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LETTER TO THE EDITOR

Intestinal glucagon-like peptide-1: A new regulator of impaired counterregulatory responses to hypoglycemia in type 1 diabetes mellitus

Le-Rong Liu, Yuan-Yuan Luo, Pei-Zhu Su, Cong Zhang, Zhao-Tao Li

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Abstract

In this article, we review the study by Jin *et al*, which examined the role of intestinal glucagon-like peptide-1 (GLP-1) in counterregulatory responses to hypoglycemia in patients with type 1 diabetes mellitus (T1DM). With the global rise of T1DM, there is an increased burden on society and healthcare systems. Due to insulin therapy and islet dysfunction, T1DM patients are highly vulnerable to severe hypoglycemia, a leading cause of mortality. In healthy individuals, counterregulatory mechanisms restore blood glucose during hypoglycemia, but repeated episodes impair these responses. Jin *et al* demonstrated that overexpression of GLP-1 attenuates the sympathetic-adrenal reflex and disrupts the secretion of counterregulatory hormones such as glucagon during hypoglycemia, leading to counterregulatory dysfunction. These findings highlight the critical role of GLP-1 in the impaired counterregulatory response to hypoglycemia in T1DM patients and provide new insights into the potential application of GLP-1-related

therapies in T1DM patients.

Key Words: Glucagon-like peptide-1; Impaired counterregulation; Type 1 diabetes mellitus; Sympathetic-adrenal reflex; Glucagon

Core Tip: Jin *et al* reported that excessive intestinal glucagon-like peptide-1 (GLP-1) exacerbates impaired counterregulatory responses in individuals with type 1 diabetes mellitus (T1DM). By elucidating the molecular mechanisms through which GLP-1 disrupts the sympathetic-adrenal reflex and inhibits glucagon secretion, the authors explored the significant role of GLP-1 in counterregulatory failure. Further research is needed to understand the potential impact of GLP-1 and its analogs on counterregulatory responses in T1DM patients and to evaluate their prospects as adjunctive treatments for preventing and treating hypoglycemia in patients with diabetes.

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TO THE EDITOR

Type 1 diabetes mellitus (T1DM) is a severe chronic metabolic disorder characterized by insufficient insulin secretion leading to hyperglycemia. T1DM patients not only experience hyperglycemia but also frequently suffer from iatrogenic hypoglycemia due to treatment with exogenous insulin[1]. Studies have shown that approximately 40% of T1DM patients experience severe hypoglycemic events[2], which can lead to coma, seizures, and even death[3]. In healthy individuals, the body initiates counterregulatory responses to restore blood glucose levels during hypoglycemia. However, repeated hypoglycemic episodes, such as those that occur within a day or over consecutive days and last more than 30 minutes each, can impair counterregulatory function, preventing timely glucose recovery and resulting in severe clinical consequences. Impaired counterregulatory responses are relatively reversible and are closely related to decreased glucagon (GCG) secretion and impaired sympathetic nerve excitation[4]. Understanding the mechanisms underlying impaired counterregulation is crucial for improving the prognosis of T1DM patients. Jin *et al*[5] revealed the critical role and molecular mechanisms of excessive GCG-like peptide-1 (GLP-1) in this process[5].

THE IMPACT OF GLP-1 ON COUNTERREGULATORY RESPONSES TO HYPOGLYCEMIA

GLP-1 receptor agonists and their analogs have become pivotal in the treatment of type 2 diabetes mellitus (T2DM) due to their superior glucose-lowering efficacy, significant weight reduction benefits, and associated cardiovascular and renoprotective effects[6,7]. GLP-1 exerts its effects by binding to its receptor (GLP-1R), delaying gastric emptying, reducing intestinal motility, and promoting satiation[6]. In addition, the efficacy and safety of GLP-1 agonists in pediatric T2DM patients have been demonstrated[8]. In recent years, studies have explored the use of GLP-1 receptor agonists as adjunctive therapies for T1DM[9,10]. Jin *et al*[5] investigated the role of GLP-1 in counterregulatory responses to hypoglycemia in T1DM patients, providing new risk-based evidence for the use of GLP-1-related drugs in T1DM treat-ment.

In this study, a T1DM hypoglycemia murine model was created through STZ intraperitoneal injection and subcutaneous insulin injection, increasing the frequency of hypoglycemic episodes to five times to establish a stable model. By monitoring the activity and plasma adrenaline and norepinephrine levels of the mice, the degree of impaired counterregulation was assessed. The results revealed that the mouse model with repeated episodes of hypoglycemia (repeated-episode hypoglycemia) exhibited impaired counterregulation, with significantly greater numbers and higher expression levels of GLP-1-positive cells when compared with the normal and single-episode hypoglycemia model groups, suggesting that GLP-1 upregulation may be associated with impaired counterregulation. In future studies, a gradient of hypoglycemic episodes should be created to observe the effects of different episode frequencies on mice and the subsequent trends in molecular changes.

