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OBESITY – PATHOPHYSIOLOGY AND MODERN TREATMENT STRATEGIES

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ABSTRACT

Obesity is one of the most significant public health challenges of the 21st century, with its prevalence continuously increasing worldwide. This condition is associated with an elevated risk of numerous metabolic, cardiovascular, and respiratory complications, leading to a substantial burden on healthcare systems. The pathophysiology of obesity is multifactorial and involves complex interactions between genetic, environmental, and neuroendocrine mechanisms regulating energy balance. Gastrointestinal hormones, including leptin, ghrelin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP), play a crucial role in the regulation of appetite and metabolism.

The aim of this study is to present current knowledge on the pathophysiology of obesity and to review contemporary and emerging treatment strategies. The article discusses classical therapeutic approaches, including lifestyle modification, dietary interventions, increased physical activity, and surgical treatment. Particular attention is given to modern pharmacological therapies targeting the incretin system.

In recent years, significant progress has been made in the pharmacological treatment of obesity with the introduction of GLP-1 receptor agonists, such as semaglutide, as well as dual-acting agents, including tirzepatide, which acts as an agonist of both GLP-1 and GIP receptors. These therapies demonstrate high efficacy in body weight reduction by influencing central mechanisms of appetite regulation, delaying gastric emptying, and improving glucose metabolism. Furthermore, promising directions in obesity treatment are discussed, including triple incretin receptor agonists such as retatrutide, as well as combination therapies utilizing amylin analogues, for example CagriSema.

In conclusion, the development of modern pharmacological therapies is significantly transforming the approach to obesity treatment and may in the future enable outcomes comparable to bariatric surgery. The integration of novel pharmacological methods with comprehensive lifestyle modification may represent the key to more effective management of obesity and reduction of its metabolic and cardiovascular complications.

KEYWORDS

Obesity, GLP-1, Semaglutide, Tirzepatide, Retatrutide, Incretins, Obesity Pharmacotherapy

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1. Introduction

Obesity is one of the most significant public health challenges of the 21st century and is currently recognized as a chronic disease with a complex etiology resulting from interactions between genetic, environmental, metabolic, and behavioral factors. In recent decades, a steady increase in the prevalence of obesity has been observed worldwide, contributing to a growing burden on healthcare systems and an increased incidence of comorbidities [1]. Given the rising scale of this problem, there is a clear need to further investigate the pathophysiology of obesity and to develop more effective therapeutic strategies [1].

The pathogenesis of obesity is multifactorial and involves disturbances in neurohormonal regulation, including impaired signaling of hormones responsible for appetite control and energy metabolism. One of the key mechanisms is the development of leptin resistance, which under physiological conditions plays a crucial role in suppressing appetite and maintaining energy homeostasis. Disruptions in leptin signaling pathways lead to impaired regulation of food intake and contribute to further weight gain [2].

Hormonal changes associated with aging also play a significant role in the pathophysiology of obesity. In older populations, a decline in testosterone levels is observed, which is associated with increased fat accumulation, particularly in visceral adipose tissue, as well as a higher risk of metabolic disorders [3]. Consequently, obesity frequently coexists with other chronic conditions, contributing to the development of cardiometabolic multimorbidity [4].

Excess body weight also affects the function of multiple organs and systems. Obesity has been shown to impact the cardiovascular system through mediators secreted by adipose tissue, which can influence vascular

smooth muscle cell function and the regulation of vascular tone [5]. Furthermore, excessive adiposity significantly affects respiratory physiology, leading to impaired breathing mechanics, reduced lung volumes, and an increased risk of chronic pulmonary diseases [6].

Due to its complex pathophysiology and wide-ranging systemic consequences, effective treatment of obesity remains one of the key challenges of modern medicine. Traditional therapeutic approaches, including lifestyle modification, dietary interventions, and increased physical activity, are often insufficient to achieve sustained weight loss in many patients. However, recent years have seen significant progress in the development of novel treatment strategies, particularly in the field of pharmacotherapy targeting hormonal and metabolic pathways involved in energy homeostasis. These advances offer new therapeutic opportunities in the management of this complex disease.

