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Mini-Review

Innovative Glucagon-based Therapies for Obesity

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Abstract

Obesity poses a significant global health challenge, with an alarming rise in prevalence rates. Traditional interventions, including lifestyle modifications, often fall short of achieving sustainable weight loss, ultimately leading to surgical interventions, which carry a significant burden and side effects. This necessitates the exploration of effective and relatively tolerable pharmacological alternatives. Among emerging therapeutic avenues, glucagon-based treatments have garnered attention for their potential to modulate metabolic pathways and regulate appetite. This paper discusses current research on the physiological mechanisms underlying obesity and the role of glucagon in energy homeostasis. Glucagon, traditionally recognized for its glycemic control functions, has emerged as a promising target for obesity management due to its multifaceted effects on metabolism, appetite regulation, and energy expenditure. This review focuses on the pharmacological landscape, encompassing single and dual agonist therapies targeting glucagon receptors (GcgRs), glucagon-like peptide-1 receptors (GLP-1Rs), glucose-dependent insulinotropic polypeptide receptors (GIPRs), amylin, triiodothyronine, fibroblast growth factor 21, and peptide tyrosine tyrosine. Moreover, novel triple-agonist therapies that simultaneously target GLP-1R, GIPR, and GcgR show promise in augmenting further metabolic benefits. This review paper tries to summarize key findings from preclinical and clinical studies, elucidating the mechanisms of action, safety profiles, and therapeutic potential of glucagon-based therapies in combating obesity and its comorbidities. Additionally, it explores ongoing research endeavors, including phase III trials, aimed at further validating the efficacy and safety of these innovative treatment modalities.

Key Words: obesity, glucagon, GLP-1, GIP, dual-agonist therapies, triple agonist therapies

Obesity

Obesity is a complex, chronic, miscellaneous disease marked by excessive fat accumulation that significantly impacts health with an alarming rise in global prevalence, affecting over 890 million adults by the year 2022. Obesity substantially increases the risk of contracting more than 200 diseases, such as arterial hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, cerebral vasculopathy, gallbladder lithiasis, arthropathy, sleep apnea syndrome, and neoplasms [1, 2]. In 2022, a World Health Organization survey stated that 16% of adults are obese and 43% are overweight. According to World Health Organization estimates, by the year 2045, around 25% of the world population will be obese, further escalating obesity's health and socioeconomic burdens [2]. While bariatric surgery remains the gold standard treatment for extremely obese patients, the need for less invasive and effective pharmacological alternatives has driven the exploration of novel therapeutic approaches in the treatment of obesity, particularly those targeting specific metabolic hormones [3].

Weight regulation involves a complex interplay of metabolic hormones interacting with key brain regions like the hypothalamus. The arcuate nucleus, the paraventricular nucleus, and the lateral hypothalamus regulate body weight by the interplay of these hormones. Pro-opiomelanocortin from the arcuate nucleus under the influence of proprotein convertase subtilisin/kexin type 1activates melanocortin-4 receptor and decreases body weight. On the other hand, neuropeptide Y (NPY)/agouti-related peptide inhibits melanocortin-4 receptor and activates the lateral hypothalamus, causing weight gain. Disruption of this fine-tuned control leads to an imbalance between energy intake and expenditure as well as dysregulation of peripheral metabolism resulting in weight gain and obesity [4].

Appetite-regulating brain areas such as the striatum, insula, and orbitofrontal cortex commonly activated by viewing rewarding and energy-dense food pictures are also involved in obesity pathophysiology. The monoamine neurotransmitters norepinephrine, serotonin, and dopamine were identified as circuitry mediators in these brain regions [5]. This laid the basis for older drugs like phentermine, a combination of phentermine and topiramate, a combination of naltrexone, and bupropion in their use to treat obesity [6].

In addition, body weight is also regulated by hormones [leptin, ghrelin, cholecystokinin, insulin, amylin, pancreatic polypeptide, peptide YY (PYY), glucose-dependent insulinotropic polypeptide (GIP), oxyntomodulin (OXM) and glucagon-like peptide-1 receptors (GLP-1R) agonist] [7]. A new generation of highly effective, hormone-based pharmacotherapeutics, including glucagon-based therapies for obesity, is on the horizon, which have both local and central (gut-brain axis) actions [5].

Glucagon

Discovered in 1923 by Charles Kimball and John Murlin, glucagon is one of the key metabolic hormones that plays a

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critical role in energy balance and glucose metabolism [8]. Glucagon has a catabolic effect (opposing the effects of insulin); increases gluconeogenesis, glycogenolysis, lipolysis, and ketogenesis; and decreases glycolysis and lipogenesis. It increases satiety, insulin secretion, resting energy expenditure, and heart rate. It is stimulated by hypoglycemia, GIP, and amino acids. Its secretion is inhibited by hyperglycemia, insulin, GLP-1, somatostatin, zinc, and amylin.

