New Chapter in Obesity Treatment: Mechanisms and Clinical Advances of Multi-Target Peptide Agonists (Postprint)

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Abstract

Obesity is a chronic, relapsing disease arising from the interaction of genetic and environmental factors, with continuously escalating global prevalence that has emerged as a major public health challenge. Traditional weight management strategies demonstrate limited efficacy. In recent years, peptide therapeutics targeting the glucagon-like peptide-1 receptor (GLP-1R), glucose-dependent insulinotropic polypeptide receptor (GIPR), and glucagon receptor (GCGR) have undergone rapid development, with multi-target agonists particularly evolving into a novel therapeutic trend. This article systematically introduces the mechanisms of action and clinical research advances of this pharmaceutical class: GLP-1R single-target agonists exhibit significant efficacy in weight reduction, glycemic control, and multi-organ protection, yet remain subject to inter-individual variability and gastrointestinal adverse effects; GLP-1R/GIPR and GLP-1R/GCGR dual-target agonists (such as tirzepatide and mazdutide) further ameliorate metabolic parameters and reduce hepatic steatosis and cardiovascular risk through synergistic modulation of food intake, energy expenditure, and lipid metabolism; whereas the GLP-1R/GIPR/GCGR triple agonist retatrutide demonstrates even more robust potential for weight reduction and body composition optimization, concurrently regulating key lipid metabolism factors including ANGPTL3/8, thereby expanding therapeutic horizons for metabolic diseases. Looking forward, the integration of multi-target drug development with long-acting formulation technologies, precise phenotyping, and individualized therapeutic strategies promises to substantially enhance treatment efficacy and medication safety in obesity, consequently alleviating the burden on public health.

Full Text

A New Chapter in Obesity Treatment: Mechanisms and Clinical Research Progress in Multi-target Peptide Agonists

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Abstract

Obesity is a chronic and relapsing disease resulting from interactions between genetic and environmental factors. Its global prevalence continues to rise, making it a major public health challenge. Traditional weight management strategies often yield suboptimal outcomes. In recent years, peptide-based therapies targeting the glucagon-like peptide-1 receptor (GLP-1R), glucose-dependent insulinotropic polypeptide receptor (GIPR), and glucagon receptor (GCGR) have advanced rapidly, with multi-target agonists emerging as a promising new therapeutic trend.

This review systematically summarizes the mechanisms and clinical progress of these agents: GLP-1R single-target agonists demonstrate significant efficacy in weight reduction, glycemic control, and multi-organ protection, though interindividual variability and gastrointestinal side effects remain limitations. Dual agonists targeting GLP-1R/GIPR and GLP-1R/GCGR (e.g., Tirzepatide, Mazdutide) further improve metabolic parameters, reduce liver fat, and mitigate cardiovascular risks through synergistic regulation of appetite, energy expenditure, and lipid metabolism. Meanwhile, the triple agonist Retatrutide (targeting GLP-1R/GIPR/GCGR) shows robust potential in weight loss and body composition improvement, while also modulating key lipid metabolic regulators such as ANGPTL3/8, thereby broadening the therapeutic horizon for metabolic diseases. Looking forward, the development of multi-target agents—combined with long-acting formulation technologies, precise subtyping, and individualized treatment strategies—is expected to significantly enhance the efficacy and safety of obesity treatments and alleviate the public health burden.

Keywords: Obesity; Multi-target peptide agonists; Glucagon-like peptide-1

receptor; Glucose-dependent insulinotropic polypeptide receptor; Glucagon receptor

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Obesity is a chronic, progressive, and relapsing disease characterized by excessive accumulation, abnormal distribution, or dysfunction of adipose tissue, resulting from the interplay of genetic and environmental factors [**?**]. According to 2022 survey data, the global population of obese adults has exceeded 890 million, accounting for approximately 16% of the adult population [**?**]. This rising prevalence poses a major public health challenge, as obesity significantly increases morbidity and mortality worldwide and is closely associated with numerous chronic diseases, including metabolic disorders [**?**], cardiovascular diseases [**?**], cancers [**?**], and osteoarthritis [**?**]. Additionally, weight stigma [**?**] often subjects patients to social and psychological stress, further exacerbating the overall disease burden.

