

Orchestrating Metabolic Homeostasis: The Role of Gut Hormones in Next-Generation Therapies for Metabolic Syndrome

Tamer A. Addissouky^{1,2,3,4}

¹Department of Biochemistry, Science Faculty, AL-Mustaqbal University, 51001, Hillah, Babylon, Iraq.

²New burg El-Arab Hospital, Ministry of Health, Alexandria, Egypt.

³Department of Chemistry, Science Faculty, Menoufia University, Menoufia, Egypt.

⁴American Society for Clinical Pathology (ASCP), Chicago, USA.

Abstract

Metabolic disorders, including obesity and type 2 diabetes, have reached epidemic proportions globally, necessitating novel therapeutic approaches. The gut-brain axis, particularly gut hormones, plays a crucial role in metabolic regulation, offering promising targets for intervention.

This review aims to synthesize current knowledge on gut hormone-based therapies for metabolic disorders, focusing on their mechanisms of action and therapeutic potential.

Gut hormones, including GLP-1, GIP, PYY, ghrelin, and oxyntomodulin, orchestrate complex physiological responses to nutrient intake, influencing insulin secretion, appetite, and energy expenditure. Recent advancements in incretin-based therapies, particularly GLP-1 receptor agonists and dual GLP-1/GIP agonists, have shown remarkable efficacy in improving glycemic control and promoting weight loss. These therapies exploit the synergistic actions of multiple gut hormones, offering a more comprehensive approach to metabolic regulation. Emerging research on PYY analogs and ghrelin antagonists further expands the therapeutic landscape. However, challenges remain in optimizing delivery methods, ensuring long-term efficacy, and mitigating potential side effects.

Gut hormone-based therapies represent a paradigm shift in the management of metabolic disorders. By harnessing the intricate signaling networks of the gut-brain axis, these innovative approaches offer the potential for more effective and targeted interventions in obesity and type 2 diabetes, paving the way for personalized treatment strategies in metabolic medicine.


Keywords: Gut-brain axis, Incretin mimetics, Metabolic syndrome, GLP-1/GIP co-agonists, Enteroendocrine signaling

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Corresponding Author:

Tamer A. Addissouky, Department of Biochemistry, Science Faculty, AL-Mustaqbal University, 51001, Hillah, Babylon, Iraq.

Email: tedesoky@science.menofia.edu.eg

Orcid ID: 0000-0003-3797-9155

Tell: (20) 106 640 1396

Introduction

O *verview of metabolic disorders* Metabolic disorders encompass a wide range of conditions, primarily characterized by disruptions in normal metabolic processes. These disorders often involve dysregulation of glucose and lipid metabolism, leading to conditions such as obesity, type 2 diabetes (T2D), and metabolic syndrome (1,2). Obesity is a key driver of various metabolic disorders and is associated with excess adiposity that affects insulin sensitivity and glucose homeostasis. Type 2 Diabetes results from insulin resistance and pancreatic β -cell dysfunction, leading to chronic hyperglycemia. Metabolic syndrome is a clustering of metabolic abnormalities, including central obesity, dyslipidemia, hypertension, and insulin resistance, which together heighten the risk for cardiovascular diseases and T2D (3-5).

The burden of metabolic disorders is staggering, with obesity and T2D reaching epidemic proportions globally. According to the World Health Organization (WHO), over 650 million adults are obese, and the prevalence of diabetes has nearly quadrupled since 1980, affecting over 422 million people worldwide. This surge in metabolic disorders has placed an immense strain on healthcare systems, leading to a rise in comorbidities like cardiovascular disease, kidney failure, and premature mortality (6-11).

Current therapeutic strategies for metabolic disorders, such as lifestyle modifications and pharmacological interventions, have been moderately effective but there are poor long-term adherence, side effects, and lack of sustained efficacy. Thus, there is a pressing need for novel therapeutic approaches that can more effectively target the underlying pathophysiology of these conditions, offering better long-term outcomes with fewer adverse effects (12).