2. Materials and Methods

This review was conducted based on a comprehensive analysis of scientific articles available in the PubMed database. The literature search was limited to publications released within the last 12 months to ensure the inclusion of the most recent evidence regarding the pathophysiology and treatment of obesity.

Only articles published in English and available in full-text form were included in the analysis. Both original research articles and review papers were considered. The selection criteria focused on studies addressing key aspects of obesity, including hormonal regulation of appetite, mechanisms involving leptin and ghrelin, the role of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), as well as classical and modern therapeutic approaches.

Articles were selected based on their relevance to the topic, scientific quality, and contribution to current knowledge in the field. Particular emphasis was placed on studies evaluating novel pharmacological therapies, including GLP-1 receptor agonists, dual agonists (GLP-1/GIP), and emerging multi-target therapies.

Publications not available in English, lacking full-text access, or not directly related to obesity pathophysiology or treatment were excluded. Duplicate studies and articles with limited scientific relevance were also omitted.

The collected data were analyzed qualitatively, with the aim of summarizing current knowledge and identifying key trends in the development of obesity treatment strategies.

3.1 Hormonal Regulation of Appetite in the Pathophysiology of Obesity

The regulation of energy homeostasis is a complex process involving interactions between the nervous, hormonal, and metabolic systems. Gastrointestinal hormones and adipokines play a key role in controlling appetite and energy balance by transmitting signals regarding the body's energy status to appetite-regulating centers in the hypothalamus. Among the most important mediators of these processes are leptin and ghrelin, whose actions are largely antagonistic [7].

Leptin is a peptide hormone primarily produced by adipocytes of adipose tissue and functions as a signal reflecting the status of energy stores in the body. Under physiological conditions, increased leptin levels suppress appetite through activation of anorexigenic neurons and inhibition of orexigenic neurons in the arcuate nucleus of the hypothalamus. This mechanism leads to reduced food intake and increased energy expenditure [7]. However, in obesity, a phenomenon known as leptin resistance is observed, in which elevated circulating levels of leptin are accompanied by diminished biological activity. This impairment results in a loss of proper appetite regulation and represents one of the key pathophysiological mechanisms contributing to the persistence of excessive body weight [7].

Another important hormone involved in appetite regulation is ghrelin, which is primarily synthesized by enteroendocrine cells of the stomach. Ghrelin exerts orexigenic effects by stimulating appetite through activation of neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons in the hypothalamus. Its levels increase prior to meals and decrease following food intake, indicating its significant role in the initiation of feeding behavior [7]. In addition to its effects on appetite, ghrelin also influences metabolic processes, including growth hormone secretion and glucose metabolism.

A key component of ghrelin signaling is its receptor, known as the growth hormone secretagogue receptor (GHSR). Activation of this receptor leads to multiple metabolic effects, including increased appetite, modulation of insulin secretion, and effects on hepatic metabolism. It has been demonstrated that activation of the ghrelin–GHSR axis may promote hyperglycemia by inhibiting insulin secretion, increasing insulin resistance, and stimulating hepatic glucose production [8]. These mechanisms highlight the important role of this system not only in the pathophysiology of obesity but also in the development of metabolic disorders such as type 2 diabetes.

In recent years, increasing attention has been given to the role of liver-expressed antimicrobial peptide 2 (LEAP2), which has been identified as an endogenous antagonist of the GHSR receptor. LEAP2 is primarily

produced in the liver and small intestine and acts by inhibiting ghrelin activity. By blocking GHSR, LEAP2 reduces the orexigenic effects of ghrelin, thereby influencing food intake and energy metabolism [9]. It has also been shown that LEAP2 levels are positively correlated with body mass index as well as blood glucose and triglyceride levels, suggesting its involvement in metabolic regulation in obesity [9].

