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Review

Gamma-aminobutyric acid in endocrine and metabolic regulation: implications for diabetes mellitus

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Abstract

Gamma-aminobutyric acid (GABA), traditionally recognized as the main inhibitory neurotransmitter in the central nervous system, has a wide range of extraneuronal effects, including regulatory roles in endocrine functions and metabolic processes, as demonstrated by increasingly new data. This review summarizes the molecular mechanisms of GABA biosynthesis and metabolism, the classification and tissue distribution of its receptors, and the functional properties of the GABAergic system in the pancreas, adrenal glands, gonads, thyroid gland, gastrointestinal tract, and vascular system. Particular attention is placed on the involvement of GABA in the pathogenesis of type 1 and type 2 diabetes mellitus, emphasizing its immunomodulatory, regenerative, and metabolic effects. These include effects on insulin secretion, insulin resistance, gluconeogenesis, and lipogenesis. The cytoprotective effects of GABA on pancreatic β-cells, its participation in PI3K/Akt signaling pathways, and the modulation of transcription factor expression are discussed. Moreover, the role of the gut microbiota as an exogenous source of GABA, and its potential involvement in the gut-brain axis, is under consideration. Available evidence suggests that GABA has significant therapeutic potential in diabetes mellitus and metabolic disorders, warranting further investigation.

Keywords: neuroendocrine signaling, metabolic homeostasis, β-cell regeneration, gut-brain axis, GABA shunt, cytoprotection

Introduction

Gamma-aminobutyric acid (GABA), one of the major inhibitory neurotransmitters in the mammalian central nervous system (CNS), was first identified in brain tissue in 1950 through the pioneering work of Eugene Roberts and colleagues [1]. Using chromatographic techniques to analyze amino acids in mammalian brain tissue, they discovered high concentrations of this compound, especially in the grey matter. In 1954, Hideo Hayashi demonstrated the inhibitory effect of GABA on the activity of crayfish, providing the first evidence of its neuroactive properties [2].

A significant breakthrough occurred during the 1960s with the introduction of electrophysiological methods. In their seminal studies on spinal cord neurons in animals (notably frogs and cats), Curtis, Watkins, and colleagues demonstrated that the local application of GABA induces membrane hyperpolarization. This effect was mediated by increased chloride ion permeability, resulting in chloride influx and a subsequent reduction in neuronal excitability. These findings provided some of the first functional evidence that GABA acts as an inhibitory neurotransmitter. An important milestone was the identification of the enzyme glutamate decarboxylase (GAD, EC 4.1.1.15), which catalyzes the synthesis of GABA from glutamate, thereby elucidating the biosynthetic pathway of this neurotransmitter [3].

During the 1970s, GABA receptors were classified into two basic types: GABA_A receptors (ionotropic receptors linked to chloride channels) and GABA_B

receptors (metabotropic receptors linked to G-proteins). The advent of molecular cloning techniques enabled detailed investigation of GABA receptor structure, revealing that GABA_A receptors are heteropentameric complexes composed of various subunits (α, β, γ, δ, and others). Concurrently, the GABA transport system was characterized, leading to the identification of specific GABA transporters, namely GAT-1, GAT-2, GAT-3, and BGT-1, responsible for the reuptake of GABA from the synaptic cleft.

GAT-1 is the predominant neuronal transporter and is known to be inhibited by the antiepileptic drug tiagabine [4]. GAT-2 is primarily expressed in the liver and kidneys, as well as in meningeal cells [5]. GAT-3 is predominantly localized in astrocytes [6], while BGT-1 (betaine/GABA transporter) is characterized by lower affinity for GABA and is mainly expressed in the liver and kidneys, with minimal presence in the CNS [7].

The role of GABA in various pathological conditions remains a subject of active research. Numerous studies have demonstrated associations between dysfunction of the GABAergic system and a range of disorders, including epilepsy, anxiety disorders, depression, schizophrenia, and neurodegenerative diseases. Particular attention is being paid to elucidating the subunit composition of GABA_A receptors in different brain regions and its relevance to specific functional outcomes of neuroplasticity. Furthermore, the involvement of GABA in nervous system development and neuroplasticity continues to attract considerable scientific attention [8].

Traditionally, GABA has been regarded primarily as a basic inhibitory mediator within the CNS, contributing to postsynaptic hyperpolarization, regulation of neuronal excitability, and synaptic plasticity. However, over the past two decades, an increasing body of evidence has indicated that GABA exerts a broad spectrum of extra-neuronal effects. Notably, considerable attention has been devoted to elucidating its role in pancreatic function [9].

Localization of GABA

The role of GABA as the principal inhibitory neurotransmitter in the CNS is underscored by its high concentrations within CNS structures. In the brain, GABA levels reach approximately 40 mmol per gram of tissue, making it one of the most prevailing neurotransmitters in neuronal networks [1]. A pivotal discovery in the early 1970s expanded the understanding of GABA's extraneuronal effects: substantial amounts of GABA were identified within the islets of Langerhans in the pancreas, where its concentration reaches approximately 20 mmol per gram of tissue – about 50% of the levels typically observed in the brain [10]. By contrast, GABA concentrations in other peripheral tissues (including the adrenal glands, kidneys, gastrointestinal tract, and placenta) generally do not exceed 1 mmol per gram of tissue [11], underscoring the unique status of the brain and pancreas as primary sites of GABA activity.

Particular attention is drawn to the topographical similarity between GABA and insulin distribution in pancreatic tissue. Immunohistochemical studies have demonstrated that GABA is predominantly localized within β-cells, alongside insulin, with GABA molecules detected inside insulin-containing granules [12]. Moreover, the expression of the key GABA biosynthetic enzyme, glutamate decarboxylase (GAD65/67), is primarily observed in β-cells, further highlighting a close molecular and functional association between GABA and insulin [13].

