Review Article

Insulin resistance and the role of gamma-aminobutyric acid

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Insulin resistance (IR) is mentioned to be a disorder in insulin ability in insulin-target tissues. Skeletal muscle (SkM) and liver function are more affected by IR than other insulin target cells. SkM is the main site for the consumption of ingested glucose. An effective treatment for IR has two properties: An inhibition of β-cell death and a promotion of β-cell replication. Gamma-aminobutyric acid (GABA) can improve beta-cell mass and function. Multiple studies have shown that GABA decreases IR probably via increase in glucose transporter 4 (GLUT4) gene expression and prevention of gluconeogenesis pathway in the liver. This review focused on the general aspects of IR in skeletal muscle (SkM), liver; the cellular mechanism(s) lead to the development of IR in these organs, and the role of GABA to reduce insulin resistance.

Key words: Gamma-aminobutyric acid, insulin resistance, skeletal muscle

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INTRODUCTION

Diabetes is an endocrine condition synonymous with glucose dysregulation and insulin release or insulin resistance, triggering persistent hyperglycemia.[1] So far, pharmacological therapies improve diabetic diseases.[2] However, the declining impact of therapeutic drugs on blood glucose is followed by multiple risks such as medication tolerance, side effects, and even toxicity.[3] Consequently, good nutrition and exercise are advised and favored as complementary treatments for the treatment of diabetic diseases. In particular, natural compounds supplemented with gamma-aminobutyric acid (GABA) have been shown to be successful in lowering blood glucose and reducing pancreatic damage. One of the main features of diabetes is insulin resistance (IR). IR can be described as a situation which higher than normal concentrations of insulin are necessary to achieve normal metabolic responses or normal concentrations of insulin fail to achieve a normal metabolic response.[4] The term IR refers to a disorder in insulin action in insulin-target tissues, such as skeletal muscle (SkM), adipocytes, brain, and liver.[5] The aim of this review is to focus on the general aspects of IR in SkM and liver; the cellular mechanisms that lead to the development of IR in these organs; and the role of GABA in reducing insulin resistance.

Search strategy

The search was performed in Web of Science, Scopus, Google Scholar, and PubMed to identify relevant studies. The search was carried out from 1978 until the end of March 2020. The search strings used in search were insulin resistance, skeletal muscle, gamma aminobutyric acid, and GABA without language or date restrictions. The title and abstract of all the articles identified and those describing mechanisms of IR and GABA effects were finally selected.

INSULIN RESISTANCE IN SKELETAL MUSCLE AND ITS CELLULAR MECHANISMS

SkM is the main site for the consumption of ingested glucose in lean individuals with normal glucose

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tolerance (NGT).[6] After a meal, nearly one-third of ingested glucose is taken by the liver and the other by the peripheral tissues, mainly SkM through the insulin-dependent mechanism.[6] Although fat tissue is responsible for only a small amount of total body glucose disposal (4%–5%), it plays a very important role in the maintenance of total body glucose homeostasis.[7] For example, IR and hyperglycemia are both associated with too much fat (obesity) and too little fat (lipodystrophy).[8] After a meal, the hyperglycemia stimulates insulin secretion from pancreatic β-cells and increases plasma insulin concentration in SkM, leading to consumption of ingested glucose.[6] After overnight fasting, most of glucose uptake occurs insulin independent in the visceral areas (liver plus gastrointestinal tissues) and brain. Glucose utilization is about 2 mg/kg/min and is exactly in line with the amount of glucose released from the liver.[7] Approximately 80%–85% of glucose uptake occurs after a meal in the muscle tissue. Maintaining normal blood glucose homeostasis depends on three closely related processes: (1) insulin production by β-cells in the pancreas, (2) stimulation of glucose uptake by splanchnic (liver and gut) and peripheral (primarily muscle) tissues, and (3) suppressing the output of hepatic glucose.[9] Although adipose tissue consumes only a small amount of glucose in the body (4%–5%), it plays a key role in maintaining glucose homeostasis.[7] In IR states, such as obesity and type 2 diabetes (T2DM), insulin-stimulated glucose uptake in SkM is markedly impaired.[6] It has been indicated that in every organ, similar to SkM, capillaries are composed of endothelial cells (ECs) that are connected by tight and adherent junctions. This continuous endothelium regulates the access of circulating macromolecules to the underlying tissue and, therefore, their ability to affect biological activity. The endothelial regulation of hormone delivery plays a substantial role in both pathophysiology and normal physiology.[10] Studies indicated that insulin is a hormone whose activity is regulated by endothelium.[11,12] The ability of insulin to stimulate glucose absorption into SkM, the major site of insulin-stimulated glucose consumption, depends on depends on the rate of insulin delivery to SkM interstitium is corrected.[13] Moreover, studies indicated that delivery of insulin to SkM impaired in the setting of diet-induced IR.[14] Therefore, the rate-limiting step of glucose uptake by insulin in SkM may be the presence of insulin in the intercellular space, which is much slower in obese IR individuals than in healthy subjects.[13] Consequently, following high-fat diet consumption and obesity, damage to SkM endothelium following intracellular cascade defect leads to IR in this tissue [Figure 1].