Currently, BMI $\geq$ 28 kg/m^2 serves as the most commonly used diagnostic criterion for obesity [**?**]. However, this metric fails to comprehensively reflect individual body composition and fat distribution characteristics. Consequently, academic and clinical communities continue to explore more precise obesity assessment methods. Some scholars have proposed that waist circumference can serve not only as an effective intervention parameter for preventing overweight and obesity [**?**], but also as a reliable predictor of insulin resistance [**?**]. Building upon this, derived indices such as waist-to-height ratio and waist-to-height index have gained research attention [**?**]. LIN et al. [**?**] further classified obesity into metabolic healthy obesity, hypermetabolic obesity (including hyperuricemic and hyperinsulinemic subtypes), and hypometabolic obesity using machine learning methods—a classification strategy that helps advance precision in obesity diagnosis, treatment, and individualized application of peptide-based drugs.

From a pathogenic perspective, obesity development is closely linked to energy homeostasis imbalance regulated by the central nervous system, with the hypothalamus playing a central role [**?**]. Pro-opiomelanocortin (POMC) neurons and agouti-related protein (AgRP) neurons in the hypothalamic arcuate nucleus integrate peripheral hormonal signals to coordinately regulate feeding behavior, energy expenditure, and glucose-lipid metabolism. Long-term high-fat diets can induce chronic hypothalamic inflammation, disrupt its regulatory functions, and consequently lead to metabolic disorders. This mechanism not only deepens our understanding of the neuroendocrine basis of obesity but also provides important insights for developing novel peptide drugs targeting the hypothalamic-peripheral axis.

More critically, dysfunctional adipose tissue plays a central role in obesity and related complications [**?**]. Beyond serving as an energy storage organ, adipose tissue participates in systemic inflammation and metabolic regulation through secretion of various adipokines. Its abnormal expansion triggers immune cell infiltration and activation, releasing excessive free fatty acids, reactive oxygen

species, and pro-inflammatory factors, thereby inducing systemic inflammatory responses and lipotoxicity that ultimately disrupt glucose homeostasis and damage multiple organ functions.

In terms of therapeutic strategies, pharmacological interventions play a key role in controlling glucolipotoxicity [**?**] in addition to lifestyle modifications. With deepening research, obesity treatment is undergoing a fundamental shift from "single-target weight loss" to "multi-target metabolic regulation." The underlying rationale is that obesity represents not merely weight gain, but rather multi-system organic damage triggered through common pathways such as chronic low-grade inflammation and metabolic dysregulation. Consequently, new-generation therapeutic strategies aim for comprehensive modulation of obesity-related multi-organ pathophysiological abnormalities. In this context, dual- and multi-target peptide agonists targeting GLP-1R, GIPR, and GCGR have emerged, demonstrating synergistic effects that not only significantly enhance weight loss efficacy but also show multiple potentials in improving systemic metabolic homeostasis and organ protection.

1. Multi-organ Pathological Effects of Obesity: Common Pathways and Unique Mechanisms

As a systemic metabolic disease, obesity' s multi-organ pathological effects primarily stem from two common pathways: chronic low-grade inflammation and metabolic dysregulation. Energy excess is considered the initiating factor for chronic inflammatory states [**?**]. When white adipose tissue expands excessively beyond local blood supply capacity, tissue hypoxia ensues, directly activating nuclear factor kappa-B (NF- B) and hypoxia-inducible factor-1α (HIF-1α) transcription factors in adipocytes and immune cells. This triggers oxidative stress and endoplasmic reticulum stress, promotes adipocyte death, and further recruits and activates macrophages, forming and amplifying inflammatory cascades.

More importantly, dysfunctional adipose tissue serves as an inflammatory hub in obesity [**?**], releasing pro-inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [**?**] that induce systemic inflammatory states. This condition not only exacerbates insulin resistance but also, through NF- B pathway activation [**?**], upregulates the ubiquitin-proteasome system and autophagy-lysosome pathway, precipitating protein metabolism imbalance in skeletal muscle and other tissues, ultimately leading to atrophy and functional failure.

