REVIEW

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Mechanisms of GLP-1 Receptor Agonist-Induced Weight Loss: A Review of Central and Peripheral Pathways in Appetite and Energy Regulation

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have become central in managing obesity and type 2 diabetes, primarily through appetite suppression and metabolic regulation. This review explores the mechanisms underlying GLP-1 RA-induced weight loss, focusing on central and peripheral pathways. Centrally, GLP-1 RAs modulate brain regions controlling appetite, influencing neurotransmitter and peptide release to regulate hunger and energy expenditure. Peripherally, GLP-1 RAs improve glycemic control by enhancing insulin secretion, reducing glucagon release, delaying gastric emptying, and regulating gut hormones. They also reduce triglycerides and low-density lipoprotein cholesterol, mitigate adipose tissue inflammation, and minimize ectopic fat deposition, promoting overall metabolic health. Emerging dual and triple co-agonists, targeting GLP-1 alongside glucose-dependent insulinotropic polypeptide, and glucagon pathways, may enhance weight loss and metabolic flexibility. Understanding these mechanisms is crucial as the therapeutic landscape evolves, offering clinicians and researchers insights to optimize the efficacy of current and future obesity treatments.

KEYWORDS: Appetite; Glucagon-like peptide-1 receptor agonist; Metabolism; Obesity; Semaglutide; Tirzepatide; Weight loss

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INTRODUCTION

Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have emerged as an important therapeutic class for managing type 2 diabetes and obesity. These agents mimic the effects of endogenous GLP-1, which is produced in the intestines in response to food intake[1] and is quickly inactivated by the enzyme dipeptidyl peptidase 4.[2] By activating the GLP-1 receptor, GLP-1 RAs enhance glucose-dependent insulin secretion, inhibit glucagon release, and slow gastric emptying.[1-4] In addition, GLP-1 RAs suppress appetite and enhance satiety by acting on the central nervous system which leads to reduced caloric consumption and weight loss.[5] Given their dual role in regulating glucose metabolism and body weight, GLP-1 RAs have gained

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considerable attention not only for diabetes management but also for their application as weight loss treatments among individuals without diabetes.

Currently, three GLP-1-based agents (liraglutide, semaglutide, and tirzepatide) are approved for chronic weight management (Table). Tirzepatide, a dual GLP-1, and glucose-dependent insulinotropic polypeptide (GIP) receptor co-agonist represents an important advancement, demonstrating enhanced efficacy in weight reduction and broadening the therapeutic landscape of anti-obesity medications. As new agents targeting multiple metabolic pathways are expected to enter the market, there is a growing need to understand how both existing and emerging therapies modulate hunger and energy balance to drive weight loss. This review provides a comprehensive analysis of the central and peripheral mechanisms underlying GLP-1 RA-induced weight loss, offering insights into current and future treatment options to inform the clinical application of these therapies.

CLINICAL SIGNIFICANCE

- GLP-1 receptor agonists promote weight loss by suppressing appetite, enhancing satiety, and delaying gastric emptying.
- They modulate central neural pathways and peripheral metabolic processes, providing cardiometabolic benefits beyond weight reduction.
- Emerging dual and triple co-agonists may enhance efficacy by targeting additional metabolic pathways.
- Understanding the mechanisms of GLP-1 receptor agonists is critical for optimizing their use and guiding future obesity treatments in clinical practice.

SEARCH STRATEGY AND SELECTION CRITERIA

Data for this review article were identified through searches of PubMed and Google Scholar using the search terms "glucagon-like peptide-1 receptor agonists," "glucagon-like peptide-1-based therapies," "liraglutide," "semaglutide," "tirzepatide," "mechanisms of action," "obesity," "weight loss," "appetite regulation," "metabolic effects," and "energy expenditure." The search period covered the years of inception to September 2024. The final reference list was generated based on originality and relevance to the broad scope of this review.