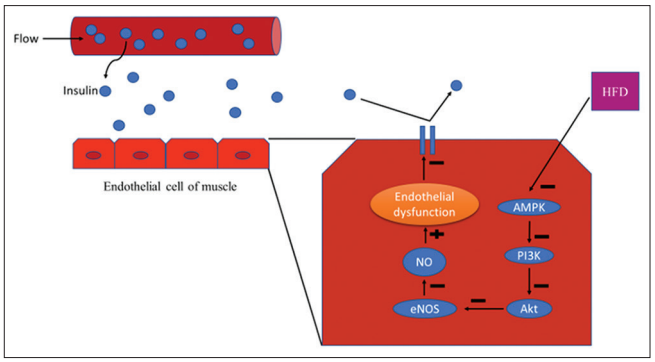

Figure 1: The role of endothelial regulation in insulin activity. The insulin activity depends on the amount of insulin released from the endothelium into the interstitium. Therefore interstitium has a main role in insulin activity.High fat diet (HFD) through the down- regulation of AMPK- PI3k- Akt- eNOS pathway lead to insulin resistance in skeletal muscle

Decreased glucose uptake by insulin stimulation depends on various disorders including insulin signaling disorder and several intracellular disorders such as impaired glucose transport and glucose phosphorylation and reduced glucose oxidation and glycogen synthesis.[15] Although glucose uptake during the hyperinsulinemic–euglycemic clamp indicates the insulin-independent glucose uptake by all peripheral tissues, the highest of this glucose uptake occurs in SkM.[16] A human study that was performed on nine noninsulin-dependent diabetic individuals showed that under euglycemic conditions using the hyperinsulinemic–euglycemic clamp in combination with the common carotid artery and jugular vein catheterization,[17] nearly 80% of the body's glucose uptake occurs in SkM. It has been shown that SkM glucose uptake increases progressively in healthy subjects in response to a physiologic increase in plasma insulin concentration, and in contrast, the rate of glucose uptake is reduced by <50% in T2DM subjects, during the last hour of the hyperinsulinemic–euglycemic clamp study. Thus, in humans with T2DM the dose–response curve relating insulin-stimulated glucose uptake and the plasma insulin concentration shifts to the right with an increase in EC50 (to ~120–140 μU/mL). It has been shown that insulin infusion for about 60 min in subjects with T2DM cannot improve glucose uptake. IR in SkM develops before the onset of hyperglycemia.[18] Therefore, healthy neonates of parents with T2DM have a significant decrease in glucose uptake by insulin.[19] IR in SkM can also be independent of familial inheritance.[20] Therefore, obese subjects with NGT and individuals with essential hypertension[21] and ischemic heart disease[22] also have a 35%–50% reduction in insulin-dependent glucose uptake. IR in SkM has been described in cases such as normal aging process,[23] dyslipidemia (decreased high-density lipoprotein cholesterol/increased plasma triglyceride [TG]),[6,24] and in association with many disease states including chronic kidney failure,[25] polycystic ovary syndrome,[26] myotonic dystrophy,[27] heart failure,[28] and lipodystrophy.[29] It has been reported that IR develops in severe acute diseases such as sepsis and injury, perhaps secondary to the acute inflammatory state, which probably occurs due to a