Importance of Gut Hormones in metabolic regulation

The gut-brain axis refers to the complex bidirectional communication between the gastrointestinal (GI) system and the central nervous system (CNS), playing a crucial role in regulating energy intake, nutrient absorption, and glucose homeostasis. Central to this communication are gut hormones, which secreted by enteroendocrine cells in response to nutrient intake and act as key signaling molecules in metabolic regulation (13-15). Gut hormones, including GLP-1, GIP, PYY, ghrelin, and oxyntomodulin, are critical mediators of energy homeostasis, influencing processes such as insulin secretion, appetite control, and gastric emptying. These hormones interact with receptors in both the brain and peripheral tissues, orchestrating a finely tuned response to food intake and energy expenditure. For example, GLP-1, secreted by the L-cells of the small intestine, enhances insulin secretion and reduces appetite, making it a promising target for therapeutic intervention (16-17). Given their pivotal role in metabolic regulation, gut hormone-based therapies have emerged as a novel therapeutic avenue for addressing metabolic disorders. These therapies aim to harness or modulate the activity of gut hormones to improve glucose control, promote weight loss, and restore metabolic balance. This innovative approach holds great potential, particularly in the context of the limitations of current treatments for obesity and T2D (18).

Key Gut Hormones in metabolism

Glucagon-Like Peptide-1 (GLP-1)

Glucagon-like peptide-1 (GLP-1) is a key incretin hormone that significantly influences metabolic processes. It secretes by the intestinal L-cells in response to food intake and plays a critical role in enhancing insulin secretion from pancreatic β -cells in a glucose-dependent manner. This action is crucial in maintaining glucose homeostasis, especially

postprandial. Additionally, GLP-1 delays gastric emptying, thereby contributing to satiety and appetite regulation, making it a vital hormone in the context of obesity and weight management (19-21). The therapeutic potential of GLP-1 realized with the development of GLP-1 receptor agonists such as liraglutide and semaglutide, which mimic the effects of endogenous GLP-1. These agents have demonstrated significant benefits in improving glycemic control, promoting weight loss, and reducing cardiovascular risk in patients with T2D and obesity. Their ability to address multiple facets of metabolic dysregulation has made them a cornerstone in the treatment of metabolic disorders (22-28).

Glucose- Dependent Insulinotropic Polypeptide (GIP)

Glucose-dependent insulinotropic polypeptide (GIP) is another incretin hormone secreted by the K-cells of the small intestine in response to nutrient ingestion. It stimulates insulin secretion in a glucose-dependent manner, similar to GLP-1, but also plays a unique role in lipid metabolism, promoting fat storage in adipose tissue. This dual role has made GIP a subject of intense research, particularly in understanding its contribution to obesity and insulin resistance (29). Recent advancements have highlighted the potential of dual incretin therapies that combine the effects of GLP-1 and GIP. GLP-1/GIP co-agonists, such as tirzepatide, have shown promising results in promoting superior glycemic control and weight loss compared to GLP-1 agonists alone. These combination

therapies may offer a more comprehensive approach to treating metabolic disorders by targeting multiple pathways involved in glucose and lipid metabolism (30-35).

Peptide YY (PYY)

Peptide YY (PYY) is a hormone predominantly secreted by the L-cells in the distal gut, particularly after meals. PYY plays a critical role in appetite suppression and energy balance by acting on receptors in the brain, particularly in the hypothalamus, to reduce food intake. It also slows gastric motility, enhancing the feeling of fullness and reducing subsequent calorie consumption. PYY interacts synergistically with other gut hormones, such as GLP-1, to regulate appetite and energy homeostasis. Its potential as a therapeutic target for obesity, with research focusing on PYY-based interventions, such as PYY analogs and PYY-enhancing strategies. However, challenges remain in optimizing its delivery and ensuring sustained efficacy in reducing body weight (36,37).

Ghrelin

Ghrelin, often referred to as the "hunger hormone," secreted primarily by the stomach and plays a fundamental role in stimulating appetite as presented in Table 1. It acts on the hypothalamus to promote hunger and increase food intake, making it a key player in energy homeostasis. Ghrelin levels rise before meals and fall after eating, closely aligning with hunger sensations. Therapeutically, ghrelin antagonists investigated as potential agents for weight loss.