The interactions between ghrelin and LEAP2 represent a dynamic mechanism regulating energy homeostasis. While ghrelin stimulates appetite and promotes energy storage, LEAP2 acts as a physiological antagonist of this process. The balance between these two peptides may play a crucial role in body weight control and in the body's adaptation to changes in energy availability [9].

Disruptions in these hormonal mechanisms lead to dysregulation of appetite control and contribute to the development of obesity and related metabolic disorders. Therefore, signaling pathways involving leptin, ghrelin, and their receptors represent important targets for research into novel therapeutic strategies for the treatment of obesity and metabolic diseases.

3.2 The Role of Incretins GLP-1 and GIP in the Regulation of Energy Homeostasis

In the regulation of energy metabolism and appetite control, gut-derived hormones known as incretins play a crucial role. The most important among them are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones are secreted by enteroendocrine cells of the gastrointestinal tract in response to food intake and are involved in the regulation of insulin secretion, glucose metabolism, and food intake. Their actions include both peripheral effects and influence on the central nervous system, particularly on the hypothalamus and brainstem structures responsible for appetite regulation.

GLP-1 is a peptide hormone primarily produced by L cells of the small intestine and colon. Following a meal, its plasma concentration increases, leading to enhanced glucose-dependent insulin secretion. At the same time, GLP-1 inhibits glucagon secretion, slows gastric emptying, and influences central mechanisms regulating appetite, resulting in increased satiety and reduced food intake. In recent years, numerous studies have indicated that GLP-1 also affects brain regions involved in cognitive processes related to food intake, highlighting its important role in the neurobiology of eating behavior.

The second key incretin is GIP, or glucose-dependent insulinotropic polypeptide, which is mainly synthesized by K cells located in the proximal part of the small intestine. This hormone is released in response to the presence of nutrients, particularly glucose and fats, in the intestinal lumen. The mechanism of GIP secretion involves activation of G protein-coupled receptors and an increase in intracellular calcium and cAMP levels, leading to exocytosis of hormone-containing vesicles.

GIP plays a significant role in regulating the postprandial insulin response. It is estimated that this hormone accounts for approximately 60–80% of insulin secretion after a meal, acting through the GIP receptor (GIPR) present on pancreatic β-cells. Activation of this receptor increases cAMP levels and activates signaling pathways involving protein kinase A (PKA) and exchange protein activated by cAMP (EPAC), which enhances calcium influx and stimulates insulin release.

In addition to its effects on pancreatic β-cells, GIP also acts on other metabolic tissues, including adipose tissue. In adipocytes, it increases the uptake of glucose and free fatty acids and stimulates lipogenesis. These mechanisms promote energy storage in the form of adipose tissue. Under conditions of excessive energy intake, this may lead to a specific "metabolic vicious cycle," in which increased GIP secretion enhances energy substrate storage in adipocytes, thereby contributing to the development of obesity and insulin resistance.

In contrast to GIP, GLP-1 exhibits more pronounced anorexigenic properties. It acts on GLP-1 receptors (GLP-1R) located in the hypothalamus and brainstem structures such as the nucleus tractus solitarius, which play a key role in integrating satiety signals. Activation of these receptors reduces appetite and decreases energy intake. Additionally, GLP-1 influences gastrointestinal motility by delaying gastric emptying, which further enhances postprandial satiety.

Both GLP-1 and GIP act on multiple organs and systems, including the brain, pancreas, liver, adipose tissue, and gastrointestinal tract, forming a complex network that regulates energy homeostasis. Their complementary actions underlie the so-called incretin effect, defined as the enhancement of insulin secretion following oral glucose intake compared to intravenous administration.

Advances in understanding the role of incretins in metabolic regulation have led to the development of new therapeutic strategies for the treatment of obesity and type 2 diabetes. Particular interest has been focused on therapies based on GLP-1 receptor agonists as well as novel dual-acting molecules targeting both GLP-1 and GIP receptors, which demonstrate significant potential in reducing body weight and improving metabolic control.