secondary inflammation.[30] IR in SkM can also be caused by pharmacological treatments such as anti-HIV therapy,[31] glucocorticoids,[32] and beta-blockers[33] [Figure 2]. These findings indicate that although IR is a feature of T2DM, IR syndrome is more prevalent, and its metabolic and clinical consequences (e.g., increased cardiovascular risk) can affect non-diabetic individuals. These studies show that IR in T2DM patients is not only triggered by a delayed onset of insulin regulation but also by a decline in insulin regulation amplitude. Furthermore, research demonstrates that although IR in SkM is characteristic of T2DM, SkM insulin tolerance and IR syndrome are more common and clinical and metabolic subsequences of IR often influence non-diabetic topics.

Insulin receptor signal transduction defects in insulin resistance

In obesity[34] and T2DM,[35] insulin-stimulated muscle glucose storage is decreased, and experiments using nuclear magnetic resonance have also shown that transporting glucose is the main step in which insulin activity fails. A study has shown that insulin affinity for monocytes and adipocytes is reduced in T2DM patients.[36] The decrease in insulin binding is caused by a reduction in the number of insulin receptors without a change in insulin receptor affinity. Besides, it has been shown that insulin receptors have not decreased in 50% of T2DM, and therefore, it can be concluded that there is a weak association between IR and decreased insulin binding.[37] Insulin receptor abnormalities have been identified in diabetic and IR syndromes. However, the genome sequence of T2DM patients has shown that except for very rare cases, physiological mutations in the insulin receptor gene have not been reported.[38] This suggests that the common cause of IR in SkM may not be a gene defect in the insulin receptor structure.

Insulin receptor tyrosine kinase activity

Insulin receptor tyrosine kinase activity in SkM has been studied in both nondiabetic obese and obese diabetic subjects. Most of them[37-40] have reported that the tyrosine kinase activity decreased but not due to the number of receptors or the affinity of receptor. However, it has been