CENTRAL MECHANISMS OF GLP-1 RA-INDUCED WEIGHT LOSS

Central Nervous System Effects on Appetite Regulation

The intake of food is regulated by several interactions between nutrients, hormones, neuropeptides, and many different areas of the brain.[6] The regulation of feeding can be categorized into homeostatic and nonhomeostatic (hedonic) feeding.[7] Homeostatic feeding maintains energy balance by adjusting food intake to stabilize energy stores. In contrast, nonhomeostatic feeding, driven by the pleasurable properties of food, can override this homeostatic mechanism and lead to overeating.[8,9]

The brainstem and hypothalamus are important structures within the regulatory pathways of homeostatic feeding as they receive, convey, and integrate peripheral signals (Figure 1).[6] The nucleus tractus solitarii in the brainstem receives signals from the gastrointestinal tract about nutrient intake. GLP-1 RAs bind to GLP-1 receptors in the nucleus tractus solitarii, enhancing the activity of serotonergic neurons in this region which promote a feeling of fullness and reduce the urge to eat.[10,11] GLP-1 activation in the nucleus tractus solitarii is also associated with the release of glutamate, an excitatory neurotransmitter, further amplifying signals sent to higher brain centers.[11]

The area postrema in the brainstem lacks a blood-brain barrier and is involved in detecting circulating signals related to hunger and satiety.[12] The activation of GLP-1 receptors in this region influences dopaminergic signaling which can reduce the reward of food intake, contributing to

Table Summary of FDA-approved GLP-1 RAs and Co-agonists

Generic Name	Trade Name	Indication	Approval Year	Class
Exenatide	Byetta	Type 2 diabetes	2005	GLP-1 receptor agonist
Liraglutide	Victoza	Type 2 diabetes	2010	GLP-1 receptor agonist
Dulaglutide	Trulicity	Type 2 diabetes	2014	GLP-1 receptor agonist
Liraglutide	Saxenda	Overweight/obesity	2014	GLP-1 receptor agonist
Lixisenatide	Adlyxin	Type 2 diabetes	2016	GLP-1 receptor agonist
Liraglutide + insulin degludec	Xultophy	Type 2 diabetes	2016	GLP-1 receptor agonist
Lixisenatide + insulin glargine	Soliqua	Type 2 diabetes	2016	GLP-1 receptor agonist
Exenatide extended-release	Bydureon BCise	Type 2 diabetes	2017	GLP-1 receptor agonist
Semaglutide	Ozempic	Type 2 diabetes	2017	GLP-1 receptor agonist
Semaglutide	Rybelsus	Type 2 diabetes	2019	GLP-1 receptor agonist
Semaglutide	Wegovy	Overweight/obesity	2021	GLP-1 receptor agonist
Tirzepatide	Mounjaro	Type 2 diabetes	2022	Dual GLP-1/GIP receptor co-agonist
Tirzepatide	Zepbound	Overweight/obesity	2023	Dual GLP-1/GIP receptor co-agonist

