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Novel therapeutic targets in the treatment of obesity: a review

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ABSTRACT

Obesity is a chronic condition that increases the risk of both complications and mortality. The development of effective and safe entero-pancreatic peptide-based pharmacotherapies (such as those targeting ghrelin, leptin, peptide YY, and related molecules) requires a nuanced understanding of the gut–brain axis and its role in regulating appetite and body weight. This brief review places particular emphasis on novel incretin-based agents co-formulated with glucagon and neuropeptide Y, which have demonstrated weight-reduction outcomes approaching those of bariatric surgery, yet without the invasiveness of surgical intervention. In cases where obesity-related comorbidities (such as type 2 diabetes mellitus) are present, such substantial weight loss may contribute to clinical improvement, especially given that many of these agents exert independent effects on glycaemic control. Additionally, we herein evaluate the therapeutic potential of ghrelin inhibition *via* ghrelin-O-acyltransferase blockade, concluding that this approach does not yield meaningful effects on satiety, body weight, or caloric intake. Finally, we discuss emerging compounds currently under clinical investigation that may offer future avenues for obesity treatment.

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1. Introduction

Excess body fat is a defining feature of obesity, which increases the risk of multiple conditions, including dyslipidaemia, hypertension, type 2 diabetes mellitus, osteoarthritis, nonalcoholic fatty liver disease, sleep apnoea, and infertility. Obesity may reduce life expectancy by 5 to 20 years and significantly elevate healthcare costs[1]. The body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, is the standard metric for assessing obesity; a BMI

PHARMAKEFTIKI, 37, 2S, 2025 | 480-483

of 18.5–24.9 kg/m^2 is considered normal, 25.0–29.9 kg/m^2 is classified as overweight, and ≥30.0 kg/m^2 is defined as obese[1].

Obesity arises from multifactorial causes, including excessive caloric intake, genetic predisposition, insufficient sleep, sedentary lifestyle, medical conditions, pharmacotherapy, ethnic background, psychosocial stressors, socioeconomic disparities, and exposure to endocrine-disrupting chemicals[2]. Although lifestyle interventions remain foundational in obesity management, even intensive programs typically yield only 5%–10% weight loss, complicating long-term maintenance. Approved pharmacotherapies for chronic weight management are limited by cost-effectiveness, clinical efficacy, and long-term cardiovascular safety concerns[1].

Several gastrointestinal peptides such as ghrelin, leptin, cholecystokinin (CCK), peptide YY (PYY), and neuropeptide Y (NPY) have been investigated as potential anti-obesity agents due to their roles in appetite regulation *via* the central nervous system[2]. This review provide a brief overview of novel therapeutic targets with potential for safe and effective anti-obesity treatment.

2. Ghrelin

Ghrelin is an orexigenic hormone that stimulates appetite and promotes adiposity through mechanisms such as the activation of orexigenic neurons, the enhancement of triglyceride uptake in white adipose tissue, and increased lipogenesis[3]. BI1356225, a ghrelin-O-acyltransferase antagonist currently in phase 1 trials, was administered to adult subjects with a BMI of 27.0–39.9 kg/m^2 for 28 days at doses of 0.2, 1.0, 2.5, or 10.0 mg. It significantly reduced the acyl-to-des-acyl ghrelin ratio (>80%), although no changes in satiety, body weight, or caloric intake were observed. The findings suggest that elevated des-acyl ghrelin may contribute to weight regulation[4].

3. PYY

PYY, secreted by intestinal endocrine cells, inhibits gastric acid secretion and gallbladder contraction. In obese individuals, elevated PYY levels suppress ghrelin release and prolong gastrointestinal (GI) transit time[5]. PYY analogs investigated in phase 1 trials (NCT02568306 and NCT03574584), were administered to overweight / obese volunteers subcutaneously (s.c.) every 7 to 14 days. These analogs demonstrated safety and potential efficacy, with weight reductions of 2.9 and 3.6 kg at 31 days and a 38%–55% decrease in food consumption compared to placebo[6].

4. Leptin

Leptin, a hormone correlated with BMI, is often elevated in obese individuals, leading to hypothalamic receptor saturation and impaired energy balance and satiety signalling. Hyperleptinaemia also affects GI function, reducing oesophageal motility. Animal studies show that exogenous leptin inhibits small intestinal motility and delays gastric emptying[5]. Mibavademab, a leptin analog in phase 2 trials, was administered to participants intravenously at doses of 0.3, 1, 3, 10, or 30 mg/kg or s.c. at 300 or 600 mg for 12 weeks; its impact on body weight varied depending on baseline leptin concentrations[7].