GABA receptors have been identified in various islet cell types, including β-, α-, and δ-cells, suggesting the existence of both autocrine and paracrine mechanisms regulating intra- and intercellular hormonal activity [14]. The functional significance of this distribution lies primarily in GABA's ability to modulate insulin secretion. In type 2 diabetes mellitus, a marked reduction in GABA levels within the islets has been documented accompanied by impaired insulin release and diminished β-cell function (from 7.7 to 1.6 nmol per mg of protein) [15]. These findings support the concept that GABA plays a critical role in maintaining pancreatic secretory activity and regulating glucose homeostasis.

In summary, GABA exhibits a distinct organ-specific distribution, with the pancreas and brain serving as key sites of its biological activity. The spatial overlap and functional interconnection with insulin suggest that GABA represents a promising therapeutic target in the treatment of diabetes mellitus.

GABA in the nervous system

The biosynthesis of GABA is initiated from the amino acid glutamate via a decarboxylation reaction catalyzed by the GAD, with vitamin B_6 serving as an essential cofactor. This biosynthetic process takes place in the cytoplasm of presynaptic neurons [16].

Within cells, GABA is primarily synthesized from glutamate through decarboxylation catalyzed by GAD,

for which pyridoxal-5'-phosphate (PLP), the active form of vitamin B_6, is a vital cofactor. PLP functions as a universal coenzyme for all decarboxylase enzymes. In mammals, two isoforms of GAD have been identified – GAD_{65} and GAD_{67} – encoded by the GAD2 and GAD1 genes, respectively.

These isoforms differ in molecular weight, subcellular localization, and regulatory mechanisms governing GABA synthesis in neuronal, endocrine, and other cell types [16].

The precursor for GABA synthesis is glutamate, which is generated in neurons from glutamine supplied by astrocytes through the glutamate/GABA–glutamine cycling pathway. In astrocytes, glutamate is converted into glutamine via glutamine synthetase; subsequently, it is transported back to neurons and hydrolyzed to glutamate by phosphate-activated glutaminase, serving as a substrate for GAD. Additionally, glutamate in astrocytes can be formed from α-ketoglutarate through aminotransferase activity, particularly via aspartate aminotransferase [17].

Beyond the main glutamate-dependent pathway, an alternative route for GABA synthesis has been described in certain tissues, such as the enteric nervous system and dopaminergic neurons of the midbrain. In this pathway, putrescine is oxidized by diamine oxidase to 4-aminobutanal, which is subsequently converted to GABA by aldehyde dehydrogenase 1A1 [17].

Following its synthesis, GABA is packaged into synaptic vesicles by the combined action of vacuolar H^+-ATPase, which generates a proton electrochemical gradient, and the vesicular inhibitory amino acid transporter, which facilitates vesicular GABA uptake against a concentration gradient [18, 19]. Following neuronal activation, GABA is released into the synaptic cleft, where it either binds to its receptors or is taken up for subsequent degradation. GABA exerts its inhibitory effects primarily through two major receptor classes: ionotropic GABAA_A receptors and metabotropic GABAB_B receptors. Activation of these receptors enables GABA to suppress excessive neuronal activity, thereby maintaining the balance of excitatory and inhibitory signaling [15].

GABA plays a pivotal role in maintaining balanced brain activity by modulating neuronal excitability. This modulatory function is essential for the regulation of a wide range of neurological processes and is implicated in the pathophysiology of various neuropsychiatric conditions, including sleep disorders, anxiety disorders, mood dysregulation, depression, epilepsy, schizophrenia [16] and autism spectrum disorders [17].

GABA in the endocrine system

GABA is now recognized not only as the principal inhibitory neurotransmitter within the central nervous system but also as a versatile signaling molecule operating in peripheral organs. Over the past few decades, a substantial body of evidence has demonstrated that GABA is synthesized and exerts distinct biological effects in various endocrine glands, where it fulfills autocrine, paracrine, and modulatory functions.

The pancreas represents one of the most prominent examples of a peripheral organ, in which GABA performs functions that are no less important than those in the central nervous system. In this context, GABA acts as a precise physiological local hormonal regulator, ensuring the delicate balance between insulin and glucagon secretion.

Insulin studies in humans have demonstrated high levels of GABA within the β-cells of pancreatic islets [20]. In a pioneering study, Taniguchi *et al.* quantified GABA concentrations in pancreatic islets of rats with streptozotocin-induced diabetes mellitus and observed that the neural fibers and nerve endings within the islets of Langerhans remained structurally intact throughout the course of the disease [20].

In the pancreas, GABA is synthesized predominantly in β-cells of the islets of Langerhans from glutamic acid via the GAD, which occurs in two isoforms: GAD65 and GAD67. Key aspects of the molecular organization of GABA synthesis were described by Kanaani *et al.*, who demonstrated that GAD65 is localized predominantly to the membranes of vesicles and the Golgi apparatus, whereas GAD67 remains within the cytosol. The co-expression of both isoforms is essential for the effective production and transport of GABA within β-cells [21].

Notably, inhibition of chloride channels has been shown to suppress insulin secretion from human pancreatic islets, indicating that GABA stimulates β-cell secretory activity through activation of these channels (Figure 1). Moreover, glucose itself enhances vesicular GABA release from β-cells, suggesting a dynamic interplay between nutrient availability and GABA-mediated hormonal regulation [22].