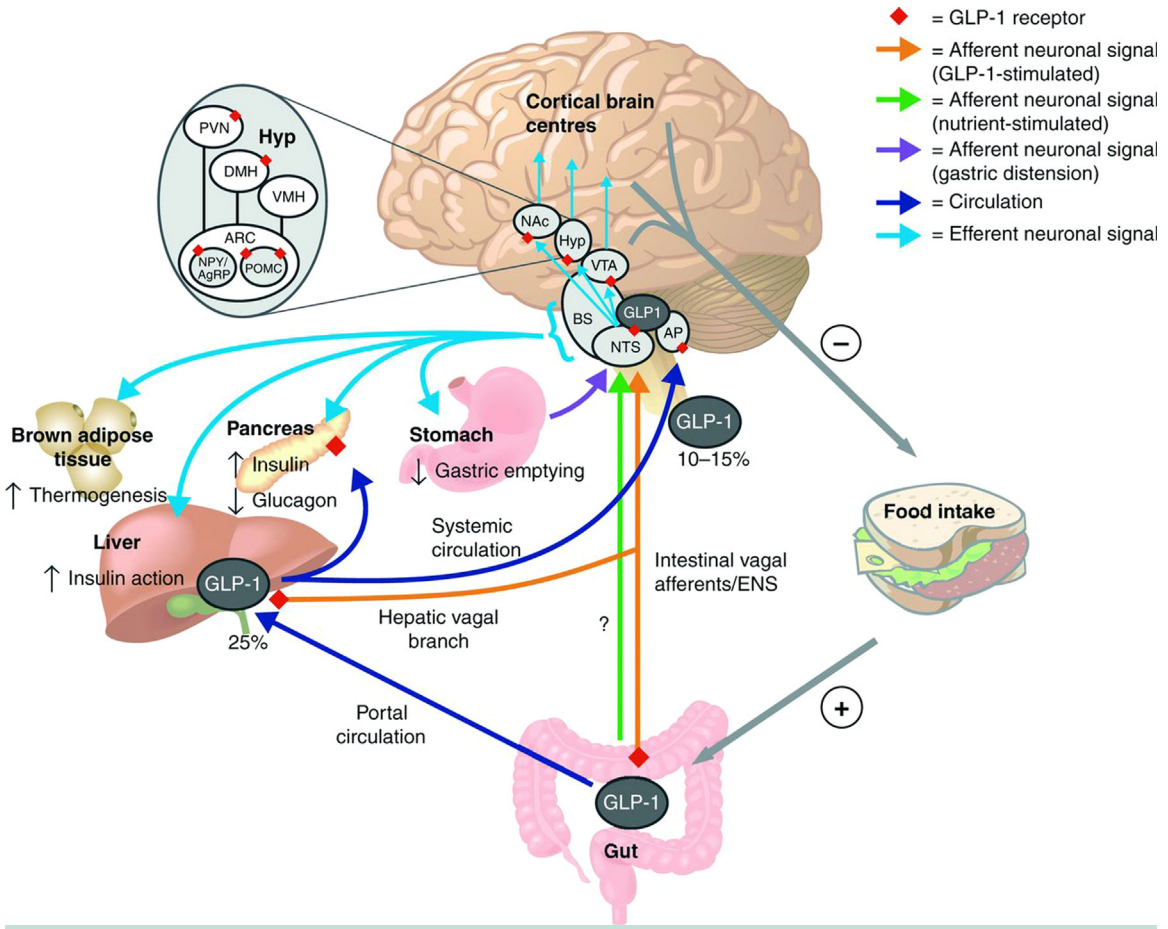

Figure 1 Proposed routes of action of GLP-1 in the central regulation of feeding and glucose metabolism. *Note.* Reprinted with permission from van Bloemendaal et al.[6] doi:10.1530/JOE-13-0414. AgRP = agouti-related peptide; AP = area postrema; ARC = arcuate nucleus; BS = brain stem; DMH = dorsomedial hypothalamus; ENS = enteric nervous system; Hyp = hypothalamus; NAc = nucleus accumbens; NPY = neuropeptide Y; NTS = nucleus tractus solitarii; POMC = pro-opiomelanocortin; PVN = paraventricular nucleus; VMH = ventromedial hypothalamus; VTA = ventral tegmental area.

the suppression of appetite.[12] The nucleus tractus solitarii and area postrema then convey these signals to the arcuate nucleus of the hypothalamus.[13]

The arcuate nucleus contains anorexigenic neurons (appetite-suppressing) and orexigenic neurons (appetite-stimulating) which collectively regulate the homeostatic control of eating.[14] When GLP-1 RAs activate GLP-1 receptors in the hypothalamus, there is an increased release of anorexigenic peptides (pro-opiomelanocortin) and decreased release of orexigenic peptides (neuropeptide Y and agouti-related peptide), resulting in reduced food intake and increased energy expenditure.[15] GLP-1 RAs also affect the paraventricular nucleus and lateral hypothalamus which are regions involved in the regulation of hunger and energy homeostasis.[16] In the paraventricular nucleus, GLP-1 signaling influences the release of corticotropin-releasing hormone, oxytocin, and thyrotropin-releasing hormone, all of which reduce food intake.[16] In the lateral hypothalamus, GLP-1 RAs inhibit orexin-producing neurons, which are involved in stimulating appetite.[16]