4. Classical Methods of Obesity Treatment

The treatment of obesity has traditionally been based on three fundamental pillars: lifestyle modification including dietary interventions, increased physical activity, and surgical treatment. These approaches form the foundation of obesity therapy and are recommended as first-line management in most patients. However, in many cases, their long-term effectiveness remains limited, which has contributed to the development of new therapeutic strategies.

4.1 Dietary Interventions

Modification of dietary habits is a fundamental component of obesity treatment. The goal of dietary therapy is to achieve a negative energy balance by reducing caloric intake while maintaining adequate diet quality. One of the most extensively studied dietary models is the Mediterranean diet, characterized by a high intake of vegetables, fruits, whole grains, olive oil, and fish. It has been demonstrated that adherence to this dietary pattern can improve metabolic parameters, including the reduction of cardiovascular risk factors and improvement of lipid profile in individuals with overweight and obesity [16].

In recent years, increasing attention has been given to dietary strategies based on time-restricted eating, such as intermittent fasting. Studies indicate that such interventions may lead to body weight reduction, improvement in body composition, and beneficial changes in cardiometabolic parameters, including insulin sensitivity and lipid profile [17].

4.2 Physical Activity

Regular physical activity represents the second key component of obesity treatment. It has been shown that exercise contributes not only to weight reduction but also to improvements in body composition, increased energy expenditure, and enhanced cardiovascular and metabolic function. Regular physical activity promotes a reduction in adipose tissue and improves insulin sensitivity [18].

In individuals with severe obesity, particular importance is attributed to exercise programs focused on improving mobility and musculoskeletal stability. Properly designed physical activity can increase exercise tolerance and reduce the risk of injuries associated with excessive joint load [19].

4.3 Surgical Treatment

In patients with severe obesity or obesity-related metabolic complications, surgical treatment plays a significant role. Bariatric surgery is currently considered one of the most effective methods of obesity treatment, enabling substantial and sustained weight loss as well as improved metabolic control. One of the most commonly performed procedures is the Roux-en-Y gastric bypass, which, in addition to reducing stomach volume, also induces hormonal changes that affect appetite regulation and metabolism [20].

Despite its high effectiveness, bariatric surgery is associated with a risk of complications and requires long-term medical care and patient monitoring [21].

4.4 Limitations of Classical Treatment Methods

Despite the use of lifestyle modification and surgical interventions, achieving sustained weight loss remains a clinical challenge. Many patients experience weight regain, which is partly due to compensatory mechanisms regulating energy balance. These limitations have driven the rapid development of new obesity treatment strategies, particularly pharmacological therapies targeting hormonal pathways involved in appetite and metabolic regulation.

5. Modern Strategies for the Treatment of Obesity

Advances in understanding the mechanisms regulating energy homeostasis have led in recent years to the development of new methods for the treatment of obesity. Of particular importance in this context are therapies targeting incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Drugs acting on these pathways demonstrate the ability to simultaneously influence appetite regulation, glucose metabolism, and overall energy balance, making them one of the most promising therapeutic strategies in obesity management [22].

5.1 GLP-1 Receptor Agonists

GLP-1 receptor agonists represent one of the most important classes of drugs currently used in the treatment of obesity. Their mechanism of action involves stimulation of GLP-1 receptors located both in the gastrointestinal tract and in the central nervous system. Activation of these receptors leads to reduced appetite, delayed gastric emptying, and increased satiety, resulting in decreased energy intake and body weight reduction [22].

One of the most extensively studied agents in this group is semaglutide, which has demonstrated high efficacy in reducing body weight in patients with overweight and obesity. Clinical trials indicate that treatment with semaglutide at a dose of 2.4 mg can lead to significant weight reduction as well as improvement in metabolic parameters, including glycemic control and lipid profile [23].

It has also been shown that semaglutide treatment may provide cardiovascular benefits. Analyses based on clinical trial data suggest a potential reduction in the incidence of cardiovascular events in patients with obesity and coexisting cardiovascular diseases [24; 25].

