Gamma Amino Butyric Acid Attenuates Liver and Kidney Damage Associated with Insulin Alteration in γ-Irradiated and Streptozotocin-Treated Rats

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ABSTRACT

Gamma aminobutyric acid (GABA) is one of the inhibitory neurotransmitters that may have the ability to relieve the intensity of stress. The aim of the current study was to evaluate the role of γ-amino butyric acid (GABA) in modulating insulin disturbance associated with liver and kidney damage in γ-irradiated and streptozotocin-treated rats. Irradiation was performed by whole body exposure to 6 Gy from a Cs-137 source. Streptozotocin (STZ) was administered in a single intraperitoneal dose (60 mg/kg body weight). GABA (200 mg/Kg body weight/day) was administered daily via gavages during 3 weeks to γ-irradiated and STZ-treated rats. The results obtained showed that γ-irradiation induced hyperglycemia, hyperinsulinemia and insulin resistance (similar to type 2 Diabetes), while STZ-treatment produced hyperglycemia, insulin deficiency with no insulin resistance detected (similar to type 1 Diabetes). In both cases, significant increases of alanine amino transferase (ALT) and aspartate amino transferase (AST) activities, urea and creatinine levels were recorded in the serum. These changes were associated with oxidative damage to the liver and kidney tissues notified by significant decreases of superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px) activities in parallel to significant increases of malondialdehyde (MDA) and advanced oxidation protein products (AOPP) levels. The administration of GABA to irradiated as well as STZ-treated rats regulated insulin and glucose levels, minimized oxidative stress and reduced the severity of liver and kidney damage. It could be concluded that GABA could be a useful adjunct to reduce some metabolic complications associated with insulin deficiency and insulin resistance.

Key Words: Radiation/ Diabetes/ GABA/ Liver/ Kidney/ Gamma

INTRODUCTION

Diabetes mellitus (DM) or simply diabetes is one of the most frequently occurring chronic diseases worldwide and one of the leading causes of death and disability (¹). DM characterized by hyperglycemia resulting from defects in insulin production and/or insulin action, is generally associated with organ dysfunction and metabolic disturbances (²). Although the etiology of the disease is not well defined, increasing evidence in both experimental and clinical studies suggests that oxidative stress due to auto-oxidation of glucose and decreased antioxidant defense (³) have a central role in the onset of DM and its complications (⁴,⁵).

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Radiation-related disorders are one of the challenging current health problems with far-reaching medical, social and economic consequences. Experimental studies demonstrated oxidative stress, to be the underlying mechanism of radiation injury (6). The most important consequences of oxidative stress are lipid peroxidation, protein oxidation, depletion of antioxidant elements and metabolic disturbances (7-9). Radiation may lead to diabetes, as it was observed in workers who cleaned up after Chernobyl (10), people in regions subjected to nuclear weapons testing (11), and in children who underwent total body irradiation (as part of a medical treatment for cancer) (12).

Efficient defense and repair mechanisms exist in living cells to protect against oxidant species as superoxide dismutase (SOD) which catalyzes the reduction of superoxide anion to H$_2$O$_2$, which is broken down by catalase and glutathione peroxidase (GSH-Px) (13). However under abnormal conditions the antioxidant system may not be adequate to protect from oxidative stress and metabolic disturbances.

GABA is considered to be a multifunctional molecule with various physiological effects throughout the body. It is the major inhibitory neurotransmitter in the central nervous system and a paracrine/autocrine signaling molecule in various peripheral tissues (14). It is one of the major autoantigens in type 1 diabetes mellitus, a disease in which β-cells are systematically destroyed by an autoimmune mechanism (15). In addition, GABA was reported to inhibit the development of inflammatory responses (16) and to possess antidiabetic (17), antioxidant and free radicals scavenging activities (18). The presence of GABA receptors has been identified in a wide variety of non-neural tissues including the liver (19), the kidney (20), and the pancreas where it exists at the highest concentration outside of the central nervous system (21). In the pancreas, GABA is localized in synaptic-like microvesicles in β-cells of the islets of Langerhans (22). In view of these considerations the aim of the current study was to evaluate the ameliorative effect of GABA on insulin disturbance, hyperglycemia, and associated liver and kidney damage in γ-irradiated and streptozotocin-treated rats.