5. NPY

NPY, a neurotransmitter secreted by the adipose tissue, is elevated in obesity and contributes to increased appetite and delayed gastric emptying[5]. Velneperit, an NPY receptor subtype 5 inhibitor, was evaluated in a phase 2a trial involving 342 obese participants. Daily doses of 1,600 mg and 400 mg resulted in weight reductions of 5.3 kg (5.6%) and 2.5 kg (2.7%), respectively, with favourable tolerability and dose-dependent efficacy[5].

6. CCK

CCK is a gut-derived peptide that modulates appetite *via* the activation of the cholecystokinin type 1 receptor (CCK1R), making it a promising target for obesity therapy[8]. In obese Göttingen minipigs, NN9056 – a CCK1R analog – was administered once

PHARMAKEFTIKI, 37, 2S, 2025 | 480-483

daily s.c. at doses of 10, 20, 40, or 80 nmol/kg for 13 weeks. Food intake decreased for two days at 20 and 40 nmol/kg, and for four days at 80 nmol/kg, with concurrent reductions in body weight[8].

7. Growth-differentiation factor 15 (GDF-15)

GDF-15, a stress-responsive cytokine secreted by adipocytes, cardiomyocytes, and macrophages, is associated with weight loss and represents a potential therapeutic target[6]. In murine models, GDF-15 enhances satiety and reduces food intake. The GDF-15 agonist LY3463251, administered to mice s.c. once weekly at doses of 1–9 mg for 12 weeks, resulted in a 3% reduction in body weight. Early-phase clinical trials also include GDF-15 agonists JNJ-9090/CIN-109 and NNC0247-0829[6].

8. Theobromine

Theobromine exhibits anti-obesity properties *in vitro* and *in vivo* by activating brown adipose tissue, inducing browning of white adipose tissue, reducing inflammation, and mitigating oxidative stress. Administration of 200 μM theobromine to 3T3-L1 preadipocytes for 6–8 days decreased adipogenesis and enhanced lipolysis[9].

9. Glucagon-like peptide 1 (GLP-1) and glucagon

Glucagon analogs may increase energy expenditure *via* hypoaminoacidaemia, but can also lead to lean mass loss. Glucagon improves lipid metabolism and promotes hepatic fatty acid oxidation. GLP-1 reduces appetite, delays gastric emptying, and enhances satiety. Dual agonists targeting both glucagon and GLP-1 may optimize weight loss while minimizing hyperglycaemia risk[10].

Survodutide, in phase 2 trials, achieved up to 18.7% weight reduction *versus* 2% with placebo at weekly doses of 0.6–4.8 mg over 46 weeks and is progressing to phase 3. Mazdutide's phase 2 trial yielded an 11.3% weight reduction after 24 weeks at weekly doses of 3, 4.5, and 6 mg; phase 3 trials (4–9 mg) are ongoing in Chinese populations. Finally, efinopegdutide, evaluated in phase 2 trials at weekly doses of 5, 7.4, and 10 mg s.c. for 26 weeks, demonstrated weight reductions of 8.5%–11.8% *versus* 1.8%–7.5% in 295 *versus* 119 participants, respectively[6].

10. Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1

GIP, an endogenous incretin, regulates weight *via* lipid storage and metabolic activation. GIP antagonism improves metabolic parameters and suppresses food intake[10]. AMG133 (maridebart cafraglutide), a biphasic molecule combining GIP antagonism and GLP-1 agonism, produced a dose-dependent weight reduction of approximately 14.5% *versus* 1.5% with placebo in a phase 1 trial, after being administered s.c. every 4 weeks. AMG133 is currently undergoing a 52-week phase 2 trial in obese and overweight individuals[6].

11. Conclusion

Obesity, a global health challenge with numerous comorbidities, necessitates innovative therapeutic strategies. Targeting appetite-regulating peptides such as ghrelin, PYY, CCK, and GDF-15 offers promising avenues. Emerging treatments (including PYY analogs, CCK-positive allosteric modulators, and ghrelin receptor modulators) may provide more effective and safer options for long-term weight management.

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Conflicts of interest

None exist.

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PHARMAKEFTIKI, 37, 2S, 2025 | 480-483

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