Moreover, clinical observations indicate that semaglutide may offer benefits in patients with comorbid conditions, including heart failure with preserved ejection fraction, where treatment may improve both metabolic parameters and cardiovascular function [26].

The literature also highlights potential differences in response to GLP-1 receptor agonists depending on patient sex, which may be relevant for future personalization of obesity therapy [27].

5.2 Dual GLP-1/GIP Therapies

Another important direction in the development of obesity pharmacotherapy includes agents targeting two hormonal pathways simultaneously—GLP-1 and GIP. The most well-known representative of this group is tirzepatide, which acts as an agonist of both GLP-1 and GIP receptors. This dual mechanism enables simultaneous modulation of appetite regulation, glucose metabolism, and lipid homeostasis.

Clinical studies have demonstrated that treatment with tirzepatide results in significant weight reduction as well as decreased appetite and energy intake. These effects are mediated, among others, by central mechanisms regulating appetite and improved insulin sensitivity [28].

Observational studies and real-world analyses have also shown substantial weight loss in patients treated with semaglutide or tirzepatide, even in populations without type 2 diabetes [29].

Importantly, tirzepatide therapy has also been associated with improvements in health-related quality of life in patients with obesity or overweight, as confirmed in clinical trials assessing long-term treatment outcomes [30].

5.3 Emerging Combination Therapies

Ongoing research is also focused on combination therapies that integrate GLP-1 receptor agonists with other hormones involved in appetite regulation. One such example is the combination of semaglutide with a peptide YY (PYY 3–36) analog, which has shown potential to enhance weight loss efficacy through synergistic effects on satiety mechanisms and appetite regulation [31].

The continued development of incretin-based therapies suggests that obesity pharmacotherapy is likely to undergo further transformation in the coming years, offering new opportunities for effective and long-term management of this complex metabolic disease.

5.4 Mechanisms of Action of Modern Anti-Obesity Drugs

Semaglutide

Semaglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist that mimics the action of the endogenous incretin hormone released in the gastrointestinal tract after food intake. Activation of GLP-1 receptors located in the pancreas, central nervous system, and gastrointestinal tract leads to a range of metabolic effects that promote weight reduction [32].

One of the key mechanisms of semaglutide action is the enhancement of glucose-dependent insulin secretion by pancreatic β-cells, along with the inhibition of glucagon secretion, which contributes to improved glycemic control. In addition, the drug influences central mechanisms of appetite regulation by acting on hypothalamic neurons responsible for hunger and satiety, leading to reduced food intake.

Semaglutide also affects gastrointestinal function by delaying gastric emptying, which prolongs the feeling of fullness after meals and reduces postprandial glycemic fluctuations. Furthermore, it has been

observed to decrease appetite and reduce preference for high-calorie foods, thereby supporting long-term weight loss.

As a result of these complex mechanisms, semaglutide leads to improved metabolic control and clinically significant weight reduction in patients with obesity and metabolic disorders.

5.5 Tirzepatide

Tirzepatide is a novel incretin-based drug described as a dual agonist of GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) receptors. Simultaneous activation of both receptors results in a synergistic metabolic effect that exceeds those observed with traditional GLP-1 receptor agonists [33].

The mechanism of action of tirzepatide involves several key physiological processes. Similar to GLP-1 receptor agonists, it enhances glucose-dependent insulin secretion and reduces glucagon secretion, leading to improved glycemic control. At the same time, activation of GLP-1 receptors in the central nervous system influences hypothalamic centers regulating hunger and satiety, resulting in reduced appetite and decreased energy intake.

Additionally, activation of GIP receptors affects lipid metabolism and adipose tissue function by improving insulin sensitivity and overall energy homeostasis. The synergistic action of GLP-1 and GIP receptors results in a more pronounced effect on weight reduction and metabolic improvement compared to therapies targeting a single receptor [33].

As a consequence, tirzepatide acts on both central mechanisms of appetite regulation and peripheral metabolic pathways, leading to significant weight loss and improved metabolic control in patients with obesity.