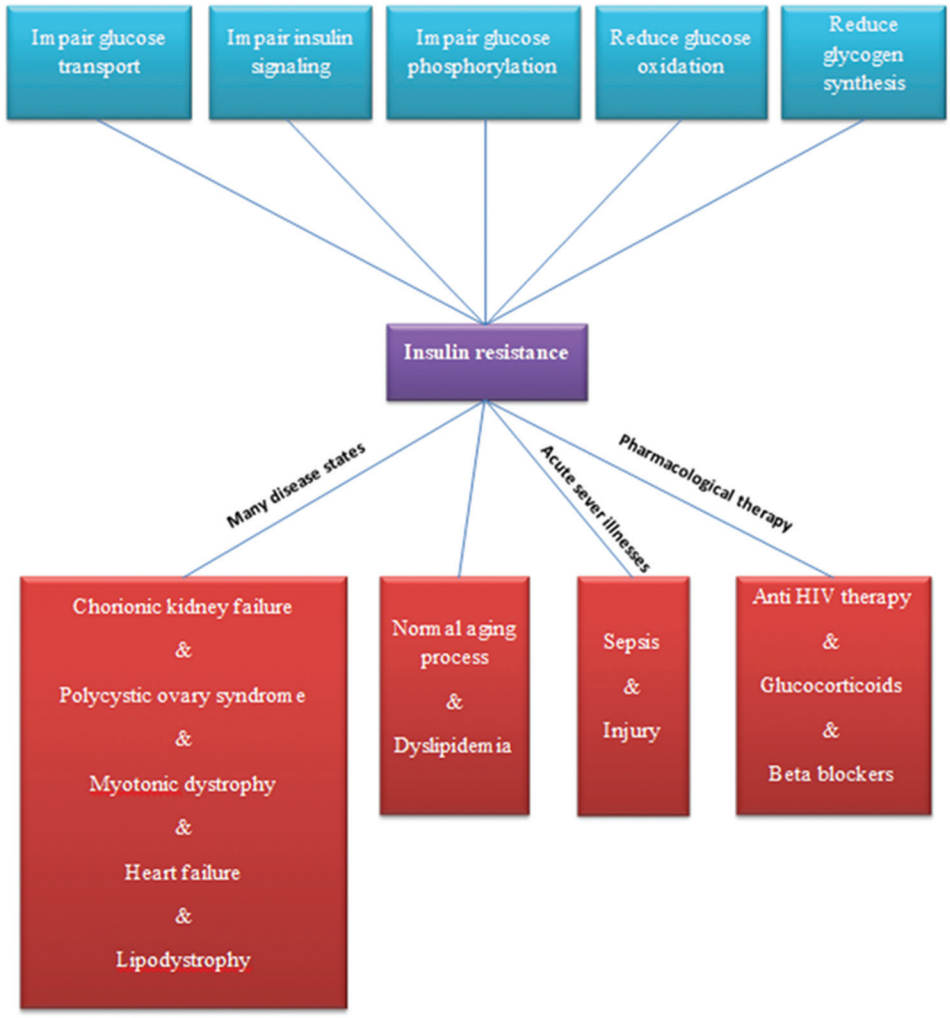

Figure 2: Insulin resistance disorders

shown that weight-loss diets can improve the deficiency of tyrosine kinase activity,[41] which suggests that impaired insulin receptor tyrosine kinase activity may be due to alterations in blood glucose, intracellular glucose metabolism, hyperinsulinemia, and insulin resistance. In an animal study, it was reported that exposure of rats to high glucose concentrations inhibits insulin receptor tyrosine kinase activity.[42] Because insulin receptor tyrosine kinase activity evaluations are performed *in vitro*, the results of these evaluations could provide confusing information concerning to insulin receptor function *in vivo*. To circumvent this problem, a study was performed on 27 volunteers (8 lean control subjects, 9 obese nondiabetics, and 10 patients with T2DM) and were used the euglycemic–hyperinsulinemic clamp together with biopsies from the quadriceps femoris muscle and antiphosphotyrosine immunoblot analysis to provide a "snapshot" of the insulin-stimulated tyrosine phosphorylation state of the receptor *in vivo*.[39] It has been demonstrated that insulin receptor tyrosine phosphorylation decreases in non-diabetic obese subjects with insulin resistance, in the NGT-IR offspring of T2DM parents, and in T2DM individuals. Furthermore, in the same study, it was reported that when insulin-stimulated insulin receptor phosphorylation was investigated in NGT insulin-resistant individuals, normal phosphorylation of the insulin receptor increased.[39] These results suggest that hyperglycemia or other metabolic deficits in T2DM individuals may be due to impaired insulin receptor tyrosine kinase activity.

In a study of obese non-diabetic and T2DM subjects, it was shown that insulin's ability to phosphorylation of tyrosine IRS-1 is significantly impaired in T2DM subjects compared to nondiabetic individuals.[39] Cusi *et al*.[39] and Krook *et al*.[43] in a clinical trial study and also Kellerer *et al*.[42] and McNeilly *et al*.[44] in an experimental study reported that the relationship between p85 subunit of PI3K with IRS-1 and activation of PI3K in T2DM and obese nondiabetic individuals are weaker than healthy control. Besides, in a study that was performed on patients in general clinical research center of the University of Texas showed that insulin-resistant in NGT offspring of T2DM parents increase because of IRS-1 tyrosine phosphorylation and the relationship between p85 protein/PI3K activity with IRS-1 are markedly decreased despite phosphorylation of the insulin receptor is normal; it has been demonstrated that these insulin signaling disorders are closely linked to the severity of IR measured with the euglycemic–hyperinsulinemic clamp technique.[45] In summary, impaired insulin signaling pathways including defective relationship between IRS-1 with PI3K and its subsequent activation are characteristic abnormalities in T2DM, and these defects are closely linked to muscle insulin resistance.