Glucagon, a 29-amino-acid peptide, is one of the endproducts of the 160-amino acid precursor peptide proglucagon, a polypeptide expressed within pancreatic alpha cells, within enteroendocrine L cells, and to a minor extent within the hypothalamus and brain stem. Other end products of proglucagon include GLP-1, glucagon-like peptide 2, glicentin, glicentin-related pancreatic polypeptide, major proglucagon fragment, intervening polypeptide 1, intervening polypeptide 2, and OXM [9, 10]. OXM contains the complete amino acid sequence of glucagon but with the addition of 8 amino acids on the C-terminal known as the intervening peptide [11]. Glicentin contains the sequence of OXM with an N-terminal extension [10]. The major proglucagon fragment is identified as the carboxy-terminal portion of proglucagon that contains 2 glucagon-related sequences [12]. Even though these peptides are derived from the same precursor protein, proglucagon, they have highly specific and sometimes opposing effects on glucose and energy metabolism. As a result, the body needs to regulate the processing of proglucagon in a tissue-specific manner. One of these regulating mechanisms is the differential tissue expression of prohormone convertase 2 and prohormone convertase 1/3, which allows tissue-specific processing of proglucagon into either glucagon (via prohormone convertase 2) or GLP-1 and glucagon-like peptide 2 via prohormone convertase 1/3 [9] (Fig. 1).

Glucagon mediates its metabolic effect through the GcgR, a member of the 7-transmembrane-spanning G protein-coupled receptor superfamily, which is expressed in the liver, kidney, intestinal smooth muscle, brain, adipose tissue, heart, pancreatic β cells, and placenta [13]. At the hypothalamus level, food intake reduction occurs either through direct action at GcgR within the arcuate nucleus or via GcgR-expressing afferent vagal nerves from the liver [14]. Different studies have shown that glucagon can, in fact, have a solid influence on the regulation of body weight. It was first in the 1950s when Schulman et al showed that glucagon reduced appetite and could even cause weight loss in men [15]. Later in 1960, Salter demonstrated using a pair-feeding paradigm that energy expenditure in rodents increases after glucagon administration; this was later confirmed by indirect calorimetry [16].

Energy expenditure enhancement associated with acute GcgR agonism predominantly originates from substrate processing within hepatic glycogenolysis and, to a lesser extent, gluconeogenesis (Fig. 2). The increase in energy expenditure due to chronic GcgR agonism seems to primarily originate from an increase in sympathetic tone, which ultimately escalates brown adipose tissue thermogenesis and browning of white adipose tissue [17]. The use of GLP-1R agonists, glucagon agonists, GLP-1–glucagon dual agonists (DualAG), GIP–GLP1–glucagon receptor agonists, and GLP1–GIP agonists has led to the premise that incorporating glucagon receptor agonists reduces energy intake, increases energy expenditure, or potentially enhances efficacy [18].

This review provides a comprehensive analysis of recent advances in the therapeutic use of glucagon and related proteins, highlighting the development of single, dual, and triple receptor agonists. These include agonists targeting GcgRs, GLP-1R, GIPRs, and other hormones involved in metabolic regulation. The article examines their mechanisms of action, efficacy, and potential as innovative treatments for obesity, with a focus on how these multireceptor approaches may offer improved outcomes in weight management.

Method

We searched PubMed at research4life, Hinari, using the following terms: (obesity) AND (glucagon mono agonist or glucagon DualAG or glucagon triple agonist). The initial search yielded 178 items. Of these, 123 were excluded because they were older studies of drugs that had already new studies or those studies that discussed out of this article's objectives. Original peer-reviewed research and review articles published in English were included, but unpublished articles or thesis were excluded from the review. Additional references were identified by reviewing standard textbooks' reference lists and were included in the review if they met the aforementioned criteria.

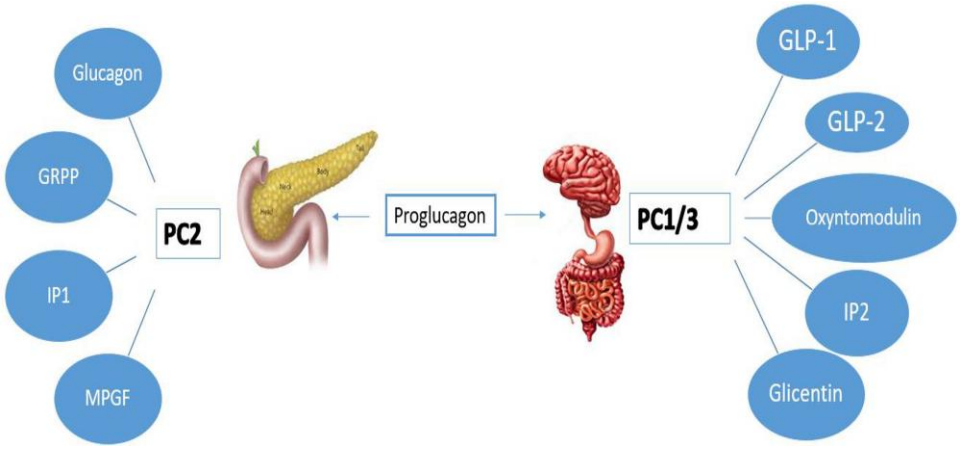

Figure 1. Proglucagon processing at different organs.

