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EC PHARMACOLOGY AND TOXICOLOGY
Review Article

Can Gamma-Aminobutyric Acid (GABA) Change the Paradigm in Diabetes Treatment?

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Received: December 18, 2024; **Published:** January 08, 2025

Abstract

Recently, experimental studies related to the role of GABA in the development of diabetes and related angio- and neuropathies have attracted great interest. Gamma-aminobutyric acid (GABA) has long been known as an inhibitory neurotransmitter in the central nervous system. At the same time, GABA has been found in many peripheral organs and, which is especially important in the context of our study, in the pancreas. Moreover, its concentration in the pancreas is the highest among other organs and is comparable to that in the central nervous system.

Healthy beta cells have been shown to continually produce and release GABA throughout their life cycle. Once released, GABA influences the activity of many types of islet cells through its ionotropic and metabotropic receptors. GABA has the ability to stimulate pancreatic beta cell function and prevent the development of diabetes. GABA stimulates beta cell division and function. GABA is able to activate Ca^{2+} - P13K/Akt dependent cell growth and survival, thereby preventing apoptosis in streptozotocin-treated islet cell lines. GABA stimulates the synthesis and release of insulin by beta cells and reduces the production of glucagon by alpha cells. *In vitro* experiments have shown that blockade of GABA receptors in isolated human islets of Langerhans leads to a decrease in the synthesis and release of insulin.

Moreover, GABA is able to protect beta cells from the aggressive action of the immune system by interacting with GABA receptors of immune cells. This leads to a decrease in the activity of lymphocytes, stopping the production of antibodies to beta cells and cytokines that initiate and enhance the immune attack. In addition, GABA regulates the release of proinflammatory cytokines in T and B cells and mononuclear cells in the peripheral blood.

In conclusion: In the endocrine part of the pancreas, GABA takes an active part in paracrine regulation, i.e. it plays the role of a tissue hormone that acts on beta cells that produce insulin and alpha cells that produce glucagon. In the first case, GABA activates cells, and in the second, it inhibits their function. Animal experiments have shown that GABA is capable of delaying the onset of diabetes and even restoring normal blood glucose levels when the disease has already begun to develop.

Keywords: *Gamma-Aminobutyric Acid (GABA); Central Nervous System; Diabetes Treatment*

Introduction

Unfortunately, in recent years, the incidence of both types of diabetes (DM1 and DM2) has become a pandemic, and its rates directly correlate with mortality rates. In Ukraine, in particular, more than 1.3 million people may suffer from diabetes, but according to statistics, 65% of patients with diabetes are unaware of their diagnosis. The situation is aggravated by wartime conditions, when the population is exposed to long-term adverse psychoemotional factors, which are also the etiological factor in the development of diabetes, and an increase in the number of such factors will inevitably lead to an increase in morbidity, disability and mortality rates from diabetes and its complications.

The study of the etiopathogenesis of diabetes and methods of its treatment may become a priority not only for Ukraine, but also for many other countries. Thus, in 2021, the National Institute of Health (USA) spent $ 1.1 billion on diabetes research. However, despite all the efforts in this direction, the success cannot be considered significant. In treatment, as before, symptomatic therapy remains preferable.

The so-called breakthrough drugs, semaglutide, exenatide, dulaglutide and other representatives of the class of glucagon-like peptide-1 antagonists, which unexpectedly change the treatment strategy for type 2 diabetes and cardiovascular failure, nevertheless also belong to pathogenetic-symptomatic agents [6]. Despite their impressive effectiveness in treating type 2 diabetes, these drugs nevertheless have serious side effects and do not solve the problem of type 1 diabetes.

In our opinion, the fundamental cause of diabetes as such lies in the area of disruption of physiological regulation of the activity of the direct producer of insulin - beta cells. In the case of type 1 diabetes, this is the generally recognized autoimmune damage to beta cells and a decrease in their mass. In the case of type 2 diabetes, this is their insufficiency and a decrease in their relative (and possibly absolute) mass due to other mechanisms that are still not fully known to us.

There is an urgent need to conduct research aimed at identifying fundamentally new cellular and molecular mechanisms of diabetes development and its treatment. This will make it possible to change some outdated paradigms and involves the development of fundamentally new concepts of etiopathogenesis and, most importantly, new methods of treating diabetes.

It is becoming clear that insufficient ß-cell mass is the root cause of the development of all major types of diabetes. When blood glucose levels rise in the body, ß-cells respond by producing more insulin. However, hyperglycemia, in turn, reduces the ability of ß-cells to produce and secrete insulin. A positive feedback loop or, as they say, a “vicious circle” arises - constantly increasing glucose levels and constantly decreasing ß-cell function. Ultimately, this leads to a fatal result, the death of ß-cells.