**MATERIALS AND METHODS**

**Experimental animals:** Male albino rats *Sprague Dawley* (10 ± 2 weeks old; 120 ± 10g) purchased from the Egyptian Holding Company for Biological Products and Vaccines (Helwan, Cairo, Egypt) were used in the current study. Animals were maintained under standard conditions of ventilation, temperature, humidity, lighting (light/dark: 13h/11h) and fed on standard pellets diet containing all nutritive elements (proteins, fats, carbohydrates, vitamins, salts and minerals). Food and water were available *ad libitum*. For biochemical analyses animals were sacrificed at 11:00 am ± 1 h. All animal procedures were performed in accordance with the Ethics Committee of the National Research Centre conformed to the “Guide for the care and use of Laboratory Animals” published by the National Institutes of Health (NIH publication No. 85–23, revised 1996).

**Gamma-irradiation treatment:** Gamma irradiation of rats was carried out at the National Center for Radiation Research and Technology (NCRRT), Nasr city, Cairo, Egypt using a Canadian Gamma Cell-40 (Cs-137), which ensured a homogeneous dose distribution all over the irradiation tray. The dose rate was 0.5 Gy/minute during the experimental periods. The rat’s whole body was exposed to gamma rays at a dose of 6 Gy administered as a single dose (acute dose).

**Streptozotocin treatment:** Streptozotocin (STZ) purchased from Sigma-Aldrich, St. Louis, Missouri, USA, in the form of 1 g vials was administered to rats by single intraperitoneal administration of 60 mg/kg of STZ, freshly dissolved in 0.1M cold citrate buffer (pH 4.5) (23). Since STZ is capable of producing fatal hypoglycemia as a result of massive pancreatic release of insulin, the rats were kept on 5% glucose for the next 24 hours to prevent hypoglycemia (24). Blood glucose levels were monitored using an Accu-check blood glucose meter (Roche Diagnostics, Basel, Switzerland) in tail vein 72 hours after STZ administration. Rats with fasting blood glucose levels ≥ 250 mg/dL were considered as diabetic and included in the study.
**Gamma amino butyric acid treatment:** Gamma amino butyric acid (GABA) purchased from Sigma-Aldrich, St Louis, Missouri, USA in the form of 25 g vials was dissolved in distilled water and administered to rats daily by gastric gavages at doses of 200 mg/Kg body weight/day\(^{(25)}\) for a period of 3 weeks.

**Animal groups:** Rats were divided into 6 groups of 10 rats and treated in parallel. Control group: administered distilled water during 3 weeks via gavages, GABA group: administered GABA (200 mg/Kg body weight/day) daily during 3 weeks via gavages, IR: 6 Gy gamma-irradiated rats were administered distilled water daily during 3 weeks via gavages. IR + GABA: gamma-irradiated rats administered GABA (200 mg/Kg body weight/day) daily during 3 weeks via gavages. STZ group: STZ-induced diabetic rats administered distilled water daily during 3 weeks via gavages. STZ + GABA group: STZ-induced diabetic rats administered GABA (200 mg/Kg body weight/day) daily during 3 weeks via gavages.

**Biochemical analysis:** At the end of the third week rats were sacrificed after a fasting period of 12 hours next day following the last dose of GABA. Blood sample was obtained via heart puncture by sterilized syringe and liver and kidney tissues were rapidly excised. A part of the blood was taken on sodium fluoride to inhibit enolase enzyme and prevent glucose breakdown to be used for the determination of plasma glucose\(^{(26)}\). Another part was left to coagulate to obtain serum after centrifugation at 1000 g for 15 minutes. Liver and kidney tissues (10% w/v) were homogenized in physiological saline using Teflon homogenizer (Glass-Col, Terre Haute, Ind., USA) and after centrifugation at 10,000 g for 15 min using refrigerated centrifuge (K3 Centurion Scientific, Ltd, London, UK) the supernatant was used for the assessment of oxidative stress parameters.