Abbreviations: GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2; GRPP, glicentin-related pancreatic polypeptide; IP1, intervening peptide 1; IP2, intervening peptide 2; MPGF, major proglucagon fragment; PC1/3, proconvertase 1/3; PC2, prohormone convertase 2.

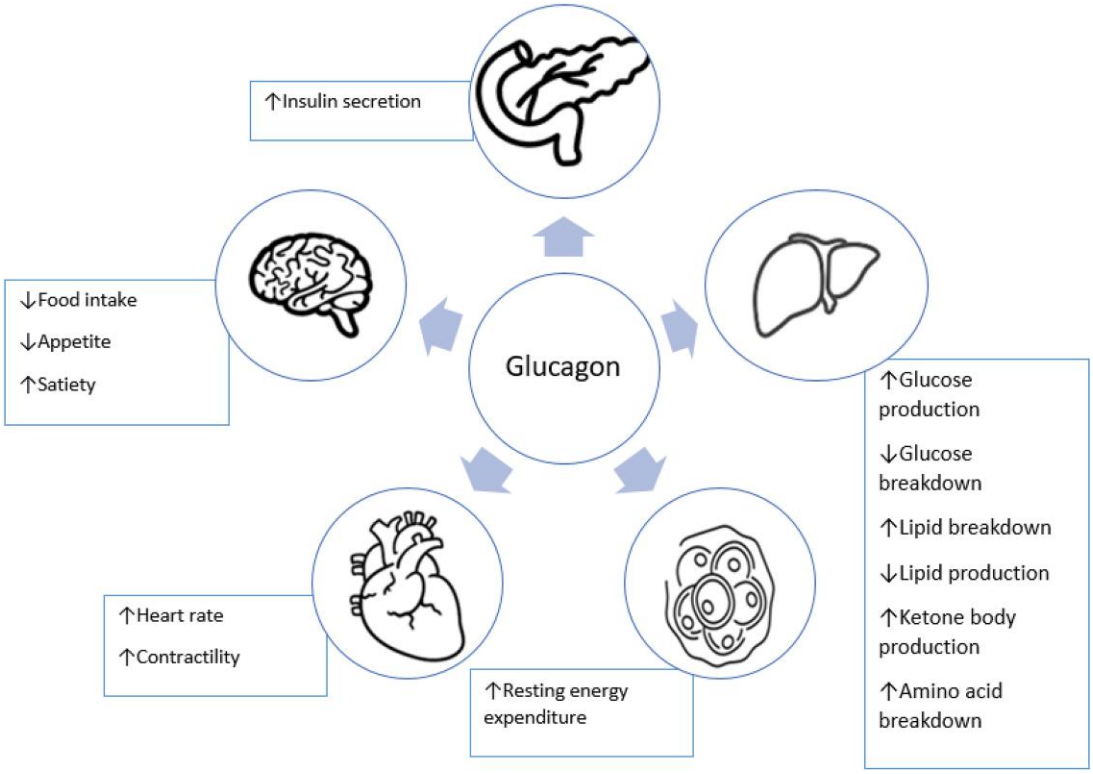

Figure 2. Physiological actions of glucagon on different organs.

Single Agonist Therapy

Two main groups of drugs are used as a single agonist therapy acting on a single specific receptor to treat obesity. These groups of drugs are GLP-1 and glucagon receptor agonists.

GLP-1R Agonist Treatment

These drugs are classified into peptide and a newer, nonpeptide GLP-1R agonist. Among the peptide GLP-1R agonists are semaglutide and liraglutide, which are widely used in the treatment of obesity. The other group includes recently discovered orforglipron and danuglipron. These drugs reduce weight mainly by reducing calory intake acting at GLP-1 receptors, which are mainly found in the hypothalamus and the hindbrain. GLP-1Rs, when activated, depolarize (stimulate) proopiomelanocortin/cocaine-and amphetamine-regulated transcript pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript neurons and hyperpolarize (inhibit) NPY/agouti-related peptide neurons. That results in reduced caloric intake leading to weight loss. GLP-1R agonism has also been shown to reduce anticipatory food reward, reducing craving for food and consummatory food reward and preventing overeating [19]. The impact of GLP-1 on food intake extends beyond homeostatic (or metabolic, need-based) food intake. There may be a potential activity of GLP-1 in areas classically associated with reward behavior such as the ventral tegmental areas and the nucleus accumbens [20].

Liraglutide is a GLP-1R agonist with 97% homology to human GLP-1 [5]. Specifically targeting obesity, liraglutide has undergone 5 randomized double-blind placebo-controlled trials in adults. In obese people, 3 mg liraglutide administered subcutaneously modifies regional body fat reserves, gut hormones, hunger, and taste preferences without lowering lean body mass [21]. The mean weight loss associated with liraglutide was 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg at different doses in the SCALE (Satiety and Clinical Adiposity Liraglutide Evidence) randomized controlled study. This was in comparison to 2.8 kg mean weight loss with placebo and 4.1 kg mean weight loss with orlistat, and it was 2.1 to 4.4 kg larger than the weight loss associated with placebo [22].