So, the diabetes pandemic continues, its consequences for human health remain extremely unfavorable, and current treatment methods still leave much to be desired. Only one thing is clear so far. Since the disease occurs due to dysfunction of pancreatic β-cells or their death, a real cure requires protecting the cells from damaging factors and restoring their normal functioning. Regeneration of β-cells directly in the pancreas is very tempting. Unfortunately, transferring experimental methods to the clinic is still a difficult problem [2].

Nevertheless, β-cell regeneration should still be the main therapeutic goal of diabetes treatment. Of course, solving this problem is not easy. First, it is due to the multicomponent nature and complexity of the system regulating the function of beta cells.

For example, a complex of genetic, epigenetic and other mechanisms and signaling pathways causes T2DM. The problem is complicated by the fact that they serve both as causes and consequences of the occurrence of T2DM and perform their function in close interaction [3].

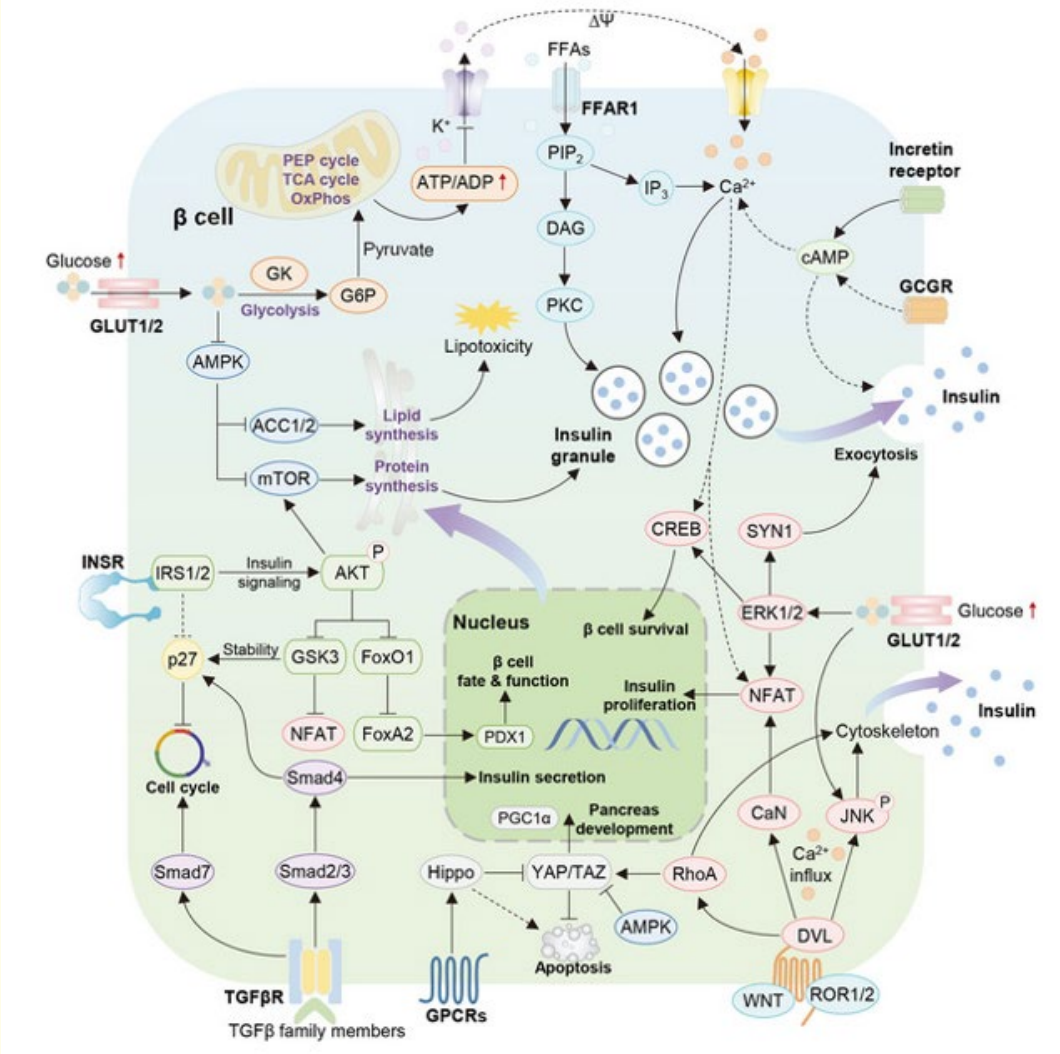

Figure 1: *The signal of elevated glucose level enters the β-cell via GLUT1/2 transporters. Its purpose is to produce ATP via glycolysis in the cytoplasm and oxidative metabolism in the mitochondria. This results in an increase in the ATP to ADP ratio. Further, the increased level of cytoplasmic ATP leads to the closure of ATP-sensitive potassium channels, depolarization of the cell membrane and subsequent entry of Ca2+. This leads to the release of insulin. Several other signaling systems are involved in the regulation of β-cell function and insulin secretion - AMPK, MAPK, WNT, PI3K/AKT, TGFβ, YAP/TAZ, etc. (Adapted from Cao, Tian, Zhang., et al. 2020 [3]).*