Chemicals and reagents were purchased from Sigma-Aldrich, St Louis, MO, USA otherwise mentioned. Measurement of absorbance was performed using a T60 UV/VIS spectrophotometer, PG instruments, London, UK.

Plasma glucose content was determined using diagnostic kit purchased from Diamond, Egypt according to the method described by Trinder\(^{(27)}\). Serum insulin level was determined by a solid phase enzyme linked immunosorbant assay (ELISA) according to Clark and Hales\(^{(28)}\). Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR)\(^{(29)}\) [fasting plasma glucose (mg/dl) x fasting serum insulin (micro IU/ml) / 405]. Insulin resistance was defined as HOMA-IR >3. Serum creatinine and urea levels were determined using diagnostic kits purchased from Diamond, Egypt following the method described by Henry et al.,\(^{(30)}\) and Patton and Crouch\(^{(31)}\), respectively. Serum ALT and AST activities were measured using diagnostic kits purchased from Spectrum, Egypt following the method described by Henry et al.,\(^{(32)}\).

The extent of lipid peroxidation was assayed as described by Yoshioka et al.,\(^{(33)}\), based on the determination of malondialdehyde (MDA) an end product of lipid peroxidation, which can react with thiobarbituric acid in acidic medium to yield a pink colored trimethine complex. Advanced Oxidation Protein Products (AOPPs) was determined according to the method of Witko-Sarsat et al.,\(^{(34)}\) based on the measurement of dityrosine containing cross-linked protein products. Superoxide dismutase activity (SOD) was determined according to the method of Nishikimi et al\(^{(35)}\). One unit of SOD activity defined as the amount of the enzyme causing half the maximum inhibition of nitroblue tetrazolium reduction. Catalase activity was determined as described by Sinha\(^{(36)}\) and expressed as μmol of H₂O₂ consumed/min/mg protein. Glutathione peroxidase (GSH-Px) activity was determined according to the method described by Necheles et al.,\(^{(37)}\), and expressed as mg GSH consumed /min /g tissue.
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Statistical analysis: Results are presented as mean ± standard deviation (SD). Groups were compared by one-way analyses of variance (ANOVA), and post hoc multiple comparisons were done with LSD test using SPSS/PC software program (version 21; SPSS Inc., Chicago, IL, USA). Correlations between the changes in the different parameters with blood insulin level were carried by Pearson correlation coefficient analysis \(^{(38)}\).

RESULTS

The results obtained revealed that the administration of GABA (200 mg/Kg/day) to normal rats via gavages daily for 3 weeks had a non-significant effect on all of the studied parameters.

Whole body gamma irradiation of rats with 6 Gy induced hyperglycemia, hyperinsulinemia, and insulin resistance (Table 1), and provoked oxidative stress in liver and kidney tissues notified by a significant decrease of SOD, catalase, and GSH-Px activities associated with a significant increase in MDA and AOPP levels (Tables 3 and 4). Increased oxidative stress in the liver and kidney tissues was accompanied by a significant increase in ALT, AST activities, creatinine and urea levels compared to their respective control values (Tables 2). The administration of streptozotocin (STZ) 60 mg/kg body weight to male albino rats produced significant hyperglycemia, and hypoinsulinemia with no insulin resistance detected (Table 1), and provoked oxidative stress in liver and kidney tissues (Tables 3 and 4) accompanied by a significant increase in liver and renal parameters compared to their respective control values (Table 2).

The administration of GABA to irradiated as well as STZ-treated rats improved insulin and glucose levels (Table 1), reduced oxidative stress in liver and kidney tissues (Tables 3 and 4) and reduced the liver and renal markers, compared to their respective values in rats that did not receive GABA (Table 2). The degree of improvement in all of the parameters studied was correlated with the degree of improvement in insulin levels (Figures 1-3). Figure (1) represents the correlations between changes in glucose, HOMA-IR, kidney and liver function markers and insulin, figure (2) represents the correlations between changes in anti-oxidative markers and insulin in both tissues and figure (3) represents the correlations between changes in oxidative markers and insulin in both tissues.