In the SCALE TEENS trial, liraglutide (3.0 mg) plus lifestyle was compared to placebo plus lifestyle therapy in obese adolescents regarding the change in body mass index [23]. In another study, the SCALE Intensive Behavioral Therapy (IBT) randomized control trial (RCT), the mean weight loss associated with liraglutide 3.0 mg plus IBT was compared to placebo plus IBT at week 56. Both trials (the SCALE TEENS and SCALE IBT trials) showed a significant body weight reduction by liraglutide 3.0 mg. The SCALE TEENS trial resulted in a significant reduction of body weight in adolescents with obesity compared to placebo using 3.0 mg liraglutide (estimated difference, 0.15; 95% confidence interval, 0.07 to 0.23) and the SCALE IBT trial showed a significant difference in weight loss when liraglutide 3.0 mg was used with IBT (7.5% mean body weight loss), compared to placebo combined with IBT (4.0% mean body weight loss) in individuals with and without diabetes [24]. Liraglutide gained Food and Drug Administration (FDA) approval on December 23, 2014, as a treatment option for chronic weight management [25].

Semaglutide is a recent-generation long-acting GLP-1R agonist that is chemically modified and designed for once-weekly subcutaneous administration [26]. Its absorption in specific brain regions may be modulated by special ependymal cells called tanycytes. The uptake of liraglutide and semaglutide into selected brain areas is similar but not fully identical (eg, semaglutide had a distribution extending more laterally and into posterior portions of the nucleus arcuatus) [19].

Semaglutide is one of the few drugs that are FDA approved for the treatment of obesity [27]. It was approved on June 4, 2021, for chronic weight management in adults with obesity or for those who are overweight and have at least 1 weight-related condition [28]. Several RCTs showed the efficacy and tolerability of semaglutide for the treatment of obesity. Among these trials are the STEP (Semaglutide Treatment Effect in People with Obesity) series of RCTs. The first of these trials, the STEP 1 trial, compared 2.4 mg of weekly semaglutide plus lifestyle intervention with placebo plus lifestyle intervention for 68 weeks in obese nondiabetic patients, and the result showed a clinically significant and sustained average weight loss among the semaglutide group (14.9%) and a difference of 12.4% compared to the placebo and lifestyle group (2.4% mean weight loss) [29].

In 1 of the RCT trials, semaglutide lowered body weight by 5.0 kg from baseline, primarily by reducing body fat mass [30]. Subsequent STEP trials on diabetic patients (STEP 2), added-on therapy on intensive lifestyles (STEP 3), a study in Asian people (STEP 6), a comparison study with liraglutide (STEP 8), a study in adolescents (STEP TEENS), a study in persons with heart failure with preserved ejection fraction (STEP-HFpEF), and a study assessing cardiovascular outcome (SELECT-Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity trial) showed significant benefit of semaglutide for treatment of obesity and cardiovascular diseases [31-37]. These trials showed that semaglutide resulted in an average body weight reduction ranging from 8.4% up to 17% from baseline weight among participants. These trials revealed that semaglutide is effective and tolerable among different population groups, age ranges, and comorbidities, especially among those with type 2 diabetes mellitus (T2DM), obesity, and HFpEF.

Higher doses (50 mg daily) of oral semaglutide showed 15.1% weight loss compared to 2.4% weight loss with placebo in individuals with obesity and without T2DM in the OASIS trials [38]. Oral semaglutide at doses of 25 and 50 mg were superior to a lower dose, 14 mg, in reducing hemoglobin A1c and body weight in adults with inadequately controlled type 2 diabetes in the PIONEER PLUS study [39]. In general, semaglutide was more effective than other drugs in this category, and this effect looks to be dose-dependent, resulting in better weight loss when higher doses are used compared to lower doses in patients with obesity regardless of their diabetes status.

Recently, in 2023, newer nonpeptide GLP-1R agonists, orforglipron and danuglipron, have been focus areas in research in the management of obesity. In 2023, a daily oral orforglipron was found to be associated with weight reduction (9.4% to 14.7%) with similar adverse events when compared to subcutaneous GLP-1R agonists [40]. A meta-analysis of these newer oral GLP-1R agonists (orforglipron and danuglipron) showed a statistically significant weight reduction in patients with T2DM or obesity compared to controls (3.26 kg and 7.52 kg, respectively) [27]. These drugs are promising to be effective for weight loss, and further development is needed until they are approved for use.

Glucagon Receptor Agonist

Glucagon receptor has been localized to the brain and pancreas, as well as the heart, kidney, liver, and adipose tissue, suggesting pleiotropic effects in the body [41]. Glucagon has been traditionally used for the treatment of hypoglycemia due to its rapid ability to increase blood glucose levels by stimulating glycogen breakdown in the liver. However, its short half-life and quick pharmacokinetics (approximately 5-8 minutes following IV administration) have limited its potential as a therapeutic option for other diseases like obesity for a long time. The solubility and stability of the glucagon peptide can be improved by an N28D substitution or the addition of the Exendin-4 CEX sequence to the glucagon C-terminal end. IUB288, GCG104, G108 peptides, and HM15136 are longer-acting glucagon agonists. Both acute and chronic administration of IUB288 increase energy expenditure, as measured by indirect calorimetry, in chow-fed mice, and this effect is similarly reflected in an increase in core temperature in diabetic mice [14].