Thus, GABA receptor signaling promotes insulin secretion through a positive autocrine feedback mechanism in human β-cells. Several important pharmacological agents target GABA_A receptors, and it is plausible that, given the expression of these receptors in β-cells, they may also affect insulin secretion from pancreatic islets. Indeed, treatment of epilepsy patients

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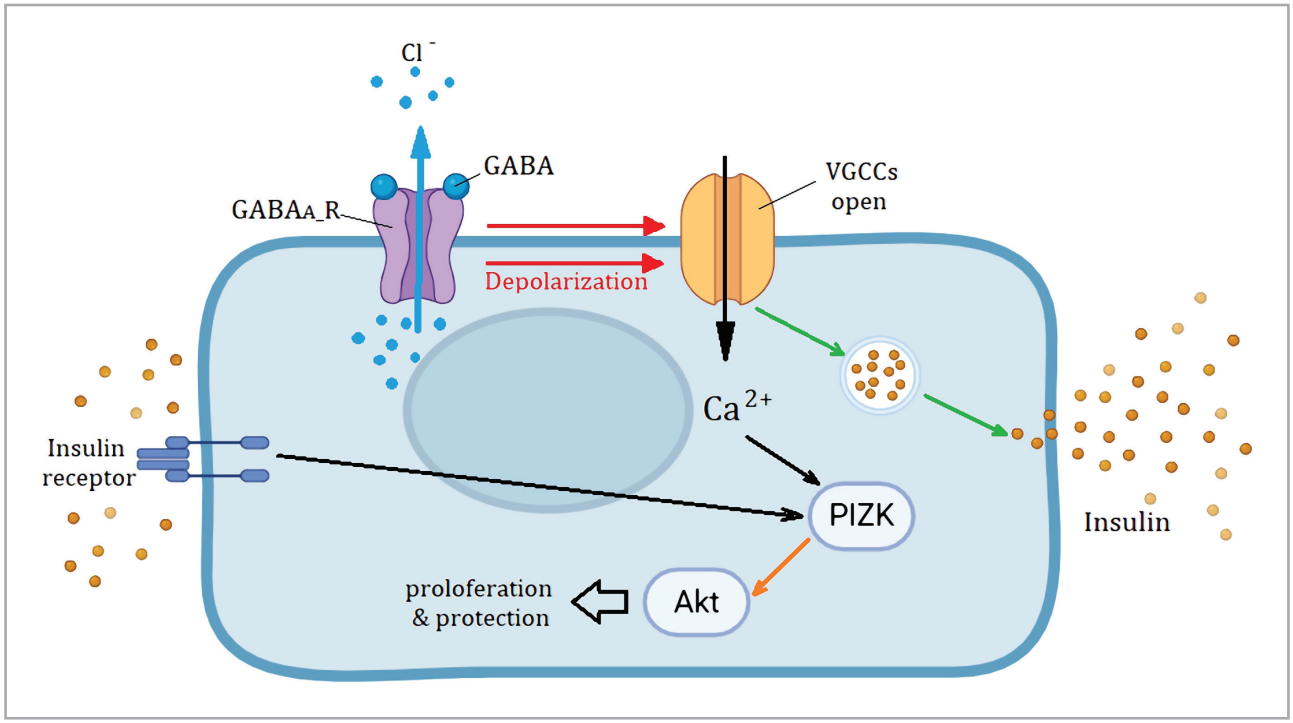

Figure 1: Intracellular changes in β-cells following the activation of GABA receptors. Binding of GABA-to-GABA receptors leads to the release of Cl^- ions, which depolarizes the cell membrane beyond the threshold required for the activation of voltage-gated calcium channels (VGCCs). This promotes insulin secretion, which in turn activates the insulin receptor and subsequently the PI3K/Akt signaling pathway. Additionally, the influx of intracellular Ca^{2+} through VGCCs further stimulates the PI3K/Akt cascade. As a result, β-cell proliferation and survival are observed.

with the antiepileptic drug valproic acid, which inhibits GABA degradation, has been reported to increase postprandial insulin levels [23].

Collectively, these findings indicate the existence of a fully functional GABAergic system within the pancreas, which is closely linked to the regulation of carbohydrate metabolism and may play a significant role in the pathogenesis and potential treatment of diabetes mellitus [14].

GABA metabolism in the pancreas

In pancreatic β-cells, GABA is synthesized and metabolized via the GABA shunt, a metabolic pathway involving several key enzymes and cofactors. The principal enzyme responsible for the decarboxylation of L-glutamate into GABA and CO_2 is GAD. In mammals, there are two isoforms of this enzyme: GAD65 (65 kDa) and GAD67 (67 kDa), encoded by the GAD2 and GAD1 genes, respectively. In β-cells, both isoforms are expressed in varying proportions depending on species, with GAD65 predominantly localized to membrane compartments, especially in secretory vesicles, while GAD67 remains cytosolic and is responsible for basal GABA synthesis. The coordinated activity of GAD65 and GAD67 is essential for maintaining adequate GABA stores and ensuring its rapid release in response to stimuli such as increased glucose levels [14].

PLP is a critical cofactor for GAD function and a universal coenzyme for all decarboxylases. A deficiency in PLP leads to a sharp decline in GAD activity, resulting in reduced GABA synthesis in β-cells. Epidemiological and experimental studies indicate a connection between vitamin B_6 deficiency, impaired glucose homeostasis, and decreased pancreatic GABA levels in type 2 diabetes mellitus [24].

The GABA shunt in β-cells consists of a sequence of metabolic reactions. Initially, GAD decarboxylates L-glutamate into GABA in a PLP-dependent reaction. Subsequently, GABA transaminase (GABAT) catalyzes the conversion of GABA and α-ketoglutarate (α-KG) into succinic semialdehyde (SSA) and glutamate. Depending on the cell's metabolic demands, α-KG may be utilized within the GABA shunt or diverted into the main tricarboxylic acid (TCA) cycle. The final step of the GABA shunt involves the oxidation of SSA to succinate by succinic semialdehyde dehydrogenase, with succinate then entering the TCA cycle to support ATP generation. In β-cells, GABAT activity is markedly

higher than that of α-ketoglutarate dehydrogenase, making the GABA shunt a crucial anabolic and anaplerotic pathway for replenishing TCA cycle intermediates during periods of high ATP demand. Upon glucose stimulation, flux through the GABA shunt increases succinate availability, contributing to the amplifying phase of insulin secretion. Pharmacological inhibition of GABAT (*e.g.*, with gabaculine) or GAD (*e.g.*, with allylglycine) attenuates the second, amplifying phase of insulin release, underscoring the metabolic significance of this pathway for β-cell function [14].