Table (1): Influence of GABA on glucose and insulin levels and insulin resistance (HOMA IR>3.0) in \(\gamma\)-irradiated (IR) and streptozotocin-treated rats (STZ).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>GABA</th>
<th>IR</th>
<th>IR+GABA</th>
<th>STZ</th>
<th>STZ+GABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>92 ± 6</td>
<td>95 ± 4</td>
<td>128 ± 6(^a)</td>
<td>100 ± 6(^b)</td>
<td>268±13(^a)</td>
<td>148±12(^ab)</td>
</tr>
<tr>
<td>Serum Insulin (µIU/ml)</td>
<td>13.0±0.8</td>
<td>12.5±0.7</td>
<td>13.9±0.9(^a)</td>
<td>11.9±1.0(^b)</td>
<td>4.4±0.4(^a)</td>
<td>8.0±0.9(^ab)</td>
</tr>
<tr>
<td>HOMA IR&gt;3.0</td>
<td>3.0 ± 0.35</td>
<td>2.9 ± 0.19</td>
<td>4.4±0.35(^a)</td>
<td>2.9 ± 0.16</td>
<td>2.95±0.25</td>
<td>2.95±0.35</td>
</tr>
</tbody>
</table>

Values are expressed as Means ± Standard Deviation (n=10).

\(^a\) : significant vs control, \(^b\) : significant vs respective groups not receiving GABA at P<0.05
Table (2): Influence of GABA on alanine amino-transferase (ALT) and aspartate-amino transferase (AST) activities, urea and creatinine levels in the serum of γ-irradiated (IR) and streptozotocin-treated rats (STZ).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>GABA</th>
<th>IR</th>
<th>IR+ GABA</th>
<th>STZ</th>
<th>STZ + GABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (U/L)</td>
<td>171±14</td>
<td>182±17</td>
<td>245±19a</td>
<td>196±11ab</td>
<td>352±15.6a</td>
<td>208±16ab</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>50±3</td>
<td>47±3</td>
<td>67±5a</td>
<td>51±5ab</td>
<td>95.0±6.45a</td>
<td>58±4.7ab</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>23±2.1</td>
<td>25±2.4</td>
<td>37±2.2a</td>
<td>28±2.4ab</td>
<td>54±3.4a</td>
<td>43.5±2.1ab</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.38±0.03</td>
<td>0.36±0.02</td>
<td>0.67±0.05a</td>
<td>0.47±0.03ab</td>
<td>0.54±0.04a</td>
<td>0.37±0.02b</td>
</tr>
</tbody>
</table>

Legends as in table 1

Table (3): Influence of GABA on superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px) activities in the liver and kidney tissues of γ-irradiated (IR) and streptozotocin-treated rats (STZ).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Tissues</th>
<th>Control</th>
<th>GABA</th>
<th>IR</th>
<th>IR+ GABA</th>
<th>STZ</th>
<th>STZ + GABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD (U/g tissue)</td>
<td>Liver</td>
<td>9.2±0.4</td>
<td>9.1±1.1</td>
<td>7.4±0.9a</td>
<td>8.5±0.4ab</td>
<td>7.5±0.31a</td>
<td>7.8±0.2a</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>7.5±0.4</td>
<td>8.0±0.5</td>
<td>6.4±0.3a</td>
<td>7.3±0.5ab</td>
<td>5.9±1.1a</td>
<td>7.4±0.7b</td>
</tr>
<tr>
<td>Catalase (µmol H2O2 consumed/min/mg protein)</td>
<td>Liver</td>
<td>34.1±1.7</td>
<td>35.2±0.8</td>
<td>9.2±0.7a</td>
<td>26.0±2.2ab</td>
<td>9.9±1.0a</td>
<td>35.7±3.7ab</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>19.2±0.7</td>
<td>19.0±1.0</td>
<td>9.8±0.3a</td>
<td>13.4±1.7b</td>
<td>8.7±0.9a</td>
<td>11.3±1.3ab</td>
</tr>
<tr>
<td>GSH-Px (mg GSH consumed/min/g tissue)</td>
<td>Liver</td>
<td>40.7±2.5</td>
<td>44.0±3.3</td>
<td>26.7±2.0a</td>
<td>29.0±1.9a</td>
<td>31.2±3.9a</td>
<td>32.3±2.1a</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>29.3±2.9</td>
<td>32.3±2.6</td>
<td>20.5±1.8a</td>
<td>23.5±1.9ab</td>
<td>21.4±1.8a</td>
<td>24.0±2.2ab</td>
</tr>
</tbody>
</table>