6. Future of Obesity Pharmacotherapy

The dynamic development of research on hormonal regulation of appetite and metabolism has led to the emergence of a new generation of anti-obesity drugs that simultaneously target multiple metabolic pathways. Among the most promising directions are triple incretin receptor agonists, combination therapies based on amylin analogues, and novel strategies modulating overall energy homeostasis.

6.1 Retatrutide

One of the most promising agents currently under development for obesity treatment is retatrutide, which represents a triple agonist of GLP-1, GIP, and glucagon receptors. Simultaneous activation of these three metabolic pathways enables a multidirectional effect on body weight regulation, including both appetite suppression and increased energy expenditure [35].

Activation of GLP-1 receptors leads to reduced appetite and delayed gastric emptying, resulting in decreased energy intake. The action on GIP receptors improves insulin sensitivity and glucose metabolism. The third component of its mechanism involves activation of glucagon receptors, which increases metabolic rate and enhances fat oxidation. The synergistic action of these three hormones allows for a more comprehensive regulation of energy balance.

In clinical trials, retatrutide has demonstrated very high efficacy in weight reduction, achieving mean weight loss exceeding 20% of baseline body weight, which is comparable to outcomes observed in bariatric surgery.

Currently, large-scale clinical trials are ongoing within the TRIUMPH program, aiming to evaluate the efficacy and safety of retatrutide in the treatment of obesity and related comorbidities, such as obstructive sleep apnea and osteoarthritis [36].

6.2 Combination Therapies – CagriSema

Another important direction in the development of obesity pharmacotherapy is combination therapy utilizing analogues of different appetite-regulating hormones. An example of this approach is CagriSema, which combines semaglutide (a GLP-1 receptor agonist) with cagrilintide, an analogue of the hormone amylin.

Amylin is a hormone co-secreted with insulin by pancreatic β-cells and plays a significant role in regulating satiety, delaying gastric emptying, and controlling postprandial glycemia [37].

The combination of amylin action with a GLP-1 receptor agonist enables simultaneous targeting of multiple mechanisms involved in energy intake regulation. Both hormones act on satiety centers in the central nervous system, but through different receptors, resulting in a synergistic effect on appetite suppression and reduction of caloric intake.

In the REDEFINE-1 trial, CagriSema therapy demonstrated significant weight reduction and favorable effects on cardiometabolic parameters, including blood pressure, in patients with overweight and obesity [38].

6.3 The Role of Amylin Analogues in Obesity Treatment

Increasing attention is being paid to amylin analogues as a potential new class of anti-obesity drugs. Amylin acts on receptors within the brainstem and hypothalamus, influencing satiety mechanisms and the regulation of meal size. Additionally, this hormone delays gastric emptying and reduces postprandial glycemic excursions, contributing to improved metabolic stability.

Studies suggest that amylin analogues may be particularly effective when used in combination with incretin-based therapies, as they act on distinct pathways involved in appetite regulation. Such an approach may result in greater efficacy in obesity treatment compared to monotherapy [37].

6.4 Future Perspectives in Therapy Development

Advances in understanding the neuroendocrine mechanisms regulating appetite and energy metabolism indicate that the future of obesity treatment will be based on multi-hormonal drugs and combination therapies targeting several key metabolic pathways simultaneously.

Strategies such as triple incretin receptor agonists or combinations of GLP-1 receptor agonists with amylin analogues may significantly transform the approach to obesity pharmacotherapy in the coming years, enabling weight reduction outcomes comparable to bariatric surgery through pharmacological treatment alone.

7. Discussion

Obesity represents one of the most significant public health challenges of the 21st century, and its complex pathophysiology involves interactions between genetic, environmental, and neuroendocrine mechanisms regulating energy homeostasis. In recent years, substantial progress has been made in understanding the hormonal regulation of appetite and metabolism, enabling the development of novel therapeutic strategies targeting specific metabolic pathways.