MECHANISMS OF GLP-1 REGULATION IN IMPAIRED COUNTERREGULATION

To clarify the role and mechanisms of GLP-1 in impaired counterregulation, this study compared plasma adrenaline and norepinephrine levels in repeated-episode hypoglycemic mice with those in single-episode hypoglycemic mice. Notably, appropriate levels of GLP-1 activate the autonomic sympathetic nervous system, increasing sensitivity to hypoglycemia,

whereas GLP-1 overexpression does not significantly activate the sympathetic nervous system. Repeated-episode hypoglycemic mice presented increased levels of GLP-1 and GLP-1R expression but reduced hypoglycemic regulatory ability, which may be related to the overactivation of the sympathetic-adrenal reflex.

Impaired counterregulation is related not only to the sympathetic nervous system but also to GCG levels. Further experiments revealed that single-episode hypoglycemic mice had significantly elevated GCG levels, whereas repeated-episode hypoglycemic mice had significantly decreased GCG levels. These findings indicate that changes in GCG secretion are regulated through endocrine rather than paracrine pathways by GLP-1.

EFFECTS OF GLP-1 ON PANCREATIC δ-CELL FUNCTION AND α-CELL SECRETION

In T1DM patients, the number of pancreatic β-cells is reduced, and GLP-1R is mainly concentrated in δ-cells. GLP-1 acts on pancreatic δ-cells through endocrine pathways, increasing GLP-1R expression and promoting somatostatin (SST) secretion. SST then inhibits the secretion of GCG by adjacent pancreatic α-cells through paracrine effects. Therefore, excessive GLP-1 caused by repeated episodes of hypoglycemia may ultimately lead to decreased secretion of the counter-regulatory hormone GCG.

POTENTIAL THERAPEUTIC IMPLICATIONS AND RISKS OF GLP-1 AND ITS RECEPTOR AGONISTS IN T1DM

Jin *et al*'s study[5] focused mainly on counterregulatory responses to hypoglycemia, extending its findings to broader aspects of T1DM management. Currently, insulin is the primary glucose-lowering drug for T1DM patients, with GLP-1 receptor agonists used as potential therapeutic drugs, especially for patients who are overweight or obese and not at glycemic goals despite aggressive insulin therapy[11]. The application of GLP-1 receptor agonists in patients with T1DM is still limited and focuses primarily on reducing cardiovascular and renal risks, glycemic variability, and the insulin dosage[10,12,13]. Randomized controlled trials of the GLP-1 receptor agonist liraglutide 1.8 mg in individuals with type 1 diabetes and a higher body mass index demonstrated reductions in HbA1c, body weight, and insulin requirements without an increased risk of hypoglycemia[14]. A meta-analysis of 24 studies involving various GLP-1 analogs, with a total of 3377 participants, revealed that liraglutide had the most substantial evidence with effect sizes of HbA1c (-0.09%/mg), weight (-2.2 kg/mg), and total daily insulin (-4.32 IU/mg). The odds of severe (OR 0.67; 95%CI: 0.43-1.04) or symptomatic hypoglycemia (OR 0.89; 95%CI: 0.53-1.51) were not significantly elevated[13]. However, the results from a study on weekly exenatide in individuals with T1DM who are overweight and have detectable levels of C-peptide showed similar improvements, but these benefits were short-lived and not maintained long term[15].

This study suggests that excessive use of GLP-1 analogs in T1DM patients may exacerbate impaired counterregulatory responses. However, this conclusion requires further validation in larger and more diverse populations to assess the effectiveness and safety of GLP-1-based therapies in different populations. Similarly, another study has shown that in T2DM, GLP-1 receptor agonists affect counterregulatory responses to hypoglycemia[16]. These studies highlight the need for clinicians to be aware of potential adverse reactions to GLP-1 or its receptor agonists in diabetes mellitus patients and to use these agents with caution. GLP-1 receptor agonists are not currently recommended as a standard treatment option for patients with T1DM in clinical practice. A notable limitation of the study is that the conclusions are based on preclinical data, which may only partially translate to human T1DM patients. Future research should focus on clinical trials to validate these findings in human populations. This manuscript would benefit from discussing the long-term safety and efficacy of GLP-1-based therapies in T1DM, particularly regarding their impact on counterregulatory mechanisms. Additionally, combining GLP-1 modulators with other treatments could provide a more comprehensive approach to managing T1DM, addressing both hyperglycemia and hypoglycemia risks.

LONG-TERM RESEARCH

Proteomics and metabolomics are recommended for studying GLP-1 target sites and exploring the role and mechanisms of GLP-1 in impaired hypoglycemic regulation from a deeper perspective. While this study mainly uses phenotypic research to explore molecular relationships, it is suggested that future studies delve deeper into the interaction and expression regulation of GLP-1, SST, and GCG to fully evaluate the safety of GLP-1 receptor agonists in T1DM.

CONCLUSION

Jin *et al*[5] reported that excessive intestinal GLP-1 expression may lead to impaired counterregulatory responses to hypoglycemia. While these preclinical findings provide important theoretical support, further clinical studies are needed for validation. Additionally, appropriate levels of GLP-1 may improve counterregulatory responses to hypoglycemia. Future research should explore whether there is a more suitable dosage or drug formulation of GLP-1 analogs that can stabilize blood glucose, protect cardiovascular and renal health, and enhance hypoglycemic counterregulation. These

findings may help to elucidate the potential and safety of GLP-1 and its receptor agonists in the treatment of T1DM.

FOOTNOTES

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