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ABOUT COVER

Peer Review of *World Journal of Diabetes*, Dimiter Avtanski, PhD, Director, Endocrine Research Laboratory, Friedman Diabetes Institute, Lenox Hill Hospital, New York, NY 10022, United States. davtanski@northwell.edu

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LETTER TO THE EDITOR

Role of intestinal glucagon-like peptide-1 in hypoglycemia response impairment in type 1 diabetes

Chun-Han Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

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Abstract

This study critically examines the novel findings presented by Jin *et al*, which explores the role of intestinal glucagon-like peptide-1 (GLP-1) in impaired counterregulatory responses to hypoglycemia in mice with type 1 diabetes. The study identifies intestinal GLP-1 as a significant determinant in the physiological responses to hypoglycemia, offering new insights into its potential implications for diabetes management. The editorial synthesizes these findings, discusses their relevance in the context of current diabetes research, and outlines potential avenues for future investigation of intestinal GLP-1 as a therapeutic target. This analysis underscores the need for continued research into the complex mechanisms underlying impaired hypoglycemia responses and highlights the potential of targeting intestinal GLP-1 pathways in therapeutic strategies for type 1 diabetes.

Key Words: Intestinal glucagon-like peptide-1; Type 1 diabetes; Hypoglycemia; Counterregulatory response; Mouse model

Core Tip: Intestinal glucagon-like peptide-1 is identified as a key factor in modulating counterregulatory responses to hypoglycemia in type 1 diabetes. Gaining a deeper understanding of its role may lead to the development of innovative therapeutic strategies for enhancing hypoglycemia management in patients with diabetes.

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TO THE EDITOR

The role of glucagon-like peptide-1 (GLP-1) in metabolic regulation has garnered considerable attention in recent research, particularly concerning its involvement in glucose homeostasis and potential implications for diabetes management. Jin *et al*'s study[1], published in the *World Journal of Diabetes*, introduces a novel perspective by identifying intestinal GLP-1 as a critical factor in the impaired counterregulatory responses to hypoglycemia observed in type 1 diabetic mice. This editorial aims to synthesize and expand on Jin *et al*'s findings[1], exploring mechanistic insights into how intestinal GLP-1 influences hypoglycemia responses. Recent studies have underscored the substantial influence of GLP-1 on various metabolic processes. For instance, GLP-1 receptor agonists have demonstrated promise in the management of type 2 diabetes and obesity-related conditions, suggesting broader therapeutic potential[2]. Additionally, the pivotal role of GLP-1 in the gut–liver axis and the management of metabolic dysfunction–associated fatty liver disease were demonstrated[3]. However, Jin *et al*'s study offers crucial insights into the specific role of intestinal GLP-1 in type 1 diabetes, with a particular focus on hypoglycemia management[1]. By exploring these mechanisms, this editorial aims to highlight the clinical relevance and potential therapeutic implications of targeting intestinal GLP-1 pathways in improving hypoglycemia management strategies for individuals with type 1 diabetes. A deeper understanding of how intestinal GLP-1 influences counterregulatory responses to hypoglycemia could pave the way for novel interventions designed to enhance glycemic control and reduce the risk of hypoglycemia. This discussion underscores the critical need for further research to elucidate the role of intestinal GLP-1 in the pathophysiology of diabetes and its broader implications for diabetes care.

Intestinal GLP-1 and hypoglycemia response

Jin *et al*[1] offers an in-depth analysis of the role of GLP-1 in the regulation of hypoglycemia responses in type 1 diabetic mice, with a particular emphasis on the hormone's complex involvement in glucose homeostasis beyond its conventional incretin effect. This study is particularly notable in its insights into how intestinal GLP-1 influences counterregulatory responses, which are crucial for preventing severe hypoglycemia, a common complication in diabetes management. Jin *et al*[1] employed genetically modified mouse models that lack GLP-1 receptors specifically in the intestine, thereby enabling the precise isolation of the effects of intestinal GLP-1 from those of other sources of GLP-1. These mice were subjected to induced hypoglycemic episodes, during which their blood glucose levels were continuously monitored. The use of continuous glucose monitoring systems (CGMS) was a notable methodological strength, because it provided real-time data on glucose fluctuations, facilitating a detailed temporal analysis of the counterregulatory mechanisms involved. To corroborate their *in vivo* findings, Jin *et al*[1] conducted *in vitro* experiments by using isolated intestinal tissues to assess GLP-1 secretion in response to various glucose concentrations. The quantification of GLP-1 Levels was achieved through enzyme-linked immunosorbent assays, a technique known for its high sensitivity and accuracy in detecting hormonal changes. Additionally, advanced imaging techniques, including immunohistochemistry, were employed to visualize the distribution of GLP-1 receptors within the intestinal mucosa, offering insights into the cellular mechanisms through which GLP-1 may modulate hypoglycemia responses. This study's analytical approach involved the use of repeated-measures analysis of variance and multivariate regression analysis to control for potential confounding variables, such as age, sex, and baseline glucose levels. This rigorous statistical framework ensured that the observed effects were directly attributable to the modulation of intestinal GLP-1, rather than external factors. Moreover, Jin *et al*[1] compared their findings with those of other incretin hormones like GIP, which further reinforced the unique role of GLP-1 in glucose regulation. The implications of these findings are substantial, particularly regarding the development of new therapeutic strategies aimed at enhancing glycemic control in diabetes. By targeting the specific pathways through which intestinal GLP-1 influences glucose levels, the management of hypoglycemia can be improved in patients with type 1 diabetes. This approach is consistent with recent advances in GLP-1 receptor agonist therapies, which have demonstrated efficacy not only in type 2 diabetes but also in the management of obesity and other metabolic disorders[2,4]. The study by Jin *et al*[1] thus lays a critical foundation for future research into the broader applications of GLP-1 in diabetes treatment, potentially leading to more effective and safer interventions for managing hypoglycemia in patients with diabetes.

