythrocytes and neutrophils morphological characteristics. These results confirmed the anticoagulant activity of GSC, evidencing that it may be used for the treatment of various thrombotic conditions [45].

GABA-Supporting Mixture restores GABA Synthesizing Enzymes

Asparagine (Asn), a non-essential amino acid, is important in various metabolic processes, including those related to DM. The study of the relationship between amino acids and insulin sensitivity indicated the importance of epy Asn level in insulin sensitivity and the risk of T2DM developing. Asn was found to be associated with improved insulin sensitivity, suggesting a potential beneficial role in glucose metabolism [46]. In the homogenate and mitochondrial fraction of rat brain, the metabolic pathways of Asn resulted in the generation of GABA, Glu and ammonia, evidenced involvement in the intracellular exchange of dicarboxylic amino acids, their amides and GABA in the brain, as well as in the inter-conversions underlying their neurotransmitter, energy and plastic functions [47]. It was shown that Asn can serve as a precursor for Gln and, consequently, for GABA, in both the brain and the pancreas. α-Ketoglutarate in brain homogenates accelerated the production Gln and aspartate upon incubation with Asn [24]. The research [48] proposed the ammonia donation by Asn for Gln synthesis, suggesting a bidirectional relationship between these amino acids. Further studies have explored the ratio of Asn to aspartate (Asp) and its association with T2DM risk: it was found that a high Asn-to-Asp ratio was linked to the increased risk of T2DM developing, with the effect being more pronounced in women and individuals over 50 years of age [49].

The composition of the previous GABA-supporting complex (GSC) was modified, attempting to reveal the enzymatic mechanisms of the investigated antidiabetic effects of the GSC. This new GABA-supporting mixture (GSM), consisting of Asn, Gln, EOS and β-Ala, was studied using an experimental model of STZ-induced DM in rats [50]. The relative analysis of the activities of the GLS and GAD enzymes was expected to expand understanding of DM pathogenesis.

The glucose levels in animals of control, STZ-diabetic, and GSM-treated groups were 5, 23, and 13 mmol/l, respectively. The GAD activity, increased in the brain, pancreas and liver of the STZ-diabetic animals with reliability of $P = 0.0001$, 0.002 and 0.003 compared to the controls, was restored to values close of the control: $P = 0.56$, 0.58 and 0.49, respectively.

In STZ diabetes, the GLS activity also increased significantly in blood plasma ($P = 0.0001$) and the pancreas ($P = 0.04$), but decreased in the brain ($P = 0.04$). GSM normalized the GLS activity, making it closer to the values in tissues from control animals with reliability of $P = 0.04$, 0.16 and 0.72, respectively.

Contrary to these tissues in the liver, the activity of GLS increased under the influence of STZ insignificantly ($P = 0.72$), but the GSM increased it to a greater extent ($P = 0.009$ compared to the control). This phenomenon can be seen as maintaining GABA levels by increasing the biosynthesis precursor of GABA, glutamate.

Summarizing, the study [50] revealed the ability of GSM, along with a pronounced hypoglycemic effect, to normalize the activity of the enzymes GLS and GAD, which were significantly compromised in animals with STZ diabetes. Considering that increased GABA level is beneficial in the struggle against DM, one can hypothesize that the new GABA-supporting mixture (GSM), which is capable of protecting enzymes involved in GABA synthesis, might serve as an additional approach in the treatment of DM. Further studies are needed with longer-term monitoring and possibly varying the ratios of the mixture components.

Conclusion. This paper presents the *in vivo* effects of compounds associated with the prevention of GABA metabolism or its synthesis in experimental models of diabetes in laboratory animals. Conventional models induced by chemical diabetogens, alloxan and STZ, were used to stimulate the DM development in laboratory animals. The investigations conducted over several years demonstrated that both the separate and combined administration of the used compounds were beneficial for mitigating chemically induced DM development.

Separately injected EOS, an inhibitor of GABA-metabolizing enzyme, GABA transaminase, and Gln, a main precursor of GABA, other neuroactive amino acids, resulted in normalization of blood glucose level and of essential amino acids concen-

trations in the brain, pancreas and liver of animals, changed due to DM induction. The study has shown more efficient action of EOS and Gln in the case of their combined [EOS+Gln] application.

Then, Prof. R. G. Kamalyan and colleagues demonstrated the successful action of a "GABA-supporting complex" (GSC), consisting of GABA, β-Ala, Gln and EOS, against the development of alloxan- and STZ-induced DM. Moreover, it was shown that GSC, in addition to neutralizing the hyperglycemic effects of STZ and alloxan, possessed anticoagulant activity, with beneficial effects on blood hemostasis disturbed by DM development and by cadmium intoxication in rats.

Afterwards, a modified GABA-supporting mixture (GSM) consisting of Asn, Gln, EOS and β-Ala was studied, using an experimental model of STZ-induced DM in rats. In the study of GSM, main attention was paid to the relative analysis of the activities of GLS and GAD enzymes involved in GABA synthesis, aiming to expand understanding of the pathogenesis of diabetes and to offer new alternative approaches to DM treatment. Application of GSM restored the activities of GLS and GAD, which were reduced in animals with STZ-caused diabetes, closer to normal values. Probably, the alternative pathway proposed by Prof. Kamalyan also works in the case of the GSM, when Gln is synthesized from Asn, a new component followed by GABA-amide formation from Gln, resulting in the synthesis of GABA. Besides, the injection of a mixture containing the GABA transaminase inhibitor EOS, together with the GABA homolog Ala, presumably increases the concentration of GABA in rat tissues, decreasing glucose levels in the blood.

Given that increased GABA levels are known to be beneficial in diabetes treatment, one can hypothesize that the studied GABA-supporting compounds, individually and in various mixtures, may serve as approaches to struggling against DM.

Further studies are needed with longer-term monitoring and possibly varying the ratios of the mixture components.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ГАМК-ЕРГІЧНА СИСТЕМА ПРИ ЕКСПЕРИМЕНТАЛЬНОМУ ДІАБЕТІ

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γ-Аміномасляна кислота (ГАМК) – це непротеїногенна амінокислота, нейромедіатор та одночасно трофічний фактор у ненейрональних периферичних тканинах. ГАМК бере участь у патофізіології ендокринних розладів, зокрема, цукрового діабету (ЦД). У цьому огляді підсумовано вплив компонентів ГАМК-ергічної системи на розвиток експериментального діабету, індукованого у лабораторних тварин. Обговорюється корисний вплив сумішей ГАМК-асоційованих амінокислот у лікуванні ЦД.

Ключові слова: ГАМК, експериментальні моделі діабету, ГАМК-ергічна система, етаноламін-О-сульфат, ГАМК-підтримуючий комплекс.

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