Insulin resistance in liver and its cellular mechanisms

Liver metabolism includes catabolic (with the predominant effects of glucagon) and anabolic (with the predominant effects of insulin) functions, which are performed concurrently without futile cycles. How does liver functional classification affect by insulin resistance?

Given that insulin can produce and develop visceral fat, therefore, losing weight via diet and the use of drugs increases insulin sensitivity. The free fatty acids (FFA) are taken up by the hepatocytes and oxidized as a source of energy, which ultimately increases oxygen consumption.[46] It has been shown that, although FFA cannot be substrates for gluconeogenesis, their oxidation provides the energy needed for gluconeogenesis.

It has been demonstrated that intracellular accumulation of diacylglycerol due to the entry of excess fatty acids into the liver leads to activation of protein kinase C (PKC). PKC through the inhibition of phosphorylation of IRS-1 leads to increased insulin resistance. In addition, excess of FFA through activation of inflammatory toll-like receptors, leading to ceramide synthesis and accumulation of ceramides in the liver via inhibiting phosphorylation of Akt induces insulin resistance.[47] It has also been shown the high content of FFA via activation of Akt phosphatase protein phosphatase 2A (PP2A) which in turn through dephosphorylation and inactivation of Akt leading to increase IR in the liver.[48] Increased FFA also causes synthesis of very-low-density lipoprotein and TG,[49] which in turn leads to elevating hypertriglyceridemia [Figure 3].

To understand insulin resistance, the human body must be thoroughly examined. The fact that insulin may be excessive or inadequate at any tissues and organs has many biologic ramifications. It should be noted that IR varies in different areas of the liver, so that it occurs in perivenous hepatocytes lipogenesis and periportal hepatocytes glucose production.

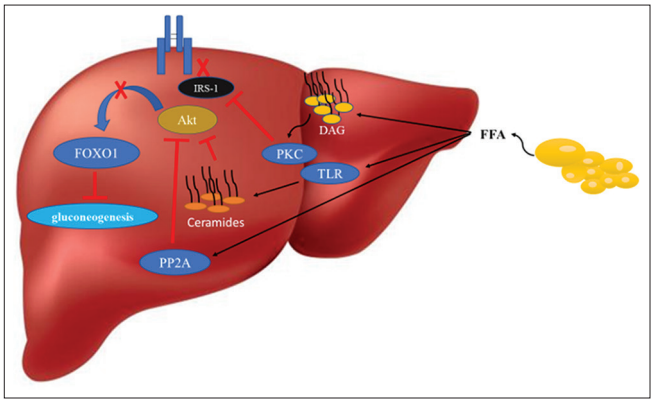

Figure 3: The liver is an important organ for glucose homeostasis, and all pathways to control carbohydrate metabolism in the liver are controlled by insulin, and fatty acids play an important role in insulin resistance in the liver and the role of fatty acids in insulin resistance in the liver has been shown in the figure

