GABA as potential target in the treatment of Type-1 Diabetes Mellitus

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ABSTRACT

Type-1 diabetes (T1D) is an autoimmune disease characterized by insulitis and islet β-cell loss. At the onset of T1D, more than 70% of β-cells are destroyed, whereas the residual β-cells most likely represent the only reservoir for the regeneration of islet β-cell mass. Indeed, an effective therapy of T1D requires suppression of the autoimmune process and restoration of islet β-cells. GABA can be a potential target for Type-1 diabetes mellitus. GABA is inhibitory neurotransmitter and released from pancreatic β-cell. It acts on GABAₐR in the α-cells, causing membrane hyperpolarization and hence suppressing glucagon secretion. GABA treatment can reduce lymphocytic islet infiltration, restore the β-cell mass, and completely reverses hyperglycemia. This is associated with increased insulin, decreased glucagon levels in the circulation, and improved metabolic conditions. So, GABA or GABA-mimic drugs may be utilized as potential therapeutic option in the prevention and treatment of Type-1 Diabetes mellitus.

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Introduction

Type 1 diabetes, T1DM, formerly insulin dependent or juvenile diabetes. It is a form of diabetes mellitus that results from autoimmune destruction of insulin producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms are polyuria, polydipsia, polyphagia, and weight loss. Statistically, the incidence rate of Type 1 diabetes is increasing globally by 3.0% every year. However, incidence rates vary from one continent to another, and variations within the same region are often significant. So, while the annual incidence rates for Type 1 diabetes in Europe range from 4.4 to 4.5 per 100,000 people, relatively low incidence rates (less than 2 per 100,000 per year) are found in Asian countries [1]. Several studies of Type 1 diabetes have been carried out but still there is a lack of promising target. The incretin hormone GLP-1 has β-cell stimulatory capacity and clinical efficacy in T2D treatment, but it is only marginally effective in T1D treatment, likely because of an insufficient effect of GLP-1 on the suppression of autoimmunity. The objective is to decrease the number of incidence of type-1 diabetes mellitus by targeting GABA. This neurotransmitter is made in the brain from the amino acid glutamate with the aid of vitamin B6.

There have been some recent studies in diabetic mice utilizing GABA to reverse inflammation on the pancreas and improve hyperglycemia. GABA was also studied in healthy human subjects demonstrated that large oral doses of GABA increased insulin secretion from the pancreas [2]. GABA receptor agonists inhibit the glucagon secretion in beta cell. So researcher can target gamma-amino butyric acid (GABA) in children with newly diagnosed T1DM.

GABA

GABA is a major neurotransmitter in the CNS synthesized from glutamate by glutamic acid decarboxylase (GAD) [3-8]. In the CNS, GABA acts at two distinct types of receptors, ligand-gated ionotropic GABA_A receptors and G protein-linked metabotropic GABA_B receptors, thus mediating both fast and slow inhibition of excitability at central synapses [9, 10]. In the adult brain, GABA induces a fast inhibition in neurons mainly through the GABA_A receptor (GABA_AR) [11]. Activation of GABA_A causes opening of ligand-gated Cl^- ion channel, results in membrane hyperpolarization as a consequence of Cl^- influx, which regulates neuronal cell proliferation and maturation [12-17].

GABA is also produced by pancreatic β-cells [18]. It exerts protective effect, regenerative effects on islet β-cells, anti-diabetic effects by acting on both the islet β-cells and immune system, suppresses insulitis and systemic inflammatory cytokine production. The β-cell regenerative and immune inhibitory effects of GABA provide insights into the role of GABA in regulating islet cell function and glucose homeostasis. In islets of Langerhans, GABA is released from β-cells and inhibits the release of glucagon from α cells [19, 20]. This inhibition is believed to be mediated through GABA_AR [20, 21, 22].

GABA released from β-cells can act on GABA_AR in the α-cells, causing membrane hyperpolarization and hence suppressing glucagon secretion as per figure 1[23, 24]. An impaired insulin-Akt-GABA_AR-glucagon
secretory pathway in the islet may be an underlying mechanism for unsuppressed glucagon secretion, despite hyperglycemia, in diabetic subjects [25]. The persistent high glucose or elevated cytoplasmic ATP levels could suppress GABA production and its release from β-cells[26]. Activation of GABA– GABA$_A$R signaling in pancreatic β-cells would have trophic activities and exert therapeutic effects in diabetic subjects. The metabolism of glucose leads to the formation of ATP in beta-cells. The increased ATP/ADP closes the ATP-dependent K$^+$ channels (K$_{ATP}$C), resulting in plasma membrane depolarization, opening of voltage dependent Ca$^{2+}$ channels (VDCC) and increase in [Ca$^{2+}$], [27]. The increased intracellular [Ca$^{2+}$] stimulates the release of insulin and GABA from beta cells which is shown in figure 1[27-29].