Table 1. Comparison of key gut hormones in metabolic regulation

| Gut Hormone | Primary Site of Secretion | Main Physiological Actions | Therapeutic Potential | Current/Potential Drug Examples |
|----------------------|----------------------------|---|--|---|
| GLP-1 | L-cells of small intestine | Enhances insulin secretion Reduces appetite Delays gastric emptying | Glycemic control Weight loss Cardiovascular protection | Liraglutide, Semaglutide |
| GIP | K-cells of small intestine | Stimulates insulin secretion Promotes fat storage | Glycemic control Potential for weight gain (limitation) | Tirzepatide (in combination with GLP-1) |
| PYY | L-cells of distal gut | Suppresses appetite Slows gastric motility | Weight loss | PYY analogs (in development) |
| Ghrelin | Stomach | Stimulates appetite Increases food intake | Weight gain (in cachexia) Weight loss (via antagonists) | Ghrelin antagonists (in development) |
| Oxyntomodulin | L-cells of small intestine | Reduces appetite Increases energy expenditure | Weight loss Glycemic control | Oxyntomodulin analogs (in development) |

By inhibiting ghrelin's action, these antagonists aim to reduce hunger and promote a negative energy balance. Despite the theoretical appeal, the clinical development of ghrelin antagonists has faced hurdles, including the challenge of achieving significant and sustained appetite suppression (38-42).

Oxyntomodulin

Oxyntomodulin is a gut hormone with a dual role in activating both the GLP-1 receptor and the glucagon receptor. This dual action positions oxyntomodulin as a unique modulator of energy balance, with the potential to enhance insulin secretion (via GLP-1 receptor activation) and increase energy expenditure (via glucagon receptor activation). Emerging evidence suggests that oxyntomodulin may have significant potential for weight loss and metabolic improvements, particularly when used in combination with other incretin therapies. However, further researches need to fully understand its mechanism of action and optimize its therapeutic application in metabolic disorders (43,44).

Other Gut Hormones

Several other gut hormones, such as cholecystokinin (CCK) and secretin, play important roles in nutrient digestion and metabolism. CCK released in response to fat and protein intake and stimulates the release of digestive enzymes from the pancreas, as well as bile from the gallbladder, aiding in nutrient digestion. Secretin primarily modulates the secretion of bicarbonate to neutralize stomach acid, facilitating digestion in the small intestine. Recent findings have also shed light on lesser-known gut hormones, such as motilin and neuropeptide Y (NPY), which may have additional roles in regulating metabolic processes. The exploration of these hormones in the context of metabolic regulation is ongoing and may reveal new therapeutic opportunities (45-48).

Mechanisms of Gut Hormone-Based Therapies

Incretin-Based Therapies

Incretin-based therapies have revolutionized the treatment landscape for metabolic disorders, particularly T2D. The most well established class of these therapies is GLP-1 receptor agonists, which enhance insulin secretion, slow gastric emptying, and reduce appetite. Clinical trials have consistently demonstrated their efficacy in improving glycemic control, promoting weight loss, and reducing cardiovascular risk. GIP analogs and GLP-1/GIP dual agonists represent the next frontier in incretin-based therapies. These agents exploit the complementary actions of GLP-1 and GIP on glucose and lipid metabolism, offering potentially superior outcomes in terms of both glycemic control and weight reduction. Early clinical trials of dual agonists, such as tirzepatide, have shown promising results, with substantial improvements in HbA1c and body weight compared to GLP-1 agonists alone (49,50).

Gut Hormone antagonists and inhibitors

The development of ghrelin antagonists has garnered interest as a potential strategy for appetite suppression and weight loss. By blocking ghrelin's action on its receptor, these antagonists aim to reduce hunger and promote negative energy balance. However, clinical trials have revealed challenges in achieving consistent and significant appetite suppression, suggesting that more researches need to optimize these therapies. Other hormone antagonists, such as neuropeptide Y (NPY) antagonists, are under investigation for their potential to reduce food intake and improve metabolic outcomes. NPY is a potent orexigenic peptide that stimulates appetite and promotes energy storage, making it an attractive target for obesity therapies (51-54).

Combination therapies

Combination therapies that target multiple gut hormones simultaneously have shown great promise in the treatment of metabolic

disorders as presented in Table 2. GLP-1/GIP/glucagon triple agonists represent an exciting development in this field, offering the potential for enhanced metabolic control by addressing multiple pathways involved in glucose and lipid metabolism. Additionally, there is growing interest in the synergistic effects of gut hormone-based therapies with other pharmacological agents, such as SGLT2 inhibitors and insulin sensitizers. These combinations may offer enhanced efficacy and more metabolic benefits (55,56).