A comparison between the water-soluble glucagon receptor monoagonist glucagon CEX (Gcg CEX) and the GLP-1R mono-agonist exendin-4 at 1 μmol/kg/day in diet-induced obesity mice demonstrated nearly equivalent degrees of body weight loss and improvements in glucose metabolism, both without signs of fasting hyperglycemia [9]. Therefore, the availability of glucagon agonists with similar efficacy would enhance personalized medicine options in metabolic disease management and could lead to innovative therapeutic combinations.

Dual Agonist Therapy

Since the discovery of dual gut hormone agonists' effect of eliminating obesity in rodents in 2009 [18], numerous other combinations of gut hormones have been in different phases of trial for the treatment of obesity. Among these dual combinations of GcgR agonists, GLP-1R agonists, amylin receptor agonists, GIPR agonists, PYY receptor agonists, and T3 receptor agonists will be reviewed next.

GLP-1R/GcgR/IP-1 Dual Agonism

Coadministration of glucagon with GLP-1 has been shown to preserve the energy expenditure effects of glucagon while nearly eliminating the net hyperglycemic excursion in both mice and humans [42, 43]. Due to the overlapping effects of glucagon and GLP-1 in eliciting food intake reductions, coadministration in humans synergistically reduces food intake, thus allowing for lower doses of GLP-1R agonist [44].

OXM is a combination of glucagon and additional IP-1. OXM shows better weight loss, lipid-lowering, and blood sugar control than GLP-1R agonists. Chronic treatment with the DualAG led to greater improvements in metabolic markers like insulin, leptin, and adiponectin compared to GLP-1R. DualAG also boosted fatty acid oxidation and reduced liver fat in diet-induced obese (DIO) mice. In a 14-day study, DIO mice treated with DualAG or GLP-1R agonists (1.9 μmol/kg) had significantly more weight loss, with DualAG causing a 25% drop vs 12% for GLP-1R [43].

The GLP-1R/GcgR dual agonist Bamadutide, SAR425899, underwent a phase I single- and multiple-ascending-dose clinical trial with daily subcutaneous administration in both healthy/overweight subjects and overweight/obese patients with T2DM. Over 21 to 28 days, SAR425899 resulted in a maximal reduction in body weight of 5.32 kg in healthy/overweight patients. Overweight/obese patients with T2DM experienced maximal reductions in body weight of 5.46 kg along with significant reductions in fasting plasma glucose and

glycated hemoglobin. However, SAR425899 was discontinued in phase II clinical trials due to the high occurrence of gastrointestinal adverse events in the subjects [45].

Cotadutide, also known as MEDI0382, is a 30-amino acid linear single-chain peptide (subcutaneous administration once daily) and a synthetic analog of the human hormone glucagon and human GLP-1, which has been modified to have a balanced agonist activity for both GLP-1 and Gcg receptors [46]. It was used in a once-daily multiple ascending dose phase Ib clinical trial and a 41-day phase IIa trial in overweight and type 2 diabetic patients, and the general safety and tolerability of MEDI0382 were established, as was its placebo-corrected efficacy in reducing fasting blood glucose (1.7 mmol/L), postprandial glucose excursions following a mixed meal test (22.6% area under the curve 0–4 hours), body weight (2.1 kg), and liver fat (19.6%). However, the number of subjects who experienced adverse effects leading to study discontinuation was approximately 5x and 20x greater than that of liraglutide for the 100 μg and 200 μg doses, respectively [47].

Efinopegdutide (MK-6024) is a synthetic peptide of OXM conjugated to the constant region of human IgG4 that acts as a dual GLP-1R and glucagon receptor agonist, with a GLP1R: glucagon receptor relative potency of approximately 2:1 [48]. Efinopegdutide weight loss effects were seen as early as 12 weeks using 5.0, 7.4, and 10 mg once-weekly treatment, which resulted in significant placebo-subtracted body weight reductions of 4.6%, 5.9%, and 7.2%, respectively [49]. However, the rate of patient discontinuation due to adverse effects from this treatment was higher than liraglutide side effects [50].

Another drug in this category is mazdutide (also known as IBI362 or LY3305677), which is potentially thought to offer superior therapeutic benefits compared to GLP-1R agonists alone. In a phase I clinical trial, patients who were overweight or obese were able to reduce their body weight by 4.8% (3 mg dosage), 6.4% (4.5 mg), and 6.0% (6 mg) after receiving a once-weekly dose of mazdutide [51]. A phase II research with Chinese individuals showed that 9 mg of mazdutide therapy resulted in an 18.6% mean body weight decrease over 48 weeks when adjusted for placebo [52]. Four phase III studies are currently investigating the benefits of this drug, enrolling patients who are overweight or obese (GLORY-1 and GLORY-2) and who have type 2 diabetes (DREAM-1 and DREAM-2) in China.