The well-known role of the GABA in the regulation of vital functions

In recent years, there has been increasing interest in studies related to the role of gamma-aminobutyric acid (GABA) in the development of diabetes and related angio- and neuropathies. Neurophysiologists have long known GABA as an inhibitory neurotransmitter in the central nervous system. Interestingly, in the developing embryonic brain, GABA, on the contrary, promotes and supports the development of neurons. Such is the ingenuity of our nature!

GABA is an organic substance that is necessary for the body to regulate various metabolic processes. It is often called a non-protein acid, since it does not participate in protein synthesis. GABA is synthesized in the process of decarboxylation of glutamate using the enzyme L-glutamic acid decarboxylase (GAD) and pyridoxal phosphate as a cofactor. This process was previously thought to occur mainly in neurons of the brain. This non-protein amino acid was first reproduced in the laboratory in 1963. Later, studies on animals and pancreatic islet cells showed that GABA and GAD are found in high concentrations in the pancreatic islets, which are the autoimmune target of type 1 diabetes.

After establishing the fact of GABA participation in the development of diabetes, the conclusion about the possibility of using it as a therapeutic agent for the treatment of diabetes became obvious. However, there were doubts whether we would encounter the same difficulties as when trying to use GABA to treat brain diseases? Would exogenously administered GABA freely pass through tissue barriers and exert its effect? How would it interact with target cells?

GABA realizes its properties by binding to specific receptors on the plasma membrane of both presynaptic and postsynaptic neurons and other cells. Generally accepted that GABA receptors are divided into two main classes depending on whether they have an ion channel, i.e. they are ionotropic (GABAA and GABAB receptors), or do not have one, i.e. they are metabotropic and use secondary messenger complexes to transmit the signal. It is known that opening of the GABA receptor ion channel in the CNS leads to the entry of chloride ions into the mature neuron, a decrease in the magnitude of its membrane potential (hyperpolarization), and the suppression of electrical activity. Activation of the GABA receptor reduces conductivity for Ca^{2+} and inhibits cAMP production through intracellular mechanisms mediated by G proteins.

It is true that GABA is the predominant inhibitory neurotransmitter in the central nervous system (CNS). However, there is another truth and other mechanisms of action of GABA. GABA is also present in other peripheral organs, such as, for example, the gastrointestinal tract, the uterus and, what is especially important in the context of our study, the pancreas, where its concentration is the highest among other organs and comparable to that in the CNS [12].

Unexpected role of GABA in the pathogenesis of diabetes and not only

Thus, it is now well known that GABA is not only found in the medulla. GABA molecules and GABA receptors are also present in the vascular endothelium, smooth muscles, respiratory epithelium, and insulin-producing beta cells of the islets of Langerhans in the pancreas. Islet cells are known to be clusters of endocrine cells in the pancreas, mainly in its caudal part. 60 - 80% of the islets are beta cells that secrete insulin, and 15 - 20% are alpha cells that secrete its antagonist hormone, glucagon. Interestingly, it is in the islets of Langerhans, where the β cells are located, that high concentrations of GABA and glutamate decarboxylase (GAD 65) have been found. Many years have passed and interest in GABA has increased after it was established that GAB 65 is one of the main autoantigens in type 1 diabetes, and its high titer is a reliable indicator of beta cell death [9].

Today, almost all leading medical laboratories in the world conduct large-scale and multidirectional studies of GABA. This oxygen is no longer considered only as the main inhibitory mediator of the central nervous system. Now it is officially recognized as an effective cytoprotective antihypoxant and antioxidant for various organs and systems, possessing pronounced antitumor and anti-inflammatory properties.

Gamma-aminobutyric acid is still used in neuropharmacology as a drug with a pronounced antidepressant effect. It causes a pronounced inhibition (relaxation) in the central nervous system in stressful situations, effectively reduces anxiety, helps with insomnia, increases the total time of the slow phase of sleep, restores long-term memory impairment, improves cognitive functions in elderly and middle-aged people, and helps prevent the occurrence of diabetic encephalopathy [1]. Interestingly, GABA also effectively reduces high blood pressure in states of hypertension of the first degree of severity, i.e. it has a pronounced vasodilating effect [20].

However, times have changed. Even in the first studies devoted to GABA metabolism in the pancreas, it was described that healthy beta cells constantly produce GABA. Once released, GABA influences the activity of all types of islet cells (but in different ways) through ionotropic and metabotropic GABA receptors [22].

