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LETTER TO THE EDITOR

Intestinal glucagon-like peptide-1 in hypoglycemic counterregulation for type 1 diabetes management

Ke-Xin Zhang, Cheng-Xia Kan, Yu-Qun Wang, Ning-Ning Hou, Xiao-Dong Sun

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Abstract

Type 1 diabetes (T1D) is characterized by the autoimmune destruction of pancreatic beta cells, leading to absolute insulin deficiency and the need for exogenous insulin. A significant concern in T1D management is hypoglycemia, which is worsened by impaired counterregulatory mechanisms. Effective counterregulation involves hormones such as glucagon and adrenaline, which work to restore normal blood glucose levels. However, in T1D, these mechanisms often fail, particularly after recurrent hypoglycemia, resulting in hypoglycemia-associated autonomic failure. Recent research indicates that elevated levels of intestinal glucagon-like peptide-1 (GLP-1) impair counterregulatory responses by reducing the secretion of glucagon and adrenaline. This editorial underscores GLP-1's role beyond its incretin effects, contributing to impaired hypoglycemic counterregulation. This understanding necessitates a nuanced approach to GLP-1-based therapies in T1D, balancing the benefits of glycemic control with potential risks. Future research should delve into the mechanisms behind GLP-1's effects and explore potential interventions to improve hypoglycemic counterregulation. The goal is to enhance the safety and quality of life for T1D patients.

Key Words: Type 1 diabetes; Glucagon-like peptide-1; Hypoglycemia; Hypoglycemic counterregulation; Hormonal reaction

Core Tip: Elevated intestinal glucagon-like peptide-1 impairs hypoglycemic counterregulation in type 1 diabetes by reducing glucagon and adrenaline secretion. This highlights the need for a balanced approach to glucagon-like peptide-1-based therapies, considering both glycemic control and the risk of hypoglycemia.

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TO THE EDITOR

Diabetes is an increasing global health challenge, with a rising incidence of type 1 diabetes (T1D)[1,2]. T1D is a chronic condition characterized by the autoimmune destruction of insulin-producing beta cells in the pancreas, leading to an absolute insulin deficiency and a lifelong dependence on exogenous insulin therapy. Hypoglycemia remains a significant concern for patients with T1D due to the inherent risks associated with insulin therapy. Effective counterregulatory mechanisms are crucial for preventing and mitigating hypoglycemia. The body's natural counterregulatory responses to hypoglycemia involve the secretion of hormones such as glucagon and adrenaline, which are essential for restoring normoglycemia. However, in individuals with T1D, these counterregulatory mechanisms often become impaired, leading to a heightened risk of severe hypoglycemic episodes[3]. This impairment complicates disease management, making it challenging for patients to maintain stable blood glucose levels. Recent research by Jin *et al*[4] elucidates the role of intestinal glucagon-like peptide-1 (GLP-1) in these impaired counterregulatory responses. Understanding the function of GLP-1 in T1D opens new avenues for mitigating this critical issue, providing hope for improved therapeutic strategies involving GLP-1 treatment for T1D.

Hypoglycemic counterregulation is the body's defense mechanism to prevent and correct low blood glucose levels[5]. In healthy individuals, glucose homeostasis is achieved through a coordinated response to hypoglycemia[6]. This response triggers a complex hormonal reaction aimed at restoring normoglycemia, involving decreased insulin secretion and the release of glucagon, epinephrine, cortisol, and growth hormone[7]. Glucagon plays a crucial role by stimulating glycogen breakdown and glucose production in the liver, ensuring an adequate supply of glucose[8]. Simultaneously, adrenaline enhances glycogen breakdown and inhibits insulin secretion, further supporting the increase in blood glucose levels[9]. These mechanisms are vital for preventing severe hypoglycemia and its potentially dangerous consequences, such as confusion, seizures, coma, and death[10]. However, in individuals with T1DM, counterregulatory mechanisms often fail, especially after recurrent hypoglycemic episodes, leading to hypoglycemia-associated autonomic failure (HAAF)[10]. HAAF is marked by reduced or absent secretion of key hormones like glucagon and adrenaline during hypoglycemia and diminished symptoms, making it hard for patients to recognize and respond to low blood glucose. This increases the risk of severe hypoglycemic events. The pathophysiology of HAAF involves repeated hypoglycemia, autonomic nervous system dysfunction, and altered central nervous system responses, reducing the body's ability to sense and correct low glucose levels[11]. Understanding these mechanisms is essential for developing strategies to prevent HAAF and improve hypoglycemia management in T1DM patients.