Survodutide (BI 456906J) is also a novel, potent GCGR/GLP-1R DualAG developed by Boehringer Ingelheim in 2024. It reduced plasma alanine and glucagon levels, indicating indirect target engagement at GcgRs and GLP-1Rs [53]. This drug achieved body weight reductions of 5.8% over 6 weeks and 13.8% over 16 weeks at the maximal dosages within a multiple rising dose phase Ib clinical study. Patient discontinuation occurred in 12.5% (6 weeks) and 17.8% (16 weeks) of patients due to gastrointestinal, vascular, or cardiac adverse effects, respectively [54]. In a randomized, double-blind, placebo-controlled, dose-finding phase II trial, the body weight reductions from baseline to week 46 were 6.2% (8.3 to 4.1; 0.6 mg), 12.5% (14.5 to 10.5; 2.4 mg), 13.2% (15.3 to 11.2; 3.6 mg), 14.9% (16.9 to 13.0; 4.8 mg), and 2.8% (4.9 to 0.7; placebo) [53]. Another RCT on the reduction in body weight caused by survodutide compared with that caused by open-label semaglutide in people with T2DM showed a dose-dependent decrease in body weight of up to a mean (95% confidence interval) of 8.7% (10.1, 7.3); 6, n = 37]; survodutide ≥1.8 mg produced greater body weight reductions than semaglutide [5.3% (6.6, 4.1); n = 45] [55]. SYNCHRONIZE-1, SYNCHRONIZE-2, and SYNCHRONIZE-CVOT are ongoing phase III studies of survodutide in people living with obesity and overweight without diabetes, people with T2DM. and people with long-term cardiovascular safety [56]. These trials are crucial for determining the full therapeutic potential of survodutide in different patient populations and its role in managing obesity, diabetes, and cardiovascular health.

Last but not least in this group is pemvidutide, which is being developed not only for the treatment of obesity but also for the treatment of T2DM and nonalcoholic fatty liver disease. With a 2.4 mg dose of pemvidutide at week 48, a phase 2 obesity trial of pemvidutide (MOMENTUM 48-week trial) found a mean weight loss of 15.6%. With a 2.4 mg dose, over 30% of the subjects lost 20% or more of their body weight by week 48 which is better than single drugs [57].

Amylin Agonist or Dual Agonism With GLP-1 and Amylin

Amylin is a pancreatic islet cell hormone, cosecreted with insulin from beta cells in response to nutrient intake [58]. Despite their similarities with GLP-1R agonist (eg, both molecular classes slow gastric emptying, decrease glucagon, and inhibit food intake), there are important distinctions between the central and/or peripheral pathways that mediate their effects on glycemia and energy balance [59]. Amylin acts on (1) appetitive/energy-regulating neurons in the hypothalamus impacting food intake, (2) dopaminergic neurons in the ventral tegmental area impacting reward and motivation, and (3) chemoreceptive neurons in the area postrema/nucleus tractus solitarius [60].

The first among long-acting novel amylin analogs is cagrilintide, which was discovered in 2021. In the phase II trial of cagrilintide, mean percentage weight reductions from baseline were greater with all doses (0.3-4.5 mg, 6.0-10.8%) vs placebo (3.0%). Weight reductions were also greater with cagrilintide 4.5 mg vs liraglutide 3.0 mg (10.8% vs 9.0%) [61]. Another drug in this group is petrelintide (ZP8396), which selectively reduces intake of a high-fat diet in DIO rats [62]. It is well tolerated with improved gastrointestinal tolerability after multiple dosing in humans too [63].

Compared with individual monotherapies, combined treatment with amylin, GLP-1, and their analogs has been shown to enhance the suppression of food intake and body weight gain [64]. This was demonstrated in a phase 2 trial, where weight loss associated with the combination of cagrilintide/semaglutide was 15.6% compared to cagrilintide (8.1%) and semaglutide (5.1%) [65]. Amycretin, a pill that targets both amylin and GLP-1Rs, caused significant weight loss in a recent phase 1 study. When taken over 3 months, a daily dose of amycretin resulted in a 10.4% loss in weight, and those who took 2 pills lost 13.1% of their body weight [66].

GIPR and GLP-1R Agonist Treatment

GIP is a 42-amino-acid nutrient-stimulated hormone secreted from entero-endocrine cells in response to nutrient intake [67]. GIP receptors have been identified in adipose tissue, bone, and the brain. GIP is thought to potentially decrease food intake through its action in the hypothalamus [68].

Tirzepatide is a GIPR and GLP-1R agonist with a half-life of ~117 hours that slows gastric emptying and decreases food intake. GLP-1 quells the potential glucagon-stimulatory effects of GIP and also (re)sensitizes beta cells to GIP's incretin effect [69].

In a SURMOUNT-1 trial of obese adults without diabetes, tirzepatide at dosages of 5, 10, or 15 mg reduced weight by an average of 15.0%, 19.5%, and 20.9%, respectively, compared with only 3.1% in those receiving a placebo [70]. The US FDA approved subcutaneous tirzepatide for chronic weight management on November 8, 2023 [71]. The subsequent SURMOUNT-2 trial confirmed that those with diabetes also had significant weight loss. In this study, 82.7% of subjects lost at least 5% of their body weight and 48.0% lost at least 15% at the highest tirzepatide dosage [72]. In the SURMOUNT-3 trial, tirzepatide demonstrated clinically meaningful additional body weight reductions (6.9%) in adults who were overweight or obese following initial weight loss with intensive lifestyle intervention [73]. Withdrawing tirzepatide in the SURMOUNT-4 trial resulted in a significant weight gain (14%), while continuing treatment preserved and increased the initial weight loss (5.5%) [74].