The mesolimbic reward pathway, which includes areas such as the ventral tegmental area and the nucleus accumbens, is critical in processing rewarding stimuli, including food or drugs.[6,17] When GLP-1 receptors in the ventral tegmental area and nucleus accumbens are activated, it results in decreased dopamine release, which diminishes the rewarding sensation typically associated with food and substance use.[17] This reduction in reward response decreases the motivation to consume high-calorie, palatable foods. GLP-1 action in the mesolimbic system can also influence serotonin levels, which are further associated with mood and satiety.[18] This broad neurotransmitter modulation contributes to their overall effect on reducing reward-driven behaviors and hedonic feeding.

Satiety Signaling

Satiety signaling plays a crucial role in regulating hunger.[19] Leptin is a hormone primarily produced by adipose tissue that acts on the hypothalamus to reduce appetite and

increase energy expenditure.[20] Satiety signals from the gut and other peripheral tissues can enhance leptin sensitivity in the hypothalamus, meaning the brain responds more effectively to leptin, promoting satiety.[19] GLP-1 RAs enhance leptin signaling by reducing leptin resistance, which increases the effectiveness of leptin in suppressing appetite.[21]

PERIPHERAL MECHANISMS OF GLP-1 RA-INDUCED WEIGHT LOSS

Gut Hormone Regulation

Gut hormones such as ghrelin, peptide YY, and cholecystokinin play significant roles in regulating appetite and digestion.[22] GLP-1 RA signaling modulates the secretion of these gastrointestinal hormones and peripherally enhances their effects on satiety. Ghrelin is known as the "hunger hormone" because it stimulates appetite, increases food intake, and promotes fat storage.[22] It is primarily produced and secreted by the stomach when it is empty. GLP-1 RAs decrease ghrelin levels, contributing to their appetite-suppressing effects.[21] Peptide YY, produced in the intestines and colon, and cholecystokinin, produced in the small intestine, are both released from the gut in response to food intake and act as potent satiety signals.[22] Peptide YY acts as a peripheral hormone that signals satiety by slowing gastric emptying and reducing appetite. Cholecystokinin acts as a peripheral hormone that promotes digestion and inhibits further food intake by inducing a feeling of fullness.[22] It is hypothesized that GLP-1 RAs enhance the release and action of peptide YY and cholecystokinin, amplifying their appetite-suppressing effects.[23,24]

Delayed Gastric Emptying

Satiety signals are produced by activation of gastric mechanoreceptors when the stomach is distended.[25] These signals are then relayed to the NTS in the brainstem via the vagal nerves. The amount of gastric distension due to food intake is partly influenced by the rate of gastric emptying and gastric motility which are significantly reduced with the elevation of plasma GLP-1. By slowing gastric emptying and gastric acid secretion, GLP-1 RA-induced dyspepsia prolongs the sensation of fullness, which results in decreased hunger and food intake.

Glucose Metabolism, Lipid Benefits, and Anti-Inflammatory Effects

GLP-1 RAs enhance glucose-dependent insulin secretion from the pancreas, which helps lower blood glucose levels and improve glycemic control.[2,6,21,26] Additionally, they inhibit the release of glucagon, reducing hepatic glucose production and contributing to lower fasting glucose levels. Stable glucose levels minimize hunger signals sent by the brain, leading to a reduction in appetite and food intake. GLP-1 RAs also improve lipid profiles by reducing triglycerides and low-density lipoprotein cholesterol levels.[27,28] Both the enhanced glycemic control and lipid metabolism leads to better mobilization and utilization of fat stores for energy, reducing the likelihood of excess fat accumulation. GLP-1 RAs also increase thermogenesis, the process of heat production in the body, which further leads to higher energy expenditure.[29]

Beyond their effects on lipid profiles, GLP-1 RAs improve the function of adipose tissue by reducing inflammation.[30] Chronic inflammation in adipose tissue is a common feature of obesity, contributing to insulin resistance and metabolic dysfunction.[31] Healthier adipose tissue is better at storing and releasing fats appropriately which reduces ectopic fat deposition and promotes weight loss.[32] GLP-1 RAs may also promote the redistribution of fat from visceral (abdominal) to subcutaneous depots.[33] Visceral fat, stored around internal organs, is more harmful and metabolically active, contributing to many conditions such as type 2 diabetes and cardiovascular disease (Figure 2).[34] Altogether, these combined effects improve overall metabolic health, aiding in sustained weight loss.