In addition to its metabolic role, GABA modulates β-cell gene expression through activation of the PI3K/Akt signaling pathway. This occurs through GABA_A receptor-mediated increases in intracellular Ca^{2+}. In various models of diabetes, GABA administration has been shown to upregulate key β-cell transcription factors, including pancreas/duodenum homeobox protein 1 (PDX1), critical for β-cell development and maintenance, and neurogenin 3 (NEUROG3), essential for endocrine differentiation within the islets. Increased PDX1 expression intensifies the transcriptional program driving insulin synthesis and secretion, whereas NEUROG3 promotes the formation of new β-cells from progenitor cells, a process particularly important for post-injury regeneration [9].

PI3K/Akt activation by GABA leads to phosphorylation of the kinase Akt, which in turn inactivates the transcription factor FOXO1 (forkhead box O1 protein). This downregulates genes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase, thereby reducing hepatic glucose production and contributing to glycemic normalization. Concurrently, Akt phosphorylates the pro-apoptotic protein BAD (Bcl-2-associated death promoter), preventing its interaction with anti-apoptotic targets and reducing β-cell apoptosis. As a result, GABA, via PI3K/Akt signaling, suppresses the expression of pro-apoptotic genes (*e.g.*, Bax, Caspase-3) and enhances the expression of anti-apoptotic genes (*e.g.*, Bcl-2, Bcl-xL), providing cytoprotection of β-cells under conditions of oxidative stress and autoimmune inflammation [14, 25, 26].

Molecular mechanisms of GABA action

GABA exerts its physiological effects through two principal classes of receptors: ionotropic GABA_A receptors (pentameric Cl^- channels) and metabotropic GABA_B receptors (G protein–coupled receptors) (Figure 2). Activation of GABA_A receptors induces membrane hyperpolarization via chloride influx, whereas GABA_B receptors initiate G protein-mediated signaling cascades that modulate adenylyl cyclase activity and ion channel function. In pancreatic β-cells, as well as in other peripheral tissues, both receptor types are expressed, mediating hormonal secretion and promoting cell survival [15]. In β-cells, GABA binding to GABA_A receptors causes membrane depolarization and activation of voltage-dependent calcium channels. The resulting increase in intracellular Ca^{2+} triggers the PI3K/Akt signaling pathway, leading to phosphorylation and activation of Akt (protein kinase B). Akt activation facilitates the translocation of the insulin-dependent glucose transporter GLUT4 to the plasma membrane, stimulates the synthesis of pro-survival proteins, and suppresses pro-apoptotic factors (*e.g.*, via phosphorylation of BAD), thereby providing cytoprotection to β-cells against apoptosis [15].

Through activation of the PI3K/Akt cascade, GABA indirectly affects the transcription of key β-cell factors. Experimental models have demonstrated that GABA administration in diabetes correlates with increased expression of PDX1 and NEUROG3. Increased PDX1 expression enhances β-cell identity maintenance and insulin synthesis, while NEUROG3 is involved in endocrine islet cell differentiation. Upregulation of these transcription factors contributes to β-cell regeneration and improved functional status [15].

GABA administration in animal models of type 2 diabetes mellitus (T2DM) has been shown to increase the expression of insulin receptor substrate 1 (IRS1) and GLUT4 in peripheral tissues. Increased IRS1 enhances insulin receptor signaling, and upregulation of GLUT4 improves glucose uptake into cells, thereby directly improving insulin sensitivity and contributing to normalization of blood glucose levels [15].

PI3K/Akt activation also results in phosphorylation of FOXO family transcription factors, particularly FOXO1, promoting their nuclear export and consequently reducing the transcription of genes involved in gluconeogenesis (*e.g.*, PEPCK). Simultaneously, Akt phosphorylates the pro-apoptotic protein BAD, preventing its interaction with pro-apoptotic targets and reducing apoptosis. Hence, GABA modulates genes involved in metabolism (gluconeogenesis and lipogenesis) and apoptosis via the PI3K/Akt pathway, contributing to improved glycemic control and β-cell cytoprotection [27].

Additionally, GABA exerts a direct inhibitory effect on glucagon secretion from pancreatic α-cells via

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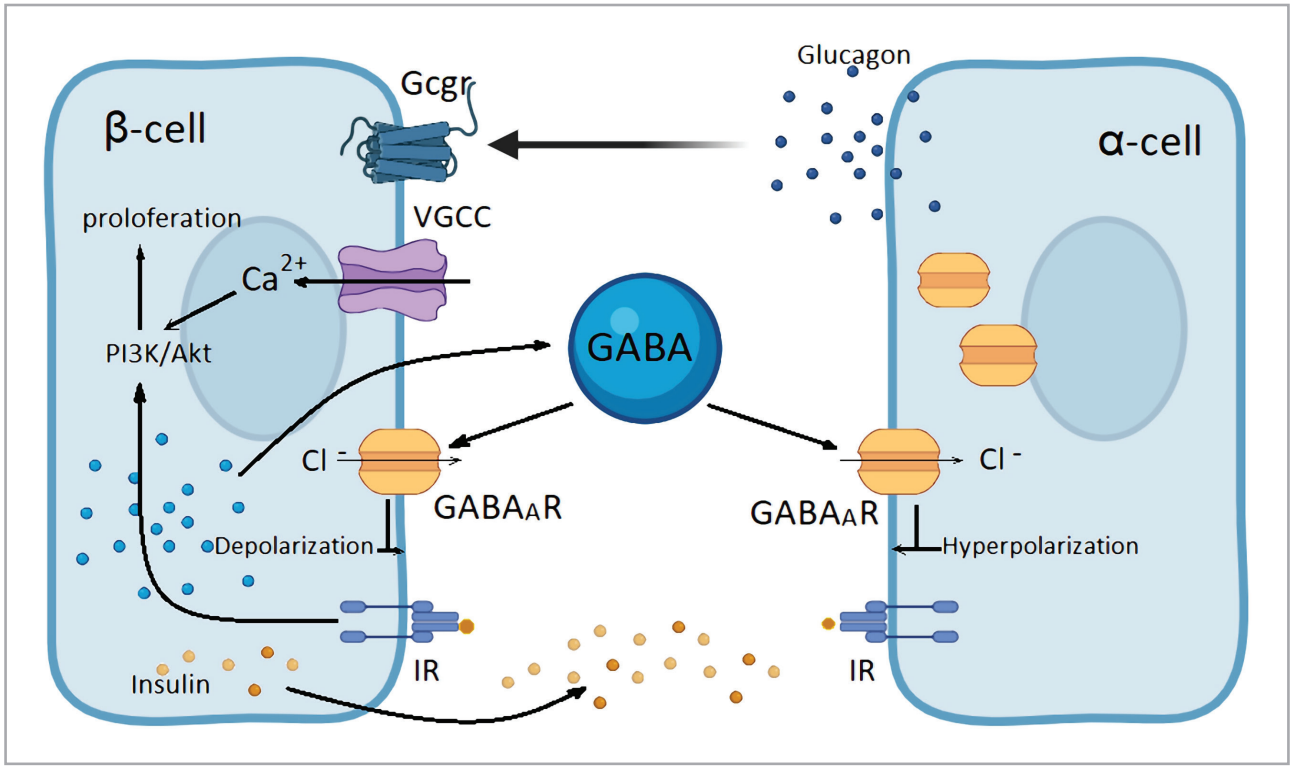