GABA may support pancreatic beta cell function and thus prevent the development of diabetes in several ways. GABA stimulates beta cell division and normal function. It prevents streptozotocin-induced apoptosis of islet cells treated *in vivo* with streptozotocin and stimulates beta cell replication. Overall, GABA plays a critical role in islet β cell survival and regeneration via the PI3K/AKT/mTOR signaling pathway, which is an intracellular signaling pathway whose central components are the enzymes phosphoinositide 3-kinase, AKT kinase, and mTOR.

In addition to stimulating the synthesis and release of insulin by beta cells, GABA reduces the production of glucagon by alpha cells. *In vitro* experiments have shown that when GABA receptors are blocked, isolated human islets of Langerhans reduce insulin secretion. It may be recalled that in type 1 diabetes, the balance between these two pancreatic hormones, insulin and glucagon, is disrupted. In healthy people, insulin promotes the selection of glucose from blood plasma by tissue cells when glucose levels are high. Conversely, glucagon, with the help of the liver, adds glucose to the bloodstream when glucose levels there become low. That is, in type 1 diabetes, when autoantibodies destroy beta cells of the pancreas, insulin secretion decreases and glucagon secretion becomes excessive. Studies in diabetic animals have shown that inhibition of glucagon secretion by GABA increases the number of insulin-secreting beta cells and normalizes glycemic levels. Finally, GABA protects beta cells from the aggressive action of the immune system by interacting with GABA receptors on immune cells. It reduces lymphocyte activity, stops the production of antibodies to beta cells, and stops the activity of cytokines that initiate and enhance the immune attack. Importantly, the suppression of cytokine synthesis was more pronounced in immune cells obtained from patients with type 1 diabetes. GABA is thought to be released from cells in the body's effort to "calm" and "prepare" the cells for the next wave(s) of insulin secretion, and in the presence of absent or diminished GABA, there would be increased risk of dysfunction and/or inflammation associated with both type 1 and type 2 diabetes. Please note that in α-cells, GABA induces membrane hyperpolarization and suppresses glucagon secretion, whereas in islet β-cells it induces membrane depolarization and increases insulin secretion.

Clinical trials support this view. It has been shown that GABA can indeed exert an immunomodulatory effect and lead to possible beta cell regeneration. Thus, in clinical trials on adult men with long-standing T1DM, a controlled-release GABA formula was used in doses of 200, 600, and 1200 mg. It was shown that taking 600 mg of GABA more than doubled the response of glucagon, adrenaline, growth hormone, and cortisol to hypoglycemia. The data obtained suggest that GABA treatment is well tolerated and can correct the response to hypoglycemia in patients with T1DM [8].

Dastgerdi., *et al*. [5] investigated the role of GABA in attenuating liver insulin resistance (IR) in type 2 diabetes parents and reducing its risk in their descendants' liver. Both sexes' rats were divided into four groups of non-diabetic control, diabetic control (DC), GABA-treated (GABA), and insulin-treated (Ins). The study duration lasted for six months and the young animals followed for four months. Consequently, hyperinsulinemic-euglycemic clamp was performed for all animals. Apart from insulin tolerance test (ITT), serum and liver lipid profile were measured in all groups. Glycogen levels, expression of Foxo1, Irs2, Akt2, and Pepck genes in the liver were assessed for all groups.

It has already been mentioned above that the loss of functional pancreatic β-cell mass is a major factor in the development of hyperglycemia in both type 1 and type 2 diabetes. Importantly, recent studies conducted on xenotransplanted human islets of Langerhans show that GABA has a pronounced regenerative effect on β-cells. It also protects β-cells from cytokine-induced apoptosis and has anti-inflammatory and immunoregulatory activity [29]. Gamma aminobutyric acid is synthesized by glutamate decarboxylase (GAD) in β-cells. Regarding Type 1 diabetes (T1D), animal/islet-cell studies found that GABA promotes insulin secretion, inhibits α-cell glucagon and dampens immune inflammation, while GAD immunization may also preserve β-cells [19].

Of course, the role of GABA in diabetes pathology is not yet fully understood. GABA levels in the islets are indeed significantly reduced in T1D and T2D, but the reason for this reduction is not yet fully understood. It can be assumed that GABA is a negative immune regulator and the loss of GABA by the islets makes them more susceptible to immune damage. In the case when diabetes has already become clinically obvious, most beta cells have either already died or become functionally incapacitated. And then the lack of a GABA signal from beta cells leads to dysfunction of both alpha and delta cells. It should be remembered that the GAD65 enzyme is one of the main autoantigens of T1D, and it is expressed precisely in alpha and delta cells [18].