Table 1: Protective effects of gamma-aminobutyric acid

Source	Dose/ model	Time of treatment/ administration	Effect	References
GABA (Sigma Aldrich, Hamburg, Germany)	1.5 g/kg	2 months (every day) i.p	Improved insulin resistance through rising GLUT4 and also decreasing the gluconeogenesis pathway and Glucagon receptor gene expression	[69]
GABA (Sigma, St. Louis, USA)	100 μM	3 moths (every day) ip	Antidiabetic effects by acting on both the islet β cells and immune system Activation of PI3-K/Akt	[53]
GABA (MilliporeSigma, Burlington, MA, USA)	6 mg/ml	10 weeks Oral	Increased pancreatic -cell mass, which led to a modest enhancement in insulin secretion and glucose tolerance	[73]
GABA (sigma)	6 mg/ml	5 weeks Oral	Increased grafted β-cell proliferation, while decreasing apoptosis, leading to enhanced β-cell mass Decreased blood glucose levels and improved glucose excursion rates	[74]
GABA (International Labortory, USA)	100 mg/ kg	21 days	Reduced body weight, body mass index and testosterone Decreased in the number of cystic follicles, and decreased in the adipocytes	[75]
GABA (N/A)	6 mg/mL	6 weeks Oral	Decreased ambient blood glucose levels and improved the glucose excursion rate.	[72]
GABA (Sigma, St. Louis, USA)	2 mg/ml	20 weeks Oral	Inhibited the HFD-induced glucose intolerance, insulin resistance, and obesity	[70]
GABA (Sigma-Aldrich)	2 or 6 mg/mL	14 days Oral	Promotes β-cell replication and functional recovery in human islets	[65]

GABA: Gamma-aminobutyric acid

Therefore, in the liver of patients with IR and obesity, fat accumulation and IR are expected to occur. However, many concepts have yet to be learned about the relationship between the mechanism of IR and liver classification. Therefore, to understand the relationship between liver metabolic classification and IR better, we need to study gene expression in parenchymal and non-parenchymal cells of the liver.

ROLE OF GABA IN REDUCING INSULIN RESISTANCE

GABA receptor in pancreatic islet cells

Probably, gamma-aminobutyric acid (GABA) tends to improve the reactions to adjustments in blood glucose levels.[50] GABA's function depends on linking GABA or its agonists to GABA receptors, expressed on islet cells. GABA has two forms of receptors in humans and rats, $GABA_AR$ and $GABA_BR$.[51] $GABA_ARs$ are observed in human islets in α-, β-, and δ-cells and in mouse islets in α- and β-cells.[52,53] GABA exerts various forms of responses in islet α and β groups of cells, including some exciting and inhibiting acts on α-cells and β-cells.[50,52] The possible explanation for these opposite reactions to GABA by α- and β-cells is the presence of K^+ -Cl^- channels (KCC2) in α-cells and its absence from β-cells.[54] Intracellular Cl^- concentration in α-cells stays small because of KCC2 activity, while large intracellular Cl^- concentrations prevail in β-cells. The mechanistic interpretation of the exciting reaction of β-cells to GABA suggests that Cl^- ions are shifted out of the cell after the opening of the $GABA_AR$ ligand-gated chloride pathway, resulting in depolarization. Contrary to that, GABA performs inhibitory behavior in α-cells by expanding the chloride pathway, which triggers Cl^- 's movement within the cells, resulting in inhibitory impact. $GABA_BRs$, on the opposite, are irreversible and consist of just two subunits, B1 and B2. They are channels associated with the G-protein (GPCR).[53,55] As a result of comprehensive studies into the action and regulatory process of GABA in pancreatic islets, the activity of GABA in pancreatic β cells is gaining momentum. T2D patients lack daily oscillatory insulin secretions. Since the GABA signaling mechanism was disrupted in T2D subject, it can be concluded that there is a defect in GABA receptors in diabetic and insulin resistant individuals.

GABA improves β-cell protection and encourages its proliferation by activating PI3K/Act. T2D is a bihormonal condition with severe hypoinsulinemia and hyperglucagonemia. Hyperglycemia in T2D arises from inadequate and unnecessarily slow insulin production in the sense of decreased insulin activity in target tissues.[56] It has been shown that beta-cell function is diminished in T2D patients.[57] It is also reported that in humans with T2D, insulin release in the first step is missing while the number of beta-cells is decreased by just 30%–60%.[56] Old postmortem experiments utilizing histochemical techniques to differentiate beta- and alpha-cells have documented a decrease in alpha-cell mass in T2D by around 35% relative to nondiabetic controls.[58,59] The function of GABA in pancreatic β-cells may be calculated as it functions as a growth factor and controls the activity of large populations of islet cells, including alpha- and beta-cells. The exciting results of GABA on β-cell secretion seem to include Ca^{2+} movement caused by membrane depolarization and voltage dependent calcium channel (VDCC).[50,52] PI3K/Akt pathway activity is affected by depolarization of the β-cell membrane via GABA-stimulation and calcium voltage channel (VDCC) via Ca^{2+} influx.[53] The stimulation of the PI3K/Akt signaling system was undisguised to play a vital role in defending and living β-cells.[60] It has been reported