Figure 2: Interaction between α- and β-cells, which may be disrupted in various types of diabetes. GABA, affecting on β-cells, stimulates insulin secretion and promotes β-cell proliferation. Paracrine GABA signaling targets α-cells, suppressing glucagon secretion. Autocrine GABA induces membrane depolarization in β-cells, leading to the activation of the Ca^{2+}-dependent PI3K/Akt signaling pathway, which supports cell proliferation and survival. Moreover, GABA enhances autocrine insulin signaling. GABAAR – γ-aminobutyric acid type A receptor; Gcgr – glucagon receptor; IR – insulin receptor; VGCC – voltage-gated calcium channel; PI3K – phosphoinositide 3-kinase; Akt – protein kinase B.

a paracrine mechanism mediated by both GABA_A and GABA_B receptors expressed on α-cell membranes. In α-cells, GABA induces the opening of chloride channels, resulting in Cl^- influx, which contrasts with Cl^- efflux observed in β-cells. This chloride current causes membrane hyperpolarization of α-cells, thereby reducing their excitability and suppressing glucagon exocytosis. This effect was experimentally confirmed by Wendt *et al*. The authors also demonstrated that activation of G-protein-coupled GABA_B receptors, which are associated with Gi-proteins, leads to decreased cAMP levels and inhibition of voltage-dependent calcium channels, further attenuating glucagon secretion [28, 29].

In T2DM, the reduction of intracellular GABA levels in islets diminishes the inhibitory control over α-cells, thereby contributing to hyperglucagonemia – a key driver of hyperglycemia in T2DM [9]. Interestingly, GABA acts synergistically with insulin and somatostatin to suppress glucagon secretion. Restoration of GABAergic signaling, achieved via exogenous GABA supplementation, has been shown to suppress glucagon secretion, particularly under hyperglycemic conditions [10].

The role of GABA in the pathophysiology of the pancreas

As outlined above, GABA plays a significant role in the pathogenesis and potential treatment of type 1 diabetes mellitus (T1DM) by acting at multiple levels, including immunomodulation, β-cell regeneration, and the regulation of hormonal balance within the islets of Langerhans.

Experimental studies in animal models have shown that GABA administration can delay the onset of T1DM, restore normoglycemia, and suppress the expression of pro-inflammatory cytokines implicated in disease pathogenesis. In addition, GABA enhances β-cell proliferation and survival, and may induce transdifferentiation of α-cells into β-cells, thereby contributing to the regeneration of β-cell mass in diabetes [30, 31].

Clinical studies have confirmed the safety and tolerability of oral GABA administration in patients with newly diagnosed T1DM. However, despite a beneficial reduction in glucagon levels, no significant improvements were observed in C-peptide secretion or glycemic control. In long-term studies involving adults with

established T1DM, GABA therapy did not restore β-cell function, although it was well tolerated [31, 32].

GABA exhibits substantial cytoprotective properties toward pancreatic β-cells. One of the key protective mechanisms involves activation of the PI3K/Akt signaling pathway. By interacting with GABA_A receptors on the surface of β-cells, GABA induces membrane depolarization and opening of voltage-dependent calcium channels. This leads to an increase in intracellular calcium concentration and activation of the PI3K/Akt pathway, which promotes β-cell survival and proliferation while reducing apoptosis. Studies in murine models of diabetes have demonstrated that GABA administration increases β-cell mass and reduces blood glucose levels [33].

In addition, GABA modulates the expression and activity of sirtuin 1 (SIRT1), an NAD^+-dependent deacetylase that plays a pivotal role in regulating metabolism and cell survival. By increasing intracellular NAD^+ levels and enhancing SIRT1 activity, GABA promotes deacetylation of the p65 subunit of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thereby suppressing NF-κB activity and mitigating inflammation and apoptosis in β-cells. This effect has been demonstrated in both pancreatic cell lines and isolated islets [34].

In summary, GABA demonstrates considerable potential as an immunomodulatory and regenerative agent in T1DM, particularly during the early stages of the disease. Nevertheless, further studies are warranted to optimize dosing regimens, treatment duration, and assess long-term therapeutic efficacy.

Reduced GABA levels in type 2 diabetes mellitus

When evaluating the role of GABA in the pathogenesis of T2DM, it is noteworthy that this neurotransmitter constitutes a significant proportion of synaptic activity within the hypothalamus, thereby influencing thermoregulation, appetite, and feeding behavior. Hypothalamic agouti-related peptide-producing neurons release GABA to regulate energy expenditure and mediate ghrelin-induced food intake [35]. This GABA-dependent signaling inhibits anorexigenic proopiomelanocortin-expressing neurons, resulting in appetite stimulation and subsequent weight gain, which contribute to obesity development. Furthermore, proopiomelanocortin-expressing neurons indirectly regulate insulin synthesis and secretion through mitofusin-1-dependent mechanisms, contributing to the modulation of energy balance and glucose metabolism [36].