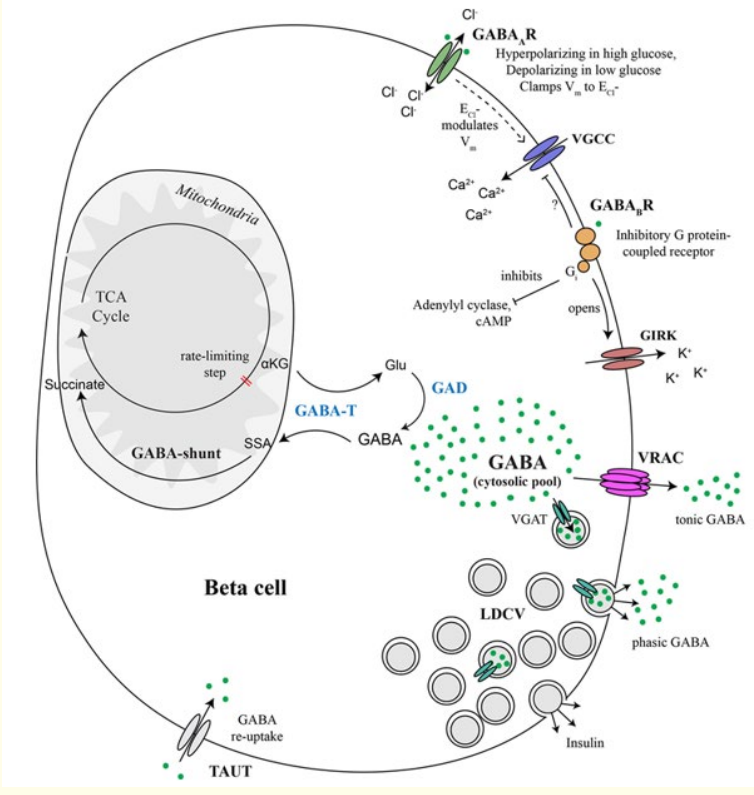

Figure 2: *Major components of the pancreatic beta-cell GABA system. GABA is synthesized in the cytosol from glutamic acid (Glu) by the enzyme glutamic acid decarboxylase (GAD), which has two isoforms, GAD65 and GAD67. GABA is transaminated with alpha-ketoglutarate (aKG) via GABA transaminase (GABA-T) to form glutamic acid (Glu) and succinate semialdehyde (SSA). SSA is in turn oxidized to succinate, which enters the tricarboxylic acid (TCA) cycle, thus coupling the GABA pool to beta-cell metabolism. GABA is secreted into the extracellular space via volume-regulated anion channels (VRACs). This non-vesicular form of GABA release is not regulated by glucose. GABA is also secreted from a subset of large dense nuclear vesicles (LDCVs) together with insulin. Vesicular packaging of GABA depends on the presence of the vesicular GABA transporter (VGAT), which is expressed only in a subset of beta cells. Following secretion, interstitial islet GABA binds to GABA A receptors (GABA ARs), which are Cl- channels. Chloride currents through open GABA Rs modulate the membrane potential (Vm) and thus control beta-cell excitability. The direction in which GABA Rs push Vm depends on whether Vm is currently above or below the equilibrium chloride potential (ECl-). Activation of GABA ARs can inhibit insulin secretion by clamping Vm toward ECl - or hyperpolarizing the membrane back toward ECl - when Vm is more electropositive in excited beta cells. GABA A R can promote beta-cell depolarization when glucose concentrations are low and V m is negative relative to ECl -. GABA also binds GABAB receptors (GABAB R), which are inhibitory G protein-coupled receptors (Gi) that stimulate the opening of G protein-coupled inwardly rectifying potassium channels (GIRKs) and inhibit adenylate cyclase. (Adapted from Hagan, Ferreira, Santos and Phelps, 2022 [14]).*

Let us try to ask ourselves this question: if GABA is formed by GAD65 and with the mediation of pyridoxal phosphate as a co-factor from glutamic acid, shouldn't exogenous administration of glutamic acid itself or together with GAD65 and GABA alleviate the course of diabetes mellitus? After all, back in 2007 [30] a significant increase in GABA levels was established with the introduction of its precursors.

The latest systematic review on the use of glutamic acid in diabetes mellitus [15] did not demonstrate a clear therapeutic effect. It should be remembered that this is exclusively about monotherapy. However, out of 19 studies, nine reported an increase in serum GLP-1 (glucagon-like peptide-1). In addition, eight studies showed a decrease in fasting serum blood sugar, four studies - a decrease in postprandial blood sugar and triglycerides after glutamine supplementation. Although glutamine led to a significant increase in insulin production in seven studies, the results for Hb-A1c levels were inconclusive.

We have not found any publications on the combined use of GABA and glutamic acid, and especially its combination with GAD65, which, given all the views analyzed and expressed in this publication, seems understandable. Our own research into the use of GABA in combination with its precursors, metabolites and cofactors is still far from complete, but preliminary results show promise in this area.