that within the mouse model type 1 diabetes, GABA avoided and reversed disease by encouraging β-cell development and survival by triggering the PI3-K/Akt pathway. PI3K/Akt functions as a downstream insulin receptor signaling cascade mediator and plays a crucial function in defending β cells from apoptosis, thereby promoting development and differentiation.[61,62] As a consequence of IR in diabetics, there is a deficiency of the GABA pathway that contributes to a malfunction in the insulin cascade.

Gamma-aminobutyric acid as an anti-inflammatory and defense agent of beta-cells

GABA has been shown to have anti-inflammatory effects and possibly protect beta-cells from damage caused by the immune system.[53] Tian *et al*. reported that daily low dose administration of GABA in type 1 diabetic mice, lead to suppression of the production of proinflammatory T-cell responses and disease progression.[63] Furthermore, it has been shown that in individual with type 1 diabetes GABA administration reduced the secretion of inflammatory cytokines from $CD4^+$ T cells, which act as immunomodulatory effects.[64] Activation of GABABRs or GABAARs via treatment with GABA, strongly suppressed β-cell apoptosis and protected pancreatic β cells in streptozotocin-induced mice diabetic rats.[65] Ligon and colleagues also noted the role of GABA in reducing apoptosis and increasing beta-cell proliferation in rat pancreatic islets.[66] Likewise, GABA elevated β-cell replication in hyperglycemic humans and mice islets.[67,68] Thus, these data demonstrate that GABA prevents β cells from apoptosis and preserves the islet β-cell mass in diabetes patients, through the use of modulation of PI3K/Akt signaling pathway.

Effect of gamma-aminobutyric acid on insulin resistance

Sohrabipour and colleagues in an experimental study reported that GABA could reduce plasma glucose more than insulin near the control level. They also showed that GABA treatment substantially increased the glucose infusion rate needed to sustain euglycemia through insulin infusion and improved insulin tolerance test relative to diabetic rats.[69] In addition, GABA has been reported to increase GLUT4 mRNA expression, which in turn reduces insulin resistance.[69] Tian *et al*. indicated that oral GABA therapy greatly decreased concentrations of blood glucose level, and enhanced glucose tolerance and insulin sensitivity in mice fed with high fat diet. Furthermore, they showed that peripheral GABA receptor activation prevented the high fat diet-induced glucose sensitivity and insulin resistance.[70] Another study demonstrated that GABA reduced blood glucose rates and increased the production of insulin in beta-cells in the pancreas.[71] As well as Liu *et al*. indicated that GABA administration in mice decreased levels of blood glucose and increased rate of excursion to glucose. This was consistent with increased plasma insulin rates and lower plasma glucagon rates.[72] Therefore, GABA via improving signaling pathway of insulin, increase expression of GLUT4 mRNA and also decrease blood glucose, lead to improving of insulin resistance [Table 1].[53, 69, 70, 72-75]

CONCLUSION

The present study demonstrates that GABA is a hormone secreted by the pancreatic islets. GABA prevents β cells from apoptosis and preserves the islet β-cell mass in diabetic patients and animal's model through the use of modulation of PI3K/Akt signaling pathway. GABA deficiency interferes with insulin signaling pathway and GABA administration in T2DM diabetic animal model could improve IR via increase in GLUT4 gene expression and GLUT4 protein translocation into the cell membrane. And it also could reduce the key enzymes in the gluconeogenesis pathway.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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