The pathophysiological mechanisms presented in this study indicate that gastrointestinal hormones and neuroendocrine signals, including leptin, ghrelin, GLP-1, and GIP, play a key role in body weight regulation. Dysregulation of these systems leads to impaired appetite control, increased energy intake, and the development of a chronic positive energy balance. Of particular importance is leptin resistance, which limits the body's ability to physiologically suppress appetite in individuals with obesity.

Despite the growing number of available therapeutic options, non-pharmacological interventions remain the cornerstone of obesity treatment. These include lifestyle modification, particularly dietary changes and increased physical activity. While such interventions have beneficial effects on body weight reduction and metabolic parameters, their long-term effectiveness is often limited due to difficulties in maintaining sustained lifestyle changes. In cases of severe obesity, bariatric surgery remains an effective therapeutic option, leading to significant and sustained weight loss as well as improvement in obesity-related comorbidities.

However, recent years have witnessed a major breakthrough in obesity pharmacotherapy with the introduction of drugs targeting the incretin system. GLP-1 receptor agonists, such as semaglutide, have demonstrated high efficacy in reducing body weight through central appetite regulation, delayed gastric emptying, and improved glycemic control. Even more promising outcomes have been observed with dual-acting agents such as tirzepatide, which simultaneously activates GLP-1 and GIP receptors, resulting in enhanced metabolic effects and greater weight reduction.

The development of multi-hormonal therapies represents the next step in the evolution of obesity pharmacotherapy. Retatrutide, a triple agonist of GLP-1, GIP, and glucagon receptors, exemplifies this approach by targeting multiple metabolic pathways simultaneously. This allows for comprehensive regulation of energy balance through appetite suppression, improved insulin sensitivity, and increased energy expenditure. Similarly, combination therapies utilizing amylin analogues together with GLP-1 receptor agonists, such as CagriSema, demonstrate synergistic effects on energy intake and body weight regulation.

Nevertheless, despite promising clinical trial results, new pharmacological therapies require further evaluation regarding their long-term safety and efficacy across diverse patient populations. Accessibility and cost also remain important considerations, as they may limit widespread clinical implementation in many healthcare systems.

In conclusion, the development of modern incretin-based and multi-hormonal therapies is significantly transforming the approach to obesity treatment. The integration of classical treatment methods with targeted pharmacotherapy addressing underlying pathophysiological mechanisms may enable more effective and individualized therapeutic strategies for patients with obesity in the future.

8. Conclusions

Obesity is a chronic metabolic disease with a complex pathophysiology, in which disturbances in hormonal regulation of appetite play a crucial role, including dysfunction of leptin, ghrelin, and incretin systems. Understanding these mechanisms has enabled the development of novel therapeutic strategies targeting key pathways regulating energy balance.

Classical therapeutic approaches, including lifestyle modification, appropriate diet, and increased physical activity, remain the foundation of obesity treatment. In cases of advanced obesity, bariatric surgery continues to be an effective treatment option, allowing for significant and sustained weight loss as well as improvement of obesity-related comorbidities.

In recent years, significant progress has been observed in obesity pharmacotherapy, particularly with the introduction of drugs targeting the incretin system. GLP-1 receptor agonists, such as semaglutide, and dual-acting agents like tirzepatide have demonstrated high efficacy in reducing body weight through their effects on appetite regulation, glucose metabolism, and energy expenditure.

Future directions in obesity pharmacotherapy include multi-hormonal therapies and combination treatments, such as triple incretin receptor agonists like retatrutide, as well as combinations of GLP-1 receptor agonists with amylin analogues. These strategies may, in the future, enable therapeutic outcomes comparable to those achieved with bariatric surgery.

However, further clinical studies are necessary to evaluate the long-term efficacy, safety, and optimal treatment regimens of these novel anti-obesity drugs. The integration of modern pharmacotherapy with comprehensive lifestyle interventions may significantly improve treatment outcomes and reduce metabolic and cardiovascular complications associated with obesity.

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