A meta-analysis revealed that, compared with the GLP-1R agonists, placebo, and insulin, tirzepatide significantly reduced body mass index, waist circumference, and body weight [75]. Patients receiving VK2735 demonstrated statistically significant reductions in body weight (more than 13.1%) compared with those receiving placebo in a phase 2 VENTURE trial with minimal side effects [66]. The compound CT-388 caused weight loss of 18.8% when adjusted for a placebo effect after 24 weeks in otherwise healthy adults with obesity [76].

Glucagon Agonist/GIPR Antagonist

Paradoxically, both GIPR agonists and GIPR antagonists have been shown to potentiate the weight reduction caused by GLP-1R agonists. GIPR antagonists may reduce fat accumulation and improve insulin sensitivity. AMG 133, for instance, combines GLP-1R agonism and GIP antagonism. This combination triggered a weight loss of 14.5% in a phase 1 trial of 110 people with obesity [77].

Glucagon-T3Combination

Thyroid hormones powerfully influence systemic metabolism through multiple pathways, with profound effects on energy expenditure, fat oxidation, and cholesterol metabolism [78]. In mice with obesity, glucagon and T3 work together to treat obesity, steatohepatitis, atherosclerosis, glucose intolerance, and hyperlipidemia. Liver-directed T3 activity counteracts glucagon's ability to cause diabetes, while glucagon-mediated delivery shields the cardiovascular system from the damaging effects of T3. After a week of glucagon/T3 treatment, an absolute 10% weight reduction from baseline was seen at a lower dose. Loss of fat mass, not lean mass, was the cause of the weight loss [79].

GLP-1 and FGF21 Combination

Fibroblast growth factor 21 is a peptide hormone that is synthesized by several organs and regulates energy homeostasis. It regulates insulin sensitivity, energy expenditure, browning of white adipose tissue, decreasing inflammation, promoting a healthier metabolic environment, and suppresses appetite [80]. Exendin-4/fibroblast growth factor 21 agonist, utilizing albumin-binding-designed ankyrin repeat proteins as carriers, displayed enhanced blood glucose lowering bioactivity and superior body weight management in the DIO mouse model. It has achieved a significant reduction of weight averaging 22.2 ± 3.7% [81].

GLP-1/PYY Combination

PYY is secreted from the L-cells of the colon and small intestine in response to food intake and is rapidly cleaved by DPP-IV to PYY $_{3–36}$. $PYY_{3–36}$ shows higher selectivity toward the Y2 receptor, which is 1 of the 4 receptors belonging to the NPY receptor family. It exhibits anorectic effects, making it an interesting target for research into obesity and diabetes [82]. A dipeptidyl peptidase IV-stabilized potent GLP-1/PYY dual-acting analog demonstrated an improved capability of lowering the food intake compared to the stand-alone effect of GLP-1 and PYY [83]. In a recent preclinical study, a combinatory treatment with a nonselective PYY analog and semaglutide led to a maximum body weight loss of 14.0 ± 4.9% vs 9.9 ± 1.5% with semaglutide alone. In this study, nonselective and NPY-Y2 receptor selective PYY analog combined with semaglutide showed a maximum weight loss of 20.5 ± 2.4% [84].

Triple Agonist Treatment

Due to the success of both DualAG approaches and the generally high sequence homology between GLP-1, GIP, and glucagon, the next step in novel pharmaceutical development was the design of chimeric GLP-1R/GIPR/GcgR unimolecular triple-agonists followed by the development of another triple agonist, a GLP-1/glucagon/Y2 receptor triple agonist [85].

GLP-1R/GIPR/GCGR Triple-Agonists Treatment

Tri-agonist analogs, which activate the glucagon, GLP-1, and GIPRs, have been developed with the aim that the additional GIP activity will further offer better protection from glucagon-induced hyperglycemia. GLP-1, GIP, and glucagon each impact food intake and satiety through disparate mechanisms, playing complementary roles in maintaining the body's defended fat mass set point. Three GLP-1R/GIPR/GcgR triple agonists, LY3437943, HM15211, and SAR441255, have surpassed preclinical testing and have entered clinical trials due to profound efficacy and safety through synergism [14].