Clinical applications and current therapeutic agents

GLP-1 Receptor Agonists

GLP-1 receptor agonists have become a cornerstone in the treatment of T2D and obesity. Agents such as semaglutide and dulaglutide have demonstrated robust efficacy in improving glycemic control, promoting weight loss, and reducing cardiovascular risk. These drugs are generally well tolerated, although common side effects include nausea, vomiting, and, in rare cases, pancreatitis. Long-term studies have shown that GLP-1 receptor agonists can lead to sustained weight loss and improvements in glucose control, making them an attractive option for patients with both T2D and obesity. Additionally, their cardiovascular benefits, particularly in reducing major adverse cardiovascular events (MACE), have made them a preferred choice in patients with T2D at high cardiovascular risk (57,58).

Dual and Triple Agonists

The development of dual and triple agonists has marked a significant advancement in the treatment of metabolic disorders. Tirzepatide, a dual GLP-1/GIP agonist, has demonstrated superior efficacy in reducing HbA1c and body weight compared to GLP-1 agonists alone. Early clinical trials of triple agonists (GLP-1/GIP/glucagon) show more promising results, with significant improvements in glycemic control, weight loss, and lipid metabolism. As these agents progress through clinical development, they hold the potential to become first-line therapies for patients with complex metabolic disorders, offering comprehensive metabolic benefits that extend beyond what is achievable with current monotherapies (59-62).

Novel Peptide therapies

In addition to incretin-based therapies, novel peptide therapies targeting hormones such as PYY, ghrelin, and oxyntomodulin explored for their potential in treating metabolic disorders. PYY analogs have shown promise in reducing appetite and promoting weight loss, although challenges remain in optimizing their delivery and ensuring sustained efficacy. Ghrelin antagonists and oxyntomodulin analogs are also under investigation, with early studies suggesting potential benefits in weight management and metabolic control.

However, the development of these therapies is still in its early stages, and further researches need to overcome challenges

Table 2. Evolution of gut hormone-based therapies for metabolic disorders

| Generation | Therapy Type | Examples | Key Features | Advantages | Limitations |
|-------------------------|------------------------------------|--|---|---|---|
| First | Single hormone agonists | GLP-1 RAs (e.g., Liraglutide) | Mimics single gut hormone action | Improved glycemic control Moderate weight loss | Single target efficacy Variable |
| Second | Dual hormone agonists | GLP-1/GIP co-agonists (e.g., Tirzepatide) | Combines actions of two gut hormones | Enhanced glycemic control Superior weight loss Potential for greater metabolic improvements | Potential for increased side effects |
| Third (Emerging) | Multi-hormone agonists | GLP-1/GIP/Glucagon tri-agonists | Targets multiple metabolic pathways | Customizable hormone ratios | Complex interactions Still in early development |
| Fourth (Future) | Personalized gut hormone therapies | Tailored combinations based on individual profiles | Optimizes therapy based on patient-specific gut hormone deficiencies or resistances | Maximized efficacy Minimized side effects | Requires advanced diagnostic tools Higher complexity in treatment planning |

related to drug delivery, bioavailability, and long-term safety (63,64).

Microbiota-Gut Hormone interactions

The gut microbiota plays a critical role in modulating gut hormone levels and, consequently, metabolic regulation. Emerging research suggests that microbiota-targeted therapies, such as probiotics, prebiotics, and fecal microbiota transplantation, may enhance the efficacy of gut hormone-based therapies by restoring the balance of beneficial gut bacteria. These interventions have shown promise in improving metabolic outcomes, particularly in patients with obesity and insulin resistance. By modulating the gut microbiota, it may be possible to enhance the secretion and activity of key gut hormones, offering a novel approach to the treatment of metabolic disorders (65-68).

Challenges and limitations

Pharmacological challenges

One of the major challenges in the development of gut hormone-based therapies is the stability and bioavailability of peptide-based drugs. Peptides are inherently unstable in the gastrointestinal tract, requiring injectable formulations for effective delivery. Attempts to develop oral formulations met limited success due to the rapid degradation of peptides in the stomach and intestines. Additionally, side effects such as nausea and vomiting, particularly with GLP-1 receptor agonists, remain a significant concern. Although these side effects are generally mild and transient, they can influence patient adherence and limit the long-term use of these therapies (69-72).