In the pancreatic islets of patients with T2DM, decreased GABA levels are associated with dysregulated expression of GABAergic system components, which may contribute to β-cell dysfunction and impaired glucose homeostasis. Specifically, it has been demonstrated that in the islets of T2DM patients, there is a significant decrease in the expression of genes encoding the α1, α2, β2, and β3 subunits of GABA_A receptors. This decrease may weaken GABA-mediated modulation of insulin and glucagon secretion, thereby disrupting the hormonal balance within the islets of Langerhans. Additionally, reduced expression of these subunits may diminish the overall GABAergic tone, potentially impairing β-cell functional activity [15, 25].

Animal studies have demonstrated that GABA administration reduces blood glucose concentrations, lowers glycated hemoglobin levels, improves insulin tolerance, and decreases body weight. These effects have been observed in both parental T2DM models and their offspring, indicating a potential transgenerational effect of GABA [37, 38].

GABA enhances insulin sensitivity, particularly in the liver and skeletal muscle. Experimental disease models have demonstrated that GABA administration reduces insulin resistance, underscoring its potential role in the regulation of glucose metabolism in T2DM [37]. Mechanistically, this improvement in insulin sensitivity involves activation of the PI3K/Akt pathway, upregulation of insulin receptor substrate 2 and Akt2 expression, as well as increased GLUT4 gene expression, thereby facilitating glucose uptake into cells. Co-administration of GABA with magnesium sulfate further augments insulin sensitivity by increasing GLUT4 levels while simultaneously reducing the expression of gluconeogenic enzyme genes and the glucagon receptor [39].

Regulation of gluconeogenesis and lipogenesis

GABA exerts an inhibitory effect on hepatic gluconeogenesis by downregulating key enzymes such as PEPCK and glucose-6-phosphatase. This suppression reduces hepatic glucose output and improves glycemic control. Moreover, GABA modulates the activity of transcription factors, including FOXO1, which are involved in the regulation of gluconeogenesis [38].

GABA also modulates lipid metabolism by reducing triglyceride and cholesterol levels in both the liver and plasma. These effects are mediated through the downregulation of lipogenic gene expression and enhancement of

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mitochondrial function in hepatocytes. Consequently, GABA contributes to the attenuation of hepatic steatosis and the overall improvement in the lipid profile [37, 38].

Adrenal glands

GABA is also functionally active in the adrenal glands, where it serves as a modulator involved in the regulation of catecholamine and steroid hormone secretion, as well as the organism's stress response. In the adrenal glands, GABA is present and functionally active in both the adrenal medulla and cortex.

GABA is synthesized locally in the adrenal glands from glutamate by the enzyme glutamate decarboxylase (GAD), primarily the GAD67 isoform, which is expressed in chromaffin cells of the adrenal medulla – the principal producers of catecholamines. Chromaffin cells also express GAT and the enzyme ABAT (aminobutyrate transaminase), which is involved in GABA degradation, indicating the presence of a fully functional peripheral GABAergic system [40].

In chromaffin cells of the adrenal medulla, GABA acts via GABA_A receptors, inducing membrane hyperpolarization, reducing excitability, and inhibiting acetylcholine-induced secretion of adrenaline and noradrenaline. This suggests that GABA serves as a local regulator of sympathetic activity, limiting excessive catecholamine release during acute stress. Additionally, during embryonic development, GABA contributes to the proliferation and differentiation of chromaffin cells, playing a morphogenetic role.

GABA and its receptors are also expressed in adrenal cortex cells, particularly within the zona fasciculata, which is responsible for glucocorticoid synthesis. Through activation of GABA_B receptors, GABA can modulate signaling cascades involving adenylyl cyclase and protein kinase A, thereby influencing steroidogenesis. Consequently, GABA is considered an endogenous inhibitory regulator of hypothalamic–pituitary–adrenal (HPA) axis activity, capable of limiting excessive cortisol production [41].

Under stress conditions, both GABA levels and the expression of its receptors in the adrenal glands can undergo adaptive changes, and this mechanism is thought to facilitate restoration of neuroendocrine homeostasis. By attenuating hypersecretion of stress hormones, GABA may help prevent the detrimental effects of prolonged stress exposure [41].

Thus, in the adrenal glands, GABA actively participates in local hormonal and stress responses, influencing the activity of both the adrenal cortex and medulla. By regulating catecholamine and glucocorticoid secretion, GABA emerges as a potential therapeutic target for the treatment of stress-related and metabolic disorders.

In the central nervous system, GABA plays a key role in the regulation of the hypothalamic-pituitary system, particularly the HPA and hypothalamic-pituitary-gonadal (HPG) axes. In the hypothalamus, GABAergic neurons inhibit neurons that produce corticotropin-releasing hormone (CRH) and gonadotropin-releasing hormone (GnRH) via both synaptic and extrasynaptic GABA_A receptors containing the δ subunit. The sensitivity of these receptors to neurosteroids suggests that GABAergic transmission can be modulated by stress and hormonal fluctuations [42].

During stress, CRH, produced by the paraventricular nucleus, serves as the primary activator of the HPA axis [43]. Importantly, GABA inhibits CRH neurons, functioning as a regulatory "brake" on the stress response. This suppression of CRH release diminishes pituitary activation, lowers adrenocorticotropic hormone (ACTH) secretion, and ultimately reduces cortisol production, thereby protecting against cortisol overexposure and its harmful consequences.

This inhibitory effect is mediated by GABA_A receptors sensitive to neurosteroids, providing negative feedback during the stress response. As cortisol levels rise, the GABAergic system, enhanced by neurosteroids, suppresses CRH signaling, helping the organism return to homeostasis and preventing chronic or excessive stress responses [44].

GABA also influences the secretion of anterior pituitary hormones. Studies have shown that administration of the GABA_A receptor antagonist bicuculline alters the levels of luteinizing hormone (LH), prolactin, growth hormone (GH), and thyroid-stimulating hormone (TSH), suggesting that GABA regulates these hormones primarily through hypothalamic mechanisms [45].