Mechanisms underlying GLP-1's role

This editorial examines the intricate mechanisms through which intestinal GLP-1 influences hypoglycemia counter regulation. Jin *et al*[1] suggested that alterations in GLP-1 signaling pathways in the intestine may disrupt the sympathetic and hormonal responses critical for glucose recovery during hypoglycemic episodes. This disruption underscores the

need for further investigation to identify the precise signaling pathways and molecular targets that mediate GLP-1's role in hypoglycemia counter regulation. A thorough understanding of these mechanisms is essential for the development of targeted therapies aimed at enhancing glucose management in patients with diabetes[1,5]. This research is pivotal as it may offer insights into more effective treatments for maintaining glucose levels and preventing severe hypoglycemia in individuals with diabetes. Recent advances in diabetes research have highlighted the complexity of the role of GLP-1 in glucose homeostasis. GLP-1 receptor agonists, which are commonly used in the treatment of type 2 diabetes, have demonstrated promise in improving glycemic control by enhancing insulin secretion and inhibiting glucagon release[4,6]. However, the influence of GLP-1 on hypoglycemia counter regulation presents a paradox because its beneficial effects on glucose regulation may inadvertently impair the body's natural responses to low blood sugar levels. The interplay between GLP-1 and the autonomic nervous system is particularly noteworthy. GLP-1 is known to influence the central nervous system, which plays a critical role in mediating counterregulatory responses during hypoglycemia[7]. Alterations in GLP-1 signaling can affect neurotransmitter release and neuronal activity, potentially leading to inadequate hormonal responses necessary for glucose recovery. This underscores the importance of investigating the neural pathways modulated by GLP-1 and their contributions to hypoglycemia unawareness. Moreover, the hormonal aspect of the action of GLP-1 involves its interaction with glucagon and other counterregulatory hormones. Although the inhibition of glucagon secretion by GLP-1 is beneficial for controlling hyperglycemia, it may also hinder the rapid glucagon release required during hypoglycemic episodes[3]. This dual role of GLP-1 necessitates a balanced approach in therapeutic applications to prevent adverse effects on hypoglycemia management. Further research into the molecular targets of GLP-1 could reveal potential interventions for mitigating its impact on hypoglycemia counter regulation. Identifying specific receptors and downstream signaling molecules involved in GLP-1-mediated pathways could lead to the development of selective modulators that preserve the hormone's glycemic benefits while minimizing risks associated with hypoglycemia[8]. Such advancements could foster the creation of next-generation GLP-1 therapies tailored to enhance patient safety and treatment efficacy. Overall, although GLP-1 plays a crucial role in diabetes management, its implications for hypoglycemia counter regulation present a complex challenge. Continued investigation into the mechanisms underlying the effects of GLP-1 on sympathetic and hormonal responses is essential for optimizing diabetes therapies and improving patient outcomes. The elucidation of the intricate pathways involved can facilitate the development of innovative treatments that harness the full potential of GLP-1 while minimizing hypoglycemia-related risks[1,2].