Individual variability

Genetic and environmental factors play a significant role in determining an individual's response to gut hormone-based therapies. Variations in receptor sensitivity, hormone secretion, and gut microbiota composition can all influence treatment outcomes. This variability underscores the need for a

personalized medicine approach that takes into account individual differences to optimize therapy (72-74).

Regulatory and cost issues

The regulatory landscape for gut hormone-based therapies is complex, with stringent requirements for demonstrating safety and efficacy. Additionally, the high cost of gut hormone therapies, particularly GLP-1 receptor agonists and dual agonists, presents a significant barrier to widespread adoption. Ensuring cost-effectiveness and improving accessibility will be critical for the long-term success of these therapies (75-76).

Future directions

Emerging therapies and research

Research into new gut hormone analogs and combination therapies is ongoing, with several promising candidates in the pipeline. Gene therapy and gut hormone modulation through CRISPR and other gene-editing technologies represent exciting new avenues for research, offering the potential to correct metabolic dysregulation at its source (77-80).

Personalized and precision medicine

The future of gut hormone-based therapies lies in personalized and precision medicine. Advances in genetic, epigenetic, and microbiome profiling will enable the tailoring of therapies to individual patients, optimizing efficacy and minimizing side effects. Identifying biomarkers that predict treatment response will be critical for developing personalized treatment protocols (81-84).

Integration of digital health

The integration of digital health technologies, such as wearables and mobile apps, into the management of metabolic disorders will play an increasingly important role in the future. These tools can provide real-time data on metabolic markers, enabling continuous monitoring and adjustments to treatment regimens. Additionally, AI and machine learning will help optimize treatment

protocols by analyzing data from large patient populations, ultimately improving outcomes for individuals with metabolic disorders (85,86).

Conclusion

This comprehensive review underscores the pivotal role of gut hormones in metabolic regulation and their immense potential as therapeutic targets for metabolic disorders. The remarkable efficacy of GLP-1 receptor agonists and the emerging promise of dual GLP-1/GIP agonists represent significant advancements in the field, offering superior glycemic control and weight loss outcomes compared to traditional therapies. The synergistic actions of multiple gut hormones, as exemplified by these novel therapies, provide a more holistic approach to addressing the complex pathophysiology of obesity and type 2 diabetes. However, while these developments are promising, challenges remain in optimizing delivery methods, ensuring long-term efficacy, and fully elucidating the intricate interplay between various gut hormones. Future research directions should focus on developing more targeted combination therapies, exploring the potential of lesser-studied gut hormones like PYY and oxyntomodulin, and investigating personalized treatment approaches based on individual gut hormone profiles. The limitations of current research, including the need for longer-term safety data and a better understanding of the gut hormone system's adaptability to chronic interventions, highlight the importance of continued investigation in this rapidly evolving field.

Recommendations

To advance the field of gut hormone-based therapies for metabolic disorders, several key recommendations emerge. Firstly, there is a need for large-scale, long-term clinical trials to assess the safety and efficacy of gut hormone modulators, particularly combination therapies, beyond the currently established GLP-1 and GIP agonists. Secondly, research

efforts should be towards developing innovative drug delivery systems that can enhance the bioavailability and targeted action of gut hormone-based therapies, potentially exploring oral formulations or long-acting depot preparations. Thirdly, integrating personalized medicine approaches, such as gut hormone profiling and genetic analysis, into treatment strategies could optimize therapeutic outcomes and minimize adverse effects. Additionally, investigating the potential of gut hormone-based therapies in preventing the progression from prediabetes to type 2 diabetes could yield significant public health benefits. Finally, elucidating the complex interactions between gut hormones, the microbiome, and host metabolism could uncover new therapeutic targets and enhance our understanding of metabolic regulation, potentially leading to more comprehensive and effective treatment strategies for metabolic disorders.

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Conflict of Interest

The authors have stated no conflict of interest.

Authors' contributions

The Corresponding author completed the study protocol and was the primary organizer of data collection and the manuscript's draft and revision process. The corresponding author wrote the article and ensured its accuracy.

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