In summary, we conclude that GABA signaling is essential for brain function from the early CNS development, during normal development and aging, as well as in psychiatric and neurological disorders, and has been studied in the CNS for more than seven decades. In contrast, the concept of GABA as an integral component of human pancreatic islet function is much younger. However, the fact that GABA influences islet hormone secretion (both insulin and glucagon), stimulates β-cell regeneration, and possibly promotes α- to β-cell transdifferentiation clearly and unambiguously identifies GABA as a vital molecule in human pancreatic islets [13,31].

It is very important that GABA has demonstrated therapeutic effects not only in rodents but also in human pancreatic islets [16,26]. Several studies have already shown that oral administration of GABA is completely safe for humans [8,18] and activates GABA receptors only in peripheral tissues, since it does not penetrate the blood-brain barrier at the concentrations used. The combination of GABA with other compounds (e.g. benzodiazepines, anesthetics, GLP-1 receptor agonists, etc.) can enhance its ability to influence the cells of the islets of Langerhans.

A few more words about how GABA protects pancreatic islet cells from apoptosis and exerts its anti-inflammatory effect. GABA has been shown to inhibit NF-κB activation in both islet cells and lymphocytes, and NF-κB activation is known to be detrimental to beta cells and promotes apoptosis [21]. Since the above effects mimic the activity of sirtuin 1 (SIRT1) in beta cells, the question arises about its possible involvement in this process. SIRT1 is a NAD(+)-dependent deacetylase that enhances insulin secretion and counteracts inflammatory signals in beta cells. Incubation of a clonal rat beta cell line with GABA was found to increase SIRT1 expression, as did GABA receptor agonists. GABA also increased the enzymatic activity of SIRT1, which led to deacetylation of the p65 component of NF-κB. Finally, GABA increased insulin production and decreased apoptosis. SIRT1 inhibitors, in turn, reversed these effects. In experiments on isolated human islet cells, GABA increased both NAD(+) and SIRT1. It protected human islet cells from spontaneous apoptosis in culture, and this was abrogated by a SIRT1 inhibitor. Thus, these results suggest that the beneficial effects of GABA can be explained by increasing SIRT1 and NAD(+), which is a new avenue for diabetes therapy [21].

Possible competitor or partner GABA in the treatment of diabetes

Before moving on to the final part of the review, we consider it necessary, for the sake of scientific political correctness, to mention one more promising way to improve the function of pancreatic beta cells. Several new molecules have been identified to date that regulate beta cell regeneration by stimulating self-replication. It is known that glucose induces beta cell replication through glucokinase (GCK), the insulin receptor substrate 2 (IRS2) signaling pathway, and activation of the nuclear factor of activated T-cells (NFAT) protein pathway. One of the mediators of glucose-induced beta cell replication is the lipogenic glucose-sensitive transcription factor (TF) binding proteins of the carbohydrate response element ChREBP (alpha and beta).

Brief information: Carbohydrate response element-binding proteins ChREBP (alfa and beta) in humans are encoded by the MLXIPL gene. The name of the protein comes from the interaction of the protein with sequences of DNA elements responsible for the carbohydrate response. The ChREBP protein forms a heterodimeric complex; it binds and activates carbohydrate response element (ChoRE) motifs in the promoters of triglyceride synthesis genes in a glucose-dependent manner. ChREBP is activated by glucose independently of insulin. In adipose tissue, ChREBP induces *de novo* lipogenesis from glucose in response to glucose uptake into adipocytes. In the liver, induction of ChREBP by glucose promotes glycolysis and lipogenesis. ChREBP translocates to the nucleus and binds to DNA after dephosphorylation of the p-Ser and p-Thr residues by PP2A, which itself is activated by xylulose 5-phosphate (Xu5p). Xu5p is produced by the pentose phosphate pathway when glucose-6-phosphate levels are high (there is enough glucose in the cell). In the liver, ChREBP mediates the activation of several regulatory enzymes of glycolysis and lipogenesis, including L-type pyruvate kinase (L-PK), acetyl-CoA carboxylase, and fatty acid synthase.

It is well known that most transformed cells consume large amounts of glucose and produce ATP via aerobic glycolysis. In cells exhibiting aerobic glycolysis, a significant proportion of glucose is also diverted to *de novo* lipogenesis and nucleotide biosynthesis. The glucose-responsive element-binding protein, carbohydrate-responsive transcription factor (ChREBP), has previously been shown to be important for the redirection of glucose metabolism toward lipogenesis in non-proliferating hepatocytes. However, it may be suggested that it has a more general role in reprogramming metabolism during cell proliferation. It has been shown that ChREBP expression can be induced in response to mitogenic stimulation and that induction of ChREBP is required for efficient cell proliferation. ChREBP inhibition resulted in decreased aerobic glycolysis, *de novo* lipogenesis, and nucleotide biosynthesis, but stimulated mitochondrial respiration, suggesting a metabolic shift from aerobic glycolysis to oxidative phosphorylation. Cells in which ChREBP was inhibited by RNAi exhibited p53 activation and cell cycle arrest. *In vivo*, ChREBP inhibition resulted in a p53-dependent reduction in tumor growth. These results indicate that ChREBP plays a key role in both redirecting glucose metabolism to anabolic pathways and suppressing p53 activity [27].