Obesity-driven chronic low-grade inflammation constitutes the core mechanism mediating multi-organ damage. The inflammatory state associated with childhood obesity has cumulative cardiovascular damaging effects [**?**], correlating closely with metabolic syndrome development, persistently aggravating insulin resistance, and participating in atherosclerosis progression from an early stage through driving macrophage infiltration, promoting low-density lipoprotein ox-

idation, and facilitating foam cell formation. When obesity persists from childhood into adulthood, these pathological processes accumulate continuously, elevating cardiovascular event risks.

In the joint system [**?**], circulating pro-inflammatory cytokines and matrix metalloproteinases synergistically accelerate synovial inflammatory responses and extracellular matrix degradation in cartilage, promoting knee osteoarthritis progression. In breast tissue, obesity-related chronic inflammation represents a significant risk factor for breast cancer development and distant metastasis [**?**], where the sphingosine kinase 1/sphingosine-1-phosphate/sphingosine-1-phosphate receptor 1 (SphK1/S1P/S1PR1) signaling axis plays a key role in tumorigenesis and metastasis by persistently activating NF- B and signal transducer and activator of transcription 3 pathways to promote IL-6, TNF-α, and other pro-inflammatory factor production. Studies have shown that targeting this axis can significantly inhibit breast cancer metastasis and prolong survival in obesity models.

In summary, chronic low-grade inflammation and metabolic dysregulation driven by obesity form an interconnected systemic pathological network. Through activation of key signaling pathways such as NF- B, this network collectively participates in and exacerbates functional impairment and organic damage in multiple organs including skeletal muscle, cardiovascular system, joints, and breast tissue, revealing a complete pathological chain from energy metabolism imbalance to multi-tissue inflammatory injury. This mechanistic elucidation provides a unified pathophysiological framework for understanding obesity-related comorbidities and establishes an important theoretical foundation for developing multi-organ protection strategies targeting common pathways.

2. Receptor Mechanisms

2.1 GLP-1 Receptor and Its Mechanism of Action

GLP-1 is an incretin hormone secreted by intestinal L cells that plays a central role in regulating energy homeostasis and glucose metabolism. GLP-1 [**?**] is primarily expressed in the intestine and brainstem, with lower expression levels in the pancreas. Its effects are mediated through GLP-1R, which possesses core functions in energy balance regulation. Studies have shown [**?**] that GLP-1R mRNA transcripts and GLP-1 binding sites are widely distributed across multiple brain regions in non-human primates, particularly in brainstem and hypothalamic areas that regulate feeding. In-depth studies of human and mouse brain samples have revealed that GLP-1R-expressing neurons in the dorsomedial hypothalamus (DMH) are likely key candidate cell populations encoding pre-ingestive satiety [**?**]. Meanwhile, neuropeptide Y/agouti-related peptide neurons (ARC NPY/AgRP neurons) [**?**] play indispensable roles in hunger and satiety regulation. GLP-1 and GLP-1R agonists (GLP-1RAs) can inhibit ARC NPY/AgRP neuron activity by activating upstream presynaptic GABAergic

neurons, thereby regulating appetite.

GLP-1 stimulates insulin release in a glucose concentration-dependent manner, significantly reducing hypoglycemia risk. Additionally, DMH neurons expressing GLP-1R participate in pancreatic function regulation through projections to the parasympathetic nervous system [**?**], and endogenous GLP-1 also contributes to glucose homeostasis maintenance via hypothalamic-pancreatic interactions. Functional experiments have confirmed [**?**] that mice with central nervous system-specific knockout of GLP-1R exhibit significantly increased food intake. Studies have found [**?**] that both peripheral and central administration of liraglutide alter arcuate POMC and NPY/AgRP neuron activity, contributing to changes in food intake and body weight. Central GLP-1R deletion markedly inhibits liraglutide' s weight loss effects, but its glucose control-improving effects remain largely preserved. These results suggest that GLP-1RA metabolic benefits may be achieved through both central and peripheral mechanisms.

GLP-1 [**?**] exerts direct effects on adipose tissue, influencing systemic energy metabolism through multiple pathways, including regulating adipocyte development, accelerating clearance of plasma glucose and triglyceride-derived fatty acids, improving insulin signaling, and promoting brown adipose tissue thermogenesis. GLP-1R activates adenylate cyclase/cyclic adenosine monophosphate (AC/cAMP) signaling pathways and downstream kinases such as extracellular signal-regulated kinase, protein kinase B, and protein kinase C, directly regulating apoptosis and preadipocyte proliferation.