**PATHWAY OF GABA IN DIABETES MELLITUS**

![Diagram of GABA pathway in diabetes mellitus](diagram.png)

**Fig1: Role of GABA in Diabetes Mellitus**

**VARIOUS MECHANISM OF GABA IN DIABETES:**

**GABA Promotes β-Cell Proliferation and Protects β-Cell from Apoptosis**

GABA could protect β-cell against apoptosis, significantly reduces streptozotocin (STZ) induced death in the clonal INS-1 cells. These observations suggest that GABA promotes both β-cell replication and survival.

**GABA Produces Depolarizing Effects and Initiates Ca$^{2+}$PI3-K/Akt Pathway.**

GABA stimulated Akt phosphorylation, which was blocked by the GABA$_A$R antagonist bicuculline, PI3K inhibition or the calcium channel blocker, i.e., nifedipine. This suggests that GABA$_A$R-mediated trophic effect is mediated by the Ca$^{2+}$-dependent PI3K/Akt pathway[30] in β-cells. Researches had found that both GABA and GABA$_A$R agonist muscimol stimulated Ca$^{2+}$ influx in the β-cells. These observations suggested that GABA induced membrane depolarization, subsequent Ca$^{2+}$ entry, and activation of the PI3K/Akt pathway, which may represent a mechanism underlying its in vivo effects in promoting β-cell growth and survival [31, 32].
GABA Prevents Diabetic Hyperglycemia in T1D Mouse Models.

GABA plays a role in the regulation of glucose homeostasis, its effects in multiple low-dose STZ-induced diabetes (MDSD) [33] in mice. In MDSD mice had a severe loss of islet β-cells, with the residual islet containing mostly α-cells. Daily GABA injections initiated 7 d before STZ treatment prevented β-cell loss. Thus, β-cell mass was preserved. Consistently, GABA treated mice showed higher circulating insulin, lower glucagon, nearly normal glycemic, and improved metabolic conditions, and maintained close to normal glucose tolerance. Insulin sensitivity was not altered, but glucagon tolerance was significantly improved, indicating that GABA prevented diabetic hyperglycemia in MDSD mice through the preservation of β-cell mass and function. The effects of GABA in non-obese diabetic (NOD) mice, a spontaneous autoimmune T1D mouse model [34]. Daily GABA injections were given in NOD mice before the onset of diabetes and in control group saline solution were injected to mice, at the age of 13 wk, control group developed severe insulitis, β-cell depletion (≈85% β-cells were destroyed), and hyperglycemia. In contrast, the GABA-treated mice showed mostly normal islets (only ≈15% islets had mild insulitis), reduced β-cell death and increased β-cell proliferation, and relatively constant glucose levels.

GABA Suppresses Inflammation and Increases Regulatory T-Cell Numbers.

The cytokines level in the normal mice were present at undetectable or very low while it was remarkably elevated in the serum of STZ-treated mice, including IL-1β, TNF-α, IFN-γ, IL-12, IL-6, and IL-10. However, some studies found that GABA-treated MDSD mice showed significantly decreased circulating inflammatory cytokines, i.e., IL-1β, TNF-α, IFN-γ, and IL-12. Notably, the levels of the anti-inflammatory cytokine IL-10 were not suppressed. These results suggest that GABA exerts an anti-inflammatory effect and produces a more favorable cytokine profile, which may be a relevant to the reduced insulitis seen in GABA-treated MDSD and NOD mice [35-37].

Conclusion

GABA therapy increases β-cell proliferation and decreases β-cell apoptosis, which in turn increases β-cell mass and induces the reversal of hyperglycemia in the mice. GABA exerts depolarizing effects and Akt plays an important role in β-cell growth and the protection from apoptosis. GABA Prevents Diabetic Hyperglycemia in T1D Mouse Models and also Suppresses Inflammation by decreased circulating inflammatory cytokines, i.e., IL-1β, TNF-α, IFN-γ, and IL-12 and Increases Regulatory T-Cell Numbers. Importantly, GABA does not cross the blood brain barrier and can be administered orally in humans in large amounts.

In the light of above, we thus conclude that GABA receptors or drugs acting on GABA receptor may be utilized as a target for the prevention and treatment of Type-1 Diabetes mellitus.
Authors’ Statements
Conflict of interest.
The authors declare there was no conflict of interest.

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