A new discovery could be a game-changer for patients with type 2 diabetes. Researchers at the Diabetes, Obesity, and Metabolism Institute (DOMI) at the Icahn School of Medicine at Mount Sinai have discovered a therapeutic target for preserving and regenerating beta cells, the cells in the pancreas. This research was recently published in the journal *Nature Communications* [17]. They have discovered a molecular mechanism involved in preserving and regenerating beta cells, involving a protein called ChREBP. It turns out that the production of a hyperactive isoform of this protein, ChREBPβ, is necessary for the production of more beta cells in response to the body's increased need for insulin. The research team found that it was possible to counteract the effects of ChREBPβ and the β-cell death they observed by increasing expression of an alternate form of the protein, ChREBPα, or by activating nuclear factor-erythroid factor 2 (Nrf2) -- a protein that protects cells from oxidative damage -- in mice and human β cells, thus preserving β-cell mass.

"ChREBP has traditionally been thought of as a mediator of glucose toxicity, but they noticed that one isoform, ChREBPα, appears to be protective of beta cells," said Donald Scott, PhD, professor of medicine (endocrinology, diabetes, and bone disease) at Icahn Mount Sinai and a member of DOMI and the Mindich Institute for Child Health and Development. "We found that ChREBPβ plays a key role in the gradual destruction of beta cells. So, we think it's a marker of hyperglycemia and glucose toxicity".

Moreover, these researchers found that if they remove ChREBPβ or counteract its action pharmacologically, they can mitigate the effects of glucose toxicity and protect beta cells. This is an exciting discovery and opens the door to developing therapeutic agents that could effectively block ChREBPβ production and thus preserve beta cell mass. This will certainly have a significant impact on diabetes treatment outcomes and patient quality of life.

Not only will this solve an important problem that has driven diabetes research for many years, but it will also prevent the development of insulin dependence in patients with type 2 diabetes due to the loss of β-cell mass. This could have a significant impact on treatment outcomes and quality of life for patients with diabetes.

Moreover, mTOR activation *in vivo* and *in vitro* in human and mouse pancreatic islets is known to play an important role in β-cell survival in diabetes, and is mediated by the ChREBP-Mlx transcriptional complex, which suppresses TXNIP expression and β-cell death [4]. It is known that some amino acids, such as leucine and its metabolites, are able to significantly activate mTORC2. This means that they can probably be considered as potential cofactors of GABA activity in beta-cell reprogramming and regeneration, and not only on their own. Possible pathways of mTOR interaction with GABA and glutamine are well represented in metabolomics databases, for example https://www.ndexbio.org/viewer/networks/f21f1558-df12-11ea-99da-0ac135e8bacf.

In recent years, several research groups have been involved in studying the effects of mTORC and NFk-b on β-cell differentiation and regeneration and the possible role of ChREBPβ overproduction in patients with type 1 diabetes. More molecular mechanisms have been screened that could potentially block ChREBPβ production and thus prevent glucose toxicity and subsequent β-cell death. The possibility of a vicious cycle in which increased ChREBPβ expression in organs such as kidney, liver and adipose tissue could contribute to diabetic complications is also being explored.

The overactive isoform of the ChREBPβ protein plays a critical role in the β-cell response to hyperglycemic stress. It is involved in the adaptive response of β-cells to metabolic challenges associated with prolonged glucose exposure. However, chronic overexpression of ChREBPβ in β-cells can lead to loss of β-cell identity, apoptosis, decreased β-cell mass, and eventually diabetes. Deletion of ChREBPβ could prevent this β-cell "glucolipotoxicity". At the same time, overexpression of ChREBPα or activation of the Nrf2 antioxidant pathway could mitigate ChREBPβ-induced β-cell death [17]. Thus, it is clear that ChREBPβ, whether adaptive or maladaptive, is an important determinant of β-cell fate and a potential pharmacological target for β-cell population preservation strategies in diabetes.

A very important question is whether GABA can influence ChREBP activity. Unfortunately, there is no clear answer yet. In this regard, it would be more correct to formulate this question as follows: how does GABA influence ChREBP under different conditions? After all, back in 2006 it became known that GABA can differently influence the level of insulin secretion at different glucose concentrations [7]. In addition, given the autoimmune nature of type 1 diabetes, the role of glucose transporters as reprogrammers of immune cells into active producers of proinflammatory cytokines should be taken into account [10]. In addition, the work [24] demonstrated that ChREBP-dependent metabolic reprogramming of macrophages prevents the progression of atherosclerotic plaques and directly indicated the existence of a causal role of glucose metabolism in the development of atherosclerosis.