GLP-1 is an incretin hormone that regulates blood sugar by enhancing insulin secretion and suppressing glucagon release[12]. It is produced by enteroendocrine L-cells in the intestines and acts through the GLP-1 receptor (GLP-1R), found in various tissues. GLP-1 slows gastric emptying and promotes satiety, aiding in weight management. These functions of GLP-1 have made it a target for therapeutic intervention in type 2 diabetes, where GLP-1R agonists and inhibitors of its degradation (by dipeptidyl peptidase-4) are used to improve glycemic control[13]. GLP-1R agonists have become first-line therapies for type 2 diabetes, providing both improved glycemic control and cardiovascular benefits, making them essential for managing the disease. However, its role in T1D is gaining interest. In T1D, the autoimmune destruction of beta cells leads to insulin deficiency and hyperglycemia[14]. While exogenous insulin is the main treatment, achieving optimal glucose control remains challenging due to the risks of hypoglycemia and glucose variability. GLP-1R agonists are being explored as adjunct therapies in T1D[15]. Studies suggest that GLP-1R agonists can improve glycemic control, reduce insulin requirements, and aid in weight management[16]. They might also exert beta-cell protective effects, although this is more relevant in early or latent autoimmune diabetes in adults, where some beta-cell function persists[17]. Additionally, GLP-1 has potential cardiovascular benefits, which is crucial given the increased cardiovascular risk in T1D patients[18]. The impact of GLP-1 on glucagon secretion might help mitigate the inappropriate glucagon release observed in T1D, thus improving glucose stability. Overall, while not a replacement for insulin therapy, GLP-1 and its analogs hold promise as complementary treatments in T1D, contributing to better overall metabolic control and potentially offering protective effects against diabetes complications.

In the context of T1D, the role of GLP-1 extends beyond its incretin effects. The study by Jin *et al*[4] reveals a more complex role for GLP-1 in relation to hypoglycemia. By inducing recurrent hypoglycemia in T1DM mice, the researchers observed a significant increase in both intestinal GLP-1 and GLP-1R expression. This elevated GLP-1 appears to impair the body's natural counterregulatory responses to hypoglycemia, specifically by reducing the secretion of glucagon and adrenaline. This impairment is a significant concern in T1D, as it leads to hypoglycemia unawareness and an increased risk of severe hypoglycemic episodes.

The study identifies several key mechanisms by which elevated intestinal GLP-1 contributes to impaired hypoglycemic counterregulation. Excessive GLP-1 weakens the sympathetic-adrenal reflex, a critical pathway for the release of adrenaline and noradrenaline during hypoglycemia, as evidenced by decreased levels of these hormones in the plasma and pancreas of mice subjected to recurrent hypoglycemia. Additionally, the study highlights the endocrine effects of GLP-1 on the pancreas: Elevated GLP-1 levels enhance the secretion of somatostatin (SST) from pancreatic δ cells, which in turn inhibits the release of glucagon from α cells. This mechanism is supported by increased pancreatic δ-cell mass,

higher cAMP levels in δ cells, and elevated plasma SST concentrations. A corresponding reduction in cAMP levels in α cells further confirms the decreased glucagon secretion in response to recurrent hypoglycemia.

These findings have profound implications for the management of T1DM. While GLP-1 and its analogs offer substantial benefits in glycemic control, their role in hypoglycemic counterregulation necessitates a more nuanced approach. Excessive GLP-1 activity, particularly in the context of recurrent hypoglycemia, may exacerbate the risk of severe hypoglycemic episodes by impairing the body's natural hormonal defenses. Clinicians must carefully consider the dosing and administration of GLP-1-based therapies in T1D patients. Monitoring GLP-1 Levels and adjusting treatment regimens to avoid excessive GLP-1 activity could help mitigate the risk of impaired counterregulatory responses. This approach requires a delicate balance to harness the benefits of GLP-1 while minimizing its potential adverse effects on hypoglycemia management.

Jin *et al*'s study underscores the critical role of intestinal GLP-1 in impaired counterregulatory responses to hypoglycemia in T1D[4]. While GLP-1 and its analogs remain valuable for diabetes management, their impact on hypoglycemic counterregulation highlights the need for careful use. Balancing the benefits of GLP-1 therapy with potential risks requires a nuanced approach that considers the complex hormonal interplay during hypoglycemia. Investigating the precise mechanisms by which GLP-1 modulates the sympathetic-adrenal reflex and endocrine pathways in the pancreas could provide deeper insights into its role in hypoglycemic counterregulation. Furthermore, exploring potential therapeutic interventions to counteract the negative effects of excessive GLP-1 may lead to more effective strategies for managing hypoglycemia in T1D.

The management of T1D is complex due to the significant risk of hypoglycemia and the impaired counterregulatory responses seen in many patients. Understanding the roles of hormones like glucagon, adrenaline, and GLP-1 in these processes is essential for developing more effective treatment strategies. Continued research in this area holds promise for improving the quality of life for individuals with T1D by potentially offering new ways to mitigate the risk of hypoglycemia.

FOOTNOTES

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