Legends as in table 1

Table (4): Influence of GABA on malondialdehyde (MDA) and advanced oxidation protein products (AOPP) levels in the liver and kidney of γ-irradiated (IR) and streptozotocin-treated rats (STZ).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Tissues</th>
<th>Control</th>
<th>GABA</th>
<th>IR</th>
<th>IR+ GABA</th>
<th>STZ</th>
<th>STZ + GABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (nmol/g tissue)</td>
<td>Liver</td>
<td>113±12</td>
<td>118±11</td>
<td>245±20a</td>
<td>232±9a</td>
<td>196±12a</td>
<td>126±9.6ab</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>272±12</td>
<td>273±12</td>
<td>390±27a</td>
<td>342±15ab</td>
<td>365±23a</td>
<td>317±15ab</td>
</tr>
<tr>
<td>AOPP (µmol/L)</td>
<td>Liver</td>
<td>64±5</td>
<td>63±9</td>
<td>176±16a</td>
<td>114±12ab</td>
<td>170±15a</td>
<td>110±12ab</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>157±12</td>
<td>152±15</td>
<td>295±12a</td>
<td>183±16ab</td>
<td>218±19a</td>
<td>180±9.6ab</td>
</tr>
</tbody>
</table>

Legends as in table 1
Fig. (1): Changes in blood markers at different treatments. The figure represents the correlations between changes in glucose, HOMA-IR, kidney and liver function markers and insulin. Lines at origin denotes the control, markers denote the % change from control.
Fig. (2): Kidney and liver tissue response to different treatments. The figure represents the correlations between changes in anti-oxidative markers and insulin in both tissues. Lines at origin denote the control, markers denote the % change from control.
Fig. (3): Kidney and liver tissue response to different treatments. The figure represents the correlations between changes in oxidative markers and insulin in both tissues. Lines at origin denotes the control, markers denote the % change from control.

DISCUSSION

Streptozotocin (STZ), an antibiotic produced by Streptomyces chromogenes, is widely used to induce diabetes. Its cytotoxic action has been shown to be mediated through the generation of reactive oxygen species (ROS) causing degeneration of β cells\(^{(39)}\). In the current study, intraperitoneal administration of 60 mg/kg of STZ induced hyperglycemia associated with hypoinsulinemia (similar to type 1 DM). Hyperglycemia appears to be a consequence of insulin deficiency caused by the degeneration of pancreatic beta cells and reduced insulin synthesis\(^{(24)}\).

On the other hand, whole body exposure of rats to gamma rays at a dose of 6 Gy induced hyperglycemia, hyperinsulinemia, and insulin resistance (similar to Type 2 DM). Hyperglycemia might result from the diminished utilization of glucose by irradiated tissues\(^{(40)}\), together with protein destruction and accelerated gluconeogenesis\(^{(41)}\). Hyperinsulinemia and insulin resistance might be attributed to radiation-induced damage to insulin receptor. Based on the fact that insulin receptor is a transmembrane receptor\(^{(42)}\), accordingly, radiation-induced lipid peroxidation verified in the current study by an increase of MDA will damage insulin receptor. Additionally, insulin receptor belongs to the large class of tyrosine kinase receptors\(^{(43)}\). Accordingly, radicals attack on tyrosine residues causes...
the formation of dityrosyl cross-links verified in the current study by an increase in the level of advanced oxidation protein products (AOPP) (34). Another explanation for insulin resistance is that adipocytes exposed to oxidative stress showed pro-inflammation and impaired insulin-stimulated glucose up-take (44).