It is obvious that the regulatory role of GABA in this process can significantly attenuate these negative effects. Namely, GABA inhibits the production of interleukin (IL)-1β by inflammatory macrophages, enhances succinate-flavin adenine dinucleotide (FAD)-lysine-specific demethylase 1 (LSD1) signaling to regulate histone Bcl2l11 and Dusp2 demethylation, and reduces the formation of the NLRP3-ASC-Caspase-1 complex. All this taken together proves that GABA is able to regulate the pro-inflammatory responses of macrophages caused by metabolic reprogramming. This allows us to outline a strategy for the treatment of inflammatory diseases associated with macrophage activity, including diabetes mellitus [11].

In the work of [25], interesting data were obtained, based on which it can be hypothesized that mTORC2 in adipose tissue (mTOR complex 1 (mTORC1), consists of mTOR, Raptor, GβL and DEPTOR and is inhibited by rapamycin. This complex is a master growth regulator that perceives and integrates various signals associated with nutrition and environmental influences and transmits information

to the liver to implement the control of insulin sensitivity and glucose homeostasis. These data suggest that mTORC2 controls ChREBP activity by regulating glucose flux. Interestingly, however, this mTORC2 function appears to operate independently of AKT (a group of enzymes involved in processes related to cell growth and survival. Akt enzymes help transmit signals within cells (Akt enzymes are a type of serine/threonine protein kinase). They are also called protein kinase B. It is a canonical mTORC2 substrate. Apparently, after Rictor deletion, AKT signaling is reprogrammed to overcome its dependence on mTORC2 for some external influences. At the same time, for some other AKT substrates, the dependence on mTORC2 is virtually impossible to overcome. A theoretical possibility is that some AKT substrates require phosphorylation of an mTORC2-dependent hydrophobic motif (S473 in AKT1; S474 in AKT2). Another possibility is that AKT-independent mTORC2 pathways also control glucose flux.

The authors propose that the mechanism by which insulin stimulates glucose uptake is via AKT-dependent phosphorylation of AS160 (an Akt substrate), which facilitates GLUT4 translocation to the plasma membrane. The problem is that AS160 phosphorylation is normal in Rictor-deficient adipocytes. It remains to be seen whether adipose tissue mTORC2 regulates GLUT4 translocation *in vivo* via other mechanisms. One possibility is that mTORC2 controls glucose uptake via transcription of Glut4. This function of mTORC2 that is most important under high glucose load. In any case, these results suggest that selective activators of mTORC2 may be useful in the treatment of diabetes.

Conclusion

In conclusion GABA - gamma-aminobutyric acid, is not only the main inhibitory neurotransmitter. In the endocrine part of the pancreas, GABA is involved in paracrine regulation, i.e. it plays the role of a tissue hormone that acts on beta cells that produce insulin and alpha cells that produce glucagon. In various animal studies, GABA has been shown to delay the onset of diabetes and restore normal blood glucose levels after diabetes has already begun. GABA treatment also leads to a significant decrease in the expression of inflammatory cytokines that are involved in the pathogenesis of diabetes, and several serious clinical trials have already confirmed these experimental data.

It is already possible to state with full confidence that the GABA content in β-cells of patients with diabetes mellitus types 1 and 2 decreases, and this correlates with the severity of the disease. Genetic suppression of GABA receptors in the pancreas leads to a decrease in the mass of β-cells and insulin secretion, which confirms the importance of GABA in ensuring glucose homeostasis and the advisability of replenishing the GABA deficiency in diabetes mellitus by its additional administration. It has been established that in animals with diabetes mellitus, GABA suppresses apoptosis and stimulates the regeneration of β-cells, increases the mass of β-cells and insulin production. There is convincing experimental data on the positive synergistic effect of GABA (in combination with glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase type 4 (DPP-4) inhibitors and sodium-glucose cotransporter 2 (SGLT-2) inhibitors). A pronounced pancreatoprotective effect is observed. This occurs due to a decrease in oxidative and nitrosative stress, inflammation, an increase in the level of Klotho protein, Nrf-2 activity and antioxidant enzymes, as well as suppression of NF-kB activity and expression of proinflammatory cytokines. All this leads to a decrease in apoptosis and death of β-cells, an increase in β-cell mass, insulin production and a simultaneous decrease in the level of glucagon and insulin resistance. It is advisable to use GABA and drugs with a positive GABAergic effect in combination with new-generation antidiabetic agents: GLP-1 receptor agonists, DPP-4 inhibitors and SGLT-2 inhibitors to enhance their antidiabetic potential [28].

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