Retatrutide (LY-3437943) is a 39 amino acid peptide with 3 noncode amino acid residues at positions 2, 20, and 13. Stability is increased by the amino acid sequence Aib2, or amino isobutyric acid, which is an inhibitor of DPP4 cleavage. The other 2 noncode amino acids affect the pharmacokinetic profile, optimal GIP activity, and glucagon levels [86]. It is an agonist for the glucagon receptors, glucagon-like peptide 1, and glucose-dependent insulinotropic polypeptide. It has more potency at the human GIPR and reduced potency at the glucagon and GLP-1Rs in humans [86]. A dose of 1 to 8 mg once weekly was given for 48 weeks in a phase 2 randomized controlled study for people with medical indications for weight management. The mean percentage weight reduction in the retatrutide groups at 48 weeks were 8.7%, 17.1%, 22.8%, and 24.2% for the groups treated with 1 mg, combined 4 mg, combined 8, and 12 mg, respectively. With just mild gastrointestinal side effects, it was able to achieve a metabolically significant (more than 5%) weight reduction in 100% of the patients who received 8 mg and above [87]. A study of

Table 1. Summary of different glucagon-based medications together with their drug class for obesity

Drug class	Specific drugs		Trial phase
Monotherapies	GLP-1R agonists	Liraglutide (SC)	SCALE trials, phase III
		Semaglutide (SC)	STEP trials, phase III
		Semaglutide (PO)	OASIS trials Phase III
		Danuglipron (PO)	Phase II
		Orforglipron (PO)	Phase II
	Glucagon receptor agonist	IUB288	Preclinical
		Glucagon CEX	Preclinical
		Exendin-4	Preclinical
	Amylin agonist	Cagrilintide	Phase II
		Petrelintide	Phase I
Dual agonists	GIPR and GLP-1R DualAG	Tirzepatide	SURMOUNT trials, phase III
		VK2735	VENTURE trial phase II
		CT-388	Phase Ib
	Amylin/GLP-1R DualAG	Cagrilintide/semaglutide	Phase II
		Amycretin	Phase I
	GLP-1R/GcgR DualAG	Mazdutide	GLORY, DREAM trials,Phase III trials
		Survodutide	SYNCHRONIZE trials, Phase III
		BI456906	
		Efinopegdutide (MK-6024)	Phase II
		Cotadutide (MEDI0382)	Phase IIa
		Pemvidutide	MOMENTUM trial, Phase II
		Bamadutide (SAR425899)	Phase I
		OXM	Preclinical
	Glucagon agonist/GIP antagonist	AMG 133	Phase I
	Glucagon—T3 combination	Glucagon and T3	Preclinical
	GLP-1 and FGF21 combination	Exendin-4 -FGF21 agonust	Preclinical
	GLP-1/PYY Combination	GLP-1/PYY dual agonist	Preclinical
Triple agonists	GLP-1R/GIPR/GcgR triple agonists	LY3437943 (Retatrutide)	Phase II
		SAR441255	Phase Ia
		HM15211	Phase II
	GLP-1R/GcgR/Y2 receptor triple agonist	Peptide 3b	Preclinical

Abbreviations: DualAG, dual agonist; FGF21, fibroblast growth factor 21; GcgR, glucagon receptors GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1R, glucagon-like peptide 1 receptor; PO, by mouth; PPY, peptide YY; SC, subcutaneous.

retatrutide (LY3437943) in participants with obesity and cardiovascular disease (TRIUMPH-3) is currently ongoing [88].

SAR441255, a recently developed triple agonist based on the exendin-4 sequence, demonstrated improved glycemic control in healthy human subjects following a mixed-meal test in a phase I single-dose clinical trial. Additionally, SAR441255 exhibited extensive improvements in body weight and glycemic control in diabetic obese monkeys [89]. Another triple agonist drug, HM15211, significantly improved body weight loss (~3.0-fold in diet-induced obese mice relative to liraglutide at a dose equivalent to 3 mg/day in humans) under similar food intake conditions. Regarding the proposed mechanism of action, HM15211 could induce increased energy expenditure compared to liraglutide. In addition, HM15211 had no hyperglycemic risk owing to its balanced GLP-1/GIP action [90].

GLP-1/Glucagon/Y2 Receptor Triple Agonist

In a preclinical study of DIO mice, peptide 3b (GLP-1/glucagon/Y2 receptor triple agonist) potently reduced food intake without triggering nausea and had a significantly better effect on lipid metabolism, body weight, and glycemic control than a higher dose of GLP-1R monoagonist, GLP-1R/GCGR DualAG and GLP-1R/Y2R DualAG counterparts [91].

Conclusion

The burgeoning field of glucagon-based therapies represents a paradigm shift in obesity management, offering novel strategies to address the escalating global burden of obesity and its associated complications. They decrease food intake, slow gastric emptying, enhance satiety, increase body metabolism, and increase energy expenditure, which, eventually, results in weight loss. Three of the FDA-approved anti-obesity medications like semaglutide 2.4 mg, liraglutide 3 mg, and tirzepatide (5-15 mg) are glucagon-based therapies. Different antiobesity drugs have varying effects on individuals, necessitating the use of several management options. Multiple newer hormonal-based fixed combination dual or triple agonist drugs are even surpassing the currently approved medications. The triple agonist retatrutide weight loss reduction is almost equivalent (as high as 24.2% weight reduction) to surgical interventions. Despite all these advancements, managing obesity remains complex, requiring ongoing research to refine multitargeted therapies that address its hormonal and metabolic challenges while minimizing the side effects of the drugs (Table 1).

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The authors have nothing to disclose.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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