DUAL/TRIPLE CO-AGONIST-INDUCED WEIGHT LOSS

Dual and triple co-agonists, such as GLP-1/GIP, GLP-1/glucagon (GCG), and GLP-1/GIP/GCG, represent an innovative approach in obesity treatment by combining different incretin pathways to potentially enhance therapeutic efficacy.[35] These co-agonists consist of a single molecule that targets multiple receptors, allowing for the simultaneous activation of different pathways that contribute to metabolic control and appetite regulation. By leveraging the complementary effects of each hormone, dual and triple co-agonists may offer a more comprehensive approach to weight management, potentially improving both glucose metabolism and energy balance more effectively than single agonists. As such, they are the focus of ongoing research to determine their full potential in clinical settings.

Glucose-Dependant Insulinotropic Polypeptide RAs

GIP RAs contribute to weight loss by modulating both insulin and lipid metabolism.[3,36] They enhance insulin secretion and decrease glucagon secretion, which helps regulate blood glucose levels. Beyond glucose control, GIP RAs influence fat metabolism by promoting lipogenesis in some tissues and inhibiting fat storage in others,[37,38] potentially leading to a more favorable lipid profile. Recent studies suggest that GIP RAs may also increase energy expenditure and improve metabolic flexibility, allowing the body to switch more effectively between glucose and fat as energy sources.[39,40] When used in combination with GLP-1 RAs, GIP RAs may complement the appetite-suppressing and glucose-lowering effects of GLP-1 RAs, leading to a more