In summary, the GABAergic system exerts a profound influence on hypothalamic-pituitary axis function by modulating the activity of neurons responsible for the secretion of key hormones, thereby supporting the organism's adaptation to stress.

Gonads

GABA plays an important role in regulating gonadal function, acting as both an autocrine and paracrine signaling mediator in the testes and ovaries. In

the testes, GABA is synthesized by Leydig cells, Sertoli cells, and spermatogonia due to the expression of glutamate decarboxylase enzymes (GAD65/67). Leydig cells, which are responsible for testosterone production, express both GABA_A and GABA_B receptors, through which GABA can modulate their proliferation and steroidogenesis. Studies on the TM3 cell line (a murine Leydig cell line derived from immature mouse testes) have shown that activation of GABA_A receptors stimulates Leydig cell proliferation, likely via regulation of gene expression associated with cell cycle progression and transcription, such as EGR-1 and CCND1 (cyclin D1) [46].

Sertoli cells, which provide structural support and nourishment to developing spermatozoa, also express components of the GABAergic system, including GABA_A receptors and GABA transporters. GABA modulates Sertoli cell functions, such as the secretion of factors that regulate spermatogenesis and the maintenance of homeostasis within the seminiferous tubules [47].

In the ovaries, the GABAergic system is likewise present and functionally active. GABA and its receptors are detected in granulosa cells and oocytes, where they may participate in the regulation of folliculogenesis and ovulation. Experimental inhibition of GABA transaminase (GABA-T), the enzyme responsible for GABA degradation, alters the expression of genes involved in reproductive function, including GnRH, Kiss1, and Rfrp-3, and reduces circulating levels of LH and progesterone [48].

Thyroid gland

GABA plays a significant role in regulating the hypothalamic-pituitary-thyroid (HPT) axis by TSH secretion and, consequently, thyroid gland function. Studies in both rats and humans have demonstrated that GABA inhibits TSH release from the pituitary, potentially through direct actions on pituitary cells or via hypothalamic thyrotropin-releasing hormone (TRH)-secreting neurons. This inhibitory effect is thought to be mediated by GABA_A receptor activation, resulting in reduced TRH neuron activity and, consequently, decreased TSH secretion [49].

Furthermore, the thyroid gland itself expresses GABA transporters and enzymatic systems for GABA synthesis and degradation, which are responsive to the gland's functional state. Experimental studies in mice have shown that GABA suppresses TSH-stimulated thyroid hormone release, suggesting a regulatory role for GABA in peripheral thyroid activity [50].

Intestine and its microbiome: features of GABA synthesis and action

GABA plays a crucial role in regulating gastrointestinal functions, acting as both a neurotransmitter and modulator within the enteric nervous system (ENS), as well as influencing the endocrine activity of the gut.

In the ENS, GABA is synthesized and released by neurons, where it interacts with multiple receptor types, including ionotropic GABA_A and GABA_C receptors, as well as metabotropic GABA_B receptors. These receptors are distributed across different layers of the intestinal wall and modulate motility, secretion, and sensory signal transmission. For instance, activation of GABA_B receptors reduces neuronal excitability, thereby decreasing peristalsis and secretion, whereas GABA_A receptors may exert excitatory effects depending on their localization and the cell type involved [51].

GABA also regulates fluid and electrolyte transport in the intestine. Its presence in submucosal neurons suggests a role in controlling mucosal transport processes, contributing to homeostasis and epithelial protection [52]. Furthermore, GABA can modulate immune responses in the gut by acting on enteric glial cells and attenuating inflammatory processes via inhibition of the NF-κB pathway, which may have relevance in inflammatory bowel diseases [53].

Interestingly, GABA can be synthesized not only by host cells but also by certain gut bacterial strains, including *Bacteroides spp.* and *Bifidobacterium spp.* Microbiota-derived GABA represents a key component of the gut–brain axis, exerting systemic effects on host neural, endocrine, and immune functions.

The microbial GABA synthesis pathway in the intestine is similar to that in mammals: GAD catalyzes the decarboxylation of glutamate to GABA with the participation of PLP, the active form of vitamin B_6. In certain bacterial species, GAD is membrane-associated, facilitating rapid export of GABA into the environment. Microbial GABA can interact with enteric neurons via GABA_A, GABA_B, and GABA_C receptors located on enteroglial and submucosal neurons, modulating intestinal motility, mucus and electrolyte secretion, and epithelial barrier function. Upon entering the portal circulation, microbial GABA can reach the central nervous system, affecting hypothalamic functions and

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modulating stress responses through interactions with neurosteroid-sensitive GABA_A receptors in the paraventricular nucleus [54].

In addition to its direct neuromodulatory effects, microbial GABA contributes to immune regulation in the gut. Through GABA_A receptors on enteric glial cells and mucosal immune cells, it suppresses NF-κB signaling, reduces pro-inflammatory cytokine production, and promotes tolerance to dietary antigens. Microbial GABA also influences the intestinal vascular network: activation of GABA_B receptors on endothelial cells increases intracellular Ca^{2+}, thereby promoting vasodilation, enhancing microcirculation, and improving epithelial nutrient delivery [55].

In the human colon, the primary GABA producers are *Bacteroides* species, particularly *Bacteroides fragilis* and *Bacteroides thetaiotaomicron*, which possess a conserved set of genes encoding GAD and related enzymes (glutaminase, GABA/glutamate antiporter, and potassium channel). This system ensures efficient GABA production at physiological pH (5.7–7.4) and protects bacteria from acid stress, enabling sustained GABA production in the gut environment [56]. Studies have shown that *Bacteroides fragilis* produces GABA under physiological colonic pH, unlike *Escherichia coli*, which synthesizes GABA mainly at lower pH, underscoring the key role of *Bacteroides* in maintaining neurochemical balance in the intestine [56]. *Bacteroides thetaiotaomicron* demonstrates a highly conserved GAD system, including glutamate decarboxylase, glutaminase, GABA/glutamate antiporter, and potassium channel [57, 58].