Clinical implications and therapeutic potential

The study by Jin *et al*[1] offers a significant advancement in understanding the role of intestinal GLP-1 in diabetes management, particularly regarding hypoglycemia unawareness and impaired counterregulatory responses. This research underscores the therapeutic potential of modulating GLP-1 activity to enhance physiological responses to hypoglycemia. As GLP-1 receptor agonists continue to gain prominence as a cornerstone in diabetes treatment, this study underscores the need for future clinical trials to investigate GLP-1-based interventions that could complement existing therapies, thereby improving patient outcomes and quality of life. Jin *et al*'s investigation into the alterations of GLP-1 signaling and its impact on glucose regulation offers a promising strategy for restoring impaired counterregulatory responses to hypoglycemia in patients with diabetes[1]. This is particularly relevant in the context of current diabetes treatments, which presents challenges due to the risk of hypoglycemia. The targeted modulation of GLP-1 activity, as suggested by Jin *et al*[1], could play a crucial role in enhancing patient safety and improving the efficacy of diabetes management. The therapeutic potential of GLP-1 receptor agonists is well established, particularly in the treatment of type 2 diabetes, obesity, and metabolic dysfunction. However, the effects of these agents on hypoglycemia counter regulation require further investigation. Studies by Sohn *et al*[4] and Yanto *et al*[9] provide additional insights into the broader metabolic effects of GLP-1 receptor agonists, suggesting that these agents may influence not only glucose regulation but also long-term outcomes related to renal and cardiovascular health. These findings are consistent with the conclusions drawn by Jin *et al*[1], reinforcing the importance of understanding the full range of GLP-1's physiological roles. Moreover, the interaction between GLP-1 receptor agonists and other diabetes treatments, such as SGLT2 inhibitors, further complicates the therapeutic landscape. Mann *et al*[10] demonstrated that combining these therapies could potentially enhance their effectiveness, particularly in patients with chronic kidney disease, a common comorbidity in diabetes. This combination approach may improve glycemic control as well as reduce the risk of hypoglycemia, which is a critical consideration highlighted by Jin *et al*[1] in their study. Jin *et al*'s study thus provides a valuable foundation for future investigations into the role of GLP-1 in diabetes management[1]. By expanding our understanding of how GLP-1 modulation can improve hypoglycemia counter regulation, this study opens new avenues for therapeutic development. Integrating findings from other studies, such as those by Yanto *et al*[9] and Mann *et al*[10], further supports the potential of GLP-1-based therapies in enhancing patient outcomes, particularly in complex cases where multiple comorbidities are present.

To advance the understanding and application of GLP-1-based therapies in diabetes management, future research should prioritize an integrated approach that combines mechanistic studies and clinical trials. Mechanistic research is essential for elucidating the specific pathways through which GLP-1 receptor agonists influence glucose homeostasis, particularly in the context of hypoglycemia unawareness and impaired counterregulatory responses[1]. Investigations should focus on the interaction between GLP-1 signaling and other metabolic pathways, such as gut–liver crosstalk, which plays a crucial role in metabolic dysfunction–associated fatty liver disease[3]. Clinical trials should be designed to evaluate the efficacy and safety of GLP-1 receptor agonists across diverse patient populations, including those with varying degrees of renal impairment. Recent studies have underscored the importance of understanding long-term renal and metabolic outcomes associated with these therapies[4]. Moreover, the integration of GLP-1-based therapies with advanced diabetes management technologies, such as CGMS and automated insulin delivery systems, could enhance

personalized care. This approach aligns with the growing emphasis on delivering tailored treatments, particularly in specific populations such as pregnant women, where the right technology must be provided at the right time[8]. Additionally, exploring the potential of GLP-1 receptor agonists in mitigating cancer risks associated with obesity in patients with type 2 diabetes is crucial. Emerging evidence suggests that these therapies may be linked to a lower incidence of cancer[2]. Overall, continued research into both the mechanistic roles and clinical applications of GLP-1 is essential for maximizing its therapeutic potential. This will ultimately lead to improved outcomes and quality of life for individuals with diabetes.

CONCLUSION

In conclusion, the study by Jin *et al*[1] represents a pivotal advancement in understanding the role of intestinal GLP-1 in disrupting counterregulatory responses to hypoglycemia in type 1 diabetic mice. By exploring the mechanisms through which intestinal GLP-1 influences glucose homeostasis and hypoglycemia responses, this research highlights the complex and multifaceted nature of GLP-1 signaling, extending beyond its well-established role in insulin secretion. The findings of this study suggest new therapeutic possibilities that target intestinal GLP-1 pathways to enhance hypoglycemia awareness and responsiveness in patients with diabetes. Further research is necessary to clarify the specific signaling pathways and molecular interactions that underlie GLP-1-mediated effects on hypoglycemia responses. Clinical trials focusing on GLP-1 agonists or antagonists could provide critical insights into their effectiveness in modulating hypoglycemia outcomes and improving diabetes management[4]. Additionally, the integration of these insights into personalized treatment protocols could reduce the incidence of hypoglycemic episodes and optimize glucose control for individuals with diabetes. This editorial underscores the necessity for ongoing research to fully harness the therapeutic potential of targeting intestinal GLP-1 in diabetes care. A deeper understanding of the role of GLP-1 in hypoglycemia regulation could lead to innovative treatment strategies, ultimately improving clinical outcomes and the quality of life for patients with type 1 diabetes. Continued exploration of the complexities of GLP-1 signaling and its broader implications is essential for substantial progress in diabetes management[3,6].

FOOTNOTES

Author contributions: Cheng CH and Hao WR contribute equally to this study as co-first authors. Cheng CH, Hao WR, and Cheng TH have contributed to this study, with Cheng CH and Hao WR primarily responsible for writing, and Cheng TH overseeing revisions; all authors have read and approved the final manuscript.

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