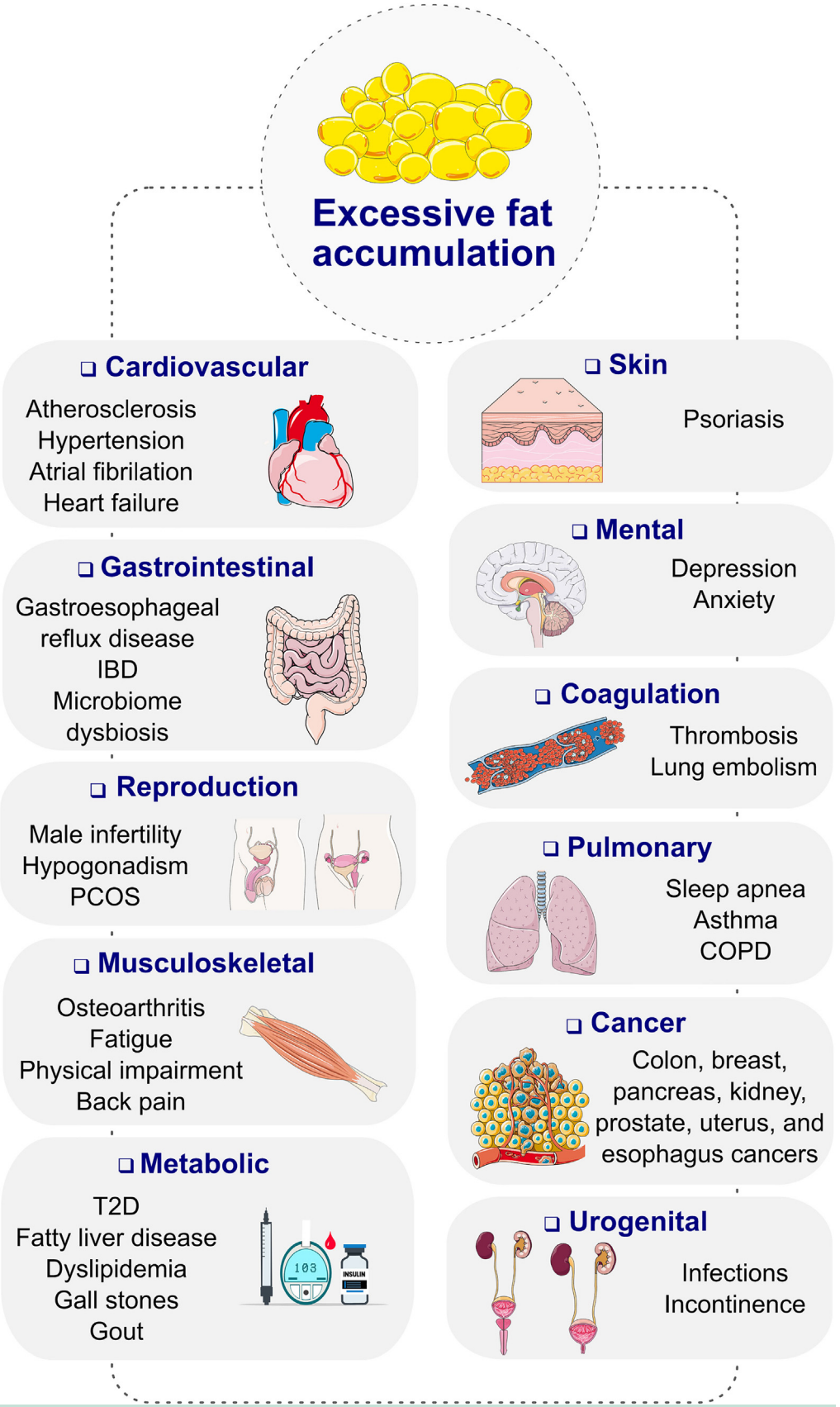

Figure 2 Complications of obesity. *Note.* Reprinted under the CC-BY 4.0 license from "Recent advances in incretin-based pharmacotherapies for the treatment of obesity and diabetes," by Q. Tan et al., 2022, *Front Endocrinol, 13*. doi:10.3389/fendo.2022.838410.

effective weight loss through a synergistic impact on multiple metabolic pathways.[41]

Glucagon RAs

GCG RAs aid in weight loss by enhancing fat metabolism and increasing energy expenditure.[42] When activated, GCG receptors stimulate lipolysis, leading to the breakdown of stored fats into free fatty acids, which are then used as an energy source.[43] This process reduces fat stores and increases overall energy expenditure, contributing to a negative energy balance essential for weight loss. Additionally, GCG RAs can boost thermogenesis, further enhancing calorie burning.[44] These effects distinguish them from the more direct appetite regulation and weight loss mechanisms of GLP-1 RAs. While GCG RAs can increase blood glucose levels through gluconeogenesis and glycogenolysis,[45] this effect is typically more pronounced during periods of fasting or when glucose levels are low.[46] In combination with GLP-1 RAs, which reduce blood glucose through insulin secretion and glucagon suppression, the increase in glucose from GCG RAs is largely mitigated, balancing the metabolic effects.[47] The weight loss effects of GCG RAs are primarily due to their ability to mobilize and utilize fat, making them a promising component of combination therapies for obesity management.

CONCLUSION

GLP-1 RAs and co-agonists contribute to weight loss through multiple interconnected physiological pathways. By acting on the central nervous system, GLP-1 RAs suppress appetite and enhance satiety signaling, leading to reduced caloric intake.[6] They also delay gastric emptying, further prolonging the sensation of fullness after meals. Beyond appetite regulation, GLP-1 RAs and co-agonists enhance energy metabolism by improving glycemic control, promoting thermogenesis, and increasing energy expenditure.[6,21,29] Additionally, their positive impact on lipid metabolism promotes healthier fat storage and utilization.[27,28] These mechanisms, working in concert, make GLP-1 RAs and co-agonists effective for sustained weight loss, which is crucial for addressing obesity and its related complications. As new agents targeting multiple metabolic pathways enter the market, their broader effects may yield more robust weight loss outcomes. By activating additional pathways, dual and triple GLP-1 co-agonists may enhance efficacy. Further research into these pathways will be essential to optimize the clinical application of these therapies.

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