The elevated AST and ALT activities, together with urea and creatinine levels recorded in the serum of γ-irradiated and STZ-treated rats in the current study, are probably due to the consequence of oxidative stress in the liver and kidney tissues. Oxidative stress induces cell membrane damage with the consequent release of their content to the blood stream (45). The significant decrease in the activity of antioxidant enzymes might result from a decrease in mRNA expressions thus reducing their synthesis (46,47), besides their increased utilization to neutralize the excess of free radicals generated in the body (46).

In the past five decades, the function of GABA in the CNS has been well documented. However, the presence of a GABAergic system within the pancreas as a potential target for treating diabetes mellitus emerged only recently. In α-cells, GABA induces membrane hyperpolarization and inhibits glucagon secretion, and this involves an insulin-mediated GABA receptor (GABA_R)-trafficking mechanism. In β-cells, GABA induces membrane depolarization and enhances insulin secretion. GABA also has beneficial effects on β-cell survival and regeneration, which results in enlarged β-cell mass (48). Furthermore, GABA suppresses insulitis and systemic inflammatory cytokine production (48). All these data hold promise for GABA therapy in regulating islet cell function, glucose homeostasis, and autoimmunity (48).

The administration of GABA (200 mg/Kg/day) to normal rats for 3 weeks had no significant effect on all of the parameters studied. The results corroborate previous findings that the chronic administration of GABA at up to 1g/kg/day in rats and dogs was well tolerated without signs of toxicity for a period of up to 1 year (49).

In the present study, the administration of GABA (200 mg/Kg/day) daily during a period of 3 weeks to STZ-treated rats improved insulin levels and hyperglycemia, supporting that GABA reverses hyperglycemia (50) and ameliorates impaired glucose metabolism (25). This could be attributed to the role of GABA in the regeneration of pancreatic cells where its interaction with GABA receptors in islet β-cells produces membrane depolarization and Ca^{2+} influx, leading to the activation of PI3-K/Akt-dependent growth and survival pathways, thus preserving β-cells (17,51). Moreover, GABA causes membrane depolarization and enhances insulin secretion (52). In addition, the action of GABA on the GABA receptors in the α-cells suppresses glucagon secretion (53) and hence reduced glucose level.

The administration of GABA (200 mg/Kg/day) daily during a period of 3 weeks to whole body gamma irradiated rat improved glucose and insulin levels and insulin resistance. The modulator role of GABA in insulin could be attributed to its antioxidant and free radical scavenging activities (18). This is based on the fact that the insulin receptor is a transmembrane receptor (44), consequently inhibition of membrane lipid peroxidation substantiated in the current study by a lower level of MDA compared to its corresponding level in irradiated rats not receiving GABA contribute to the improvement of insulin resistance. Moreover, minimizing radicals attack on tyrosine residues diminish the formation of dityrosyl cross-links verified in the current study by a lower level of AOPP compared to its respective value in irradiated rats not receiving GABA. The results corroborate previous findings that GABA improves insulin sensitivity (18). Antioxidants have been shown to improve insulin sensitivity (54), and the previous findings that insulin resistance is associated in humans with reduced intracellular antioxidant defense also support this hypothesis (55).

The improvement in liver and kidney functions observed in the present study may be attributed to the attenuation of oxidative stress in these tissues supporting the free radicals scavenging activities
of GABA (56), and its efficiency in inhibiting the formation of reactive carbonyl intermediates through its interaction with MDA to form different conjugated complexes (18).

According to the results obtained in the current study, the administration of GABA to irradiated as well as STZ-treated rats regulates insulin and glucose levels, minimizes oxidative stress and reduces the severity of liver and kidney damage. The improvement in tissue functions and oxidative markers are correlated with the degree of insulin correction. It could be concluded that GABA could be a useful adjunct to reduce some metabolic complications associated with insulin deficiency and insulin resistance.

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