The genus *Bifidobacterium*, particularly *Bifidobacterium adolescentis*, also significantly contributes to GABA production. Genomic analyses of over 1,000 *Bifidobacterium* strains identified *B. adolescentis* as a model GABA producer in the human gastrointestinal tract. Specific strains, such as PRL2019 and HD17T2H, have demonstrated the ability to modulate GABA levels both *in vitro* and *in vivo*, with associated impacts on host psycho-emotional states [20].

Lactobacillus plantarum, especially strain L5, is also known for high GABA production. Studies on mouse models of essential tremor have shown that administration of *L. plantarum* L5 reduces tremor severity, improves motor activity, and increases brain GABA concentrations, indicating the therapeutic potential of such probiotics in neurodegenerative diseases associated with GABA deficiency [59].

In conclusion, GABA exerts key regulatory functions in the gastrointestinal tract, acting as a neurotransmitter within the ENS and as a modulator of motility, secretion, barrier function, and mucosal immune responses. The significant role of gut microbiota in GABA synthesis underscores the microbiome as an active component of the gut–brain axis. The combined action of endogenous and microbial GABA ensures multi-level neuroendocrine and immune regulation, essential for maintaining homeostasis and adaptive responses in the host.

GABA in the cardiovascular system

GABA exerts significant effects on the vascular system, including arteries, veins, and capillaries, through interactions with various types of receptors expressed in endothelial and vascular smooth muscle cells [60].

In arteries, particularly resistance vessels such as mesenteric and tail arteries in mice and human omental arteries, GABA_A receptors have been identified in vascular smooth muscle cells. Activation of these receptors induces membrane hyperpolarization and decreases intracellular calcium concentration, thereby promoting vascular relaxation and reducing vascular tone. These findings suggest a direct role for GABA in the regulation of arterial blood pressure and vascular resistance [61, 62]. Notably, GABA_A receptor subunits α1, α2, α3, α4, and α5 have been detected in the thoracic aorta of rats, where their activation contributes to vasodilatory effects [62].

GABA also exerts important effects in capillaries and microvessels. Endothelial cells of capillaries express both GABA_A and GABA_B receptors, the activation of which increases intracellular calcium via release from intracellular stores and activation of calcium channels. This promotes vasodilation and enhances microcirculation, particularly in cerebral vessels [63].

Moreover, endothelial cells are capable of synthesizing and releasing GABA, which regulates angiogenesis and vascular network development, especially during embryogenesis. Impaired GABA release from endothelial cells results in defects in vascular network formation and neuronal migration, highlighting the essential role of endothelial GABA in the coordinated development of both vascular and nervous systems [64].

Perspectives and limitations of GABA use

Despite its predominantly peripheral action, exogenous GABA can penetrate the CNS in small but

clinically significant concentrations, especially at high doses or in cases of blood-brain barrier disruption. Neurological studies report that increased GABA levels in the brain lead to pronounced sedative effects, impaired cognitive function, and reduced perception of hypoglycemia warning signals (such as hunger and sweating). In patients with type 2 diabetes, who often already exhibit CNS micro- and macroangiopathies (*e.g.*, vascular dementia, diabetic neuropathy), this may exacerbate cognitive impairment and increase the risk of severe hypoglycemic episodes due to blunted counterregulatory responses to low blood glucose levels [65].

The presence of GABA receptors in neuroendocrine nuclei of the hypothalamus and pituitary indicates that systemic administration of GABA can disrupt hypothalamic-pituitary regulation. This is facilitated by the activation of neurosteroid-sensitive GABA_A receptors in the paraventricular and arcuate nuclei of the hypothalamus, leading to reduced secretion of corticotropin-releasing hormone and GnRH. As a result, in patients with type 1 diabetes, who frequently already have dysfunction of the HPA axis, this may further impair hormonal counterregulation (including cortisol, ACTH, and glucagon), increasing the risk of poorly coordinated stress responses and complicating the management of comorbid endocrine disorders.

Similarly, in patients with type 2 diabetes, excessive inhibitory effect on the HPG axis may lead to reduced levels of LH and follicle-stimulating hormone (FSH), particularly in women with coexisting obesity and polycystic ovary syndrome, thereby impairing fertility outcomes and aggravating metabolic disorders [66, 67].

Despite extensive preclinical evidence demonstrating that GABA stimulates β-cell proliferation and exerts cytoprotective effects, clinical studies in humans have not shown significant improvements in insulin secretion or C-peptide recovery. In patients with newly diagnosed type 1 diabetes, single and repeated oral GABA administration resulted in only a modest reduction in glucagon levels without statistically significant increases in C-peptide levels or improvements in glycemic control. Moreover, in adults with long-standing type 1 diabetes, exogenous GABA failed to restore β-cell function and often required increasing doses due to tolerance development. High doses and prolonged use were associated with gastrointestinal side effects (such as nausea and diarrhea) and an additional risk of hypoglycemia, particularly when combined with other hypoglycemic agents [68].

Conclusion

The accumulated body of evidence highlights GABA as a multifunctional signaling molecule with substantial influence beyond the central nervous system. Its pivotal role in endocrine regulation, especially within the pancreas, adrenal glands, hypothalamus, and peripheral tissues, underscores its therapeutic potential in metabolic disorders such as type 1 and type 2 diabetes mellitus. GABA modulates insulin and glucagon secretion, enhances β-cell survival, reduces apoptosis, and improves insulin sensitivity via the PI3K/Akt signaling pathway. The ability of GABA to act through both autocrine and paracrine mechanisms, including effects mediated by gut microbiota, places it at the intersection of neuroendocrine and metabolic regulation. Despite promising preclinical data, the clinical efficacy of exogenous GABA remains limited, requiring further studies to optimize treatment protocols and overcome pharmacokinetic and central side effects. GABA represents a promising yet underexplored target for the pharmacological management of endocrine and metabolic disorders.

Conflict of interest

The authors declare no conflict of interest.

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