Furthermore, studies have shown [**?**] that GLP-1 and GLP-1R upregulation in the paraventricular nucleus may partially contribute to sympathetic overactivation, thereby participating in hypertension pathogenesis. Other research indicates that metabolic diseases correlate with immune dysfunction [**?**], and the GLP-1/GLP-1R signaling axis also plays an important role in immune modulation [**?**]. GLP-1RAs can directly regulate immune responses through GLP-1R-expressing immune cells and may indirectly influence the immune system via metabolic regulation and neurotransmitter release.

2.2 GIP Receptor and Its Mechanism of Action

GIP is primarily secreted by intestinal K cells in response to food intake [**?**] and regulates postprandial glucose homeostasis by promoting insulin release through binding to its specific receptor [**?**]. In healthy individuals [**?**], GIP injection inhibits glucagon secretion under normal or hyperglycemic conditions but stimulates counter-regulatory hormone secretion during hypoglycemia. Studies have found that insulin response to GIP stimulation is significantly diminished in diabetic patients [**?**], with GIP failing to effectively promote insulin secretion even at supraphysiological concentrations. Consequently, the GIP axis was once considered less therapeutically promising than the GLP-1 axis [**?**].

However, recent research indicates [**?**] that if hyperglycemia is normalized through pharmacological intervention, GIP' s insulinotropic effects in dia-

betic patients can be restored. This finding suggests that GIPR agonists retain potential pharmacological value when combined with glucose-lowering medications. GIPR [?] primarily mediates signal transduction through the Gαs/adenylate cyclase-cyclic AMP (Gαs/AC-cAMP) pathway: in pancreatic β-cells, elevated cAMP levels activate protein kinase A and exchange protein directly activated by cAMP 2 (EPAC2), subsequently increasing intracellular calcium concentration and ultimately promoting insulin secretion.

Unlike GLP-1, GIP plays a more prominent role in lipid metabolism: GIPR activation [?] promotes fatty acid uptake in adipocytes, enhances insulin-induced free fatty acid incorporation, inhibits lipolysis, and improves adipose tissue blood flow. Studies have also shown [?] that GIPR agonism directly participates in adipocyte growth regulation, promoting proliferation of cultured human omental preadipocytes and downregulating pro-apoptotic factors such as Bcl-2-associated death promoter (BAD). Additional research has found that GIP can stimulate 3T3-L1 preadipocyte differentiation into mature adipocytes within 96 hours, promoting lipid accumulation and upregulating key genes in lipogenesis and lipolysis [?]. These results highlight GIP' s unique role in promoting fat storage and redistribution, contrasting sharply with GLP-1' s tendency to promote lipid breakdown and energy expenditure.

2.3 GCG Receptor and Its Mechanism of Action

GCG [?] plays a central role in maintaining glucose and lipid homeostasis during fasting states, primarily by stimulating glycogenolysis, gluconeogenesis, fatty acid oxidation, and inhibiting de novo lipogenesis. GCGR [?] is considered a candidate gene in type 2 diabetes pathogenesis, with specific GCGR mutations found to be associated with diabetes development.

Recent studies have further revealed that the GCG-GCGR signaling pathway plays an important role in energy metabolism regulation, with its agonists demonstrating significant effects in promoting hepatic lipid metabolism and increasing energy expenditure in various rodent models [?]. Regarding lipid metabolism, GCG markedly promotes white adipose tissue lipolysis, increases free fatty acid release, and simultaneously activates brown adipose tissue while inducing white adipose browning. Some studies show that exogenous GCG increases oxygen consumption in mice through a pathway independent of uncoupling protein 1 (UCP1) but dependent on fibroblast growth factor 21 (FGF21) [?]. GCG can also directly act on GCGR on adipocytes, enhancing UCP1 expression and mitochondrial biogenesis to promote non-shivering thermogenesis. Additionally, GCG can stimulate hepatic ketone body production, providing alternative energy sources for the brain and muscles, and participating in systemic energy redistribution. Although GCG significantly regulates lipid metabolism, its potent glucose-raising effects have limited its clinical application. Historically, GCGR has been viewed as a primary target for developing antagonists rather than agonists. However, recent GCGR activation [?] has also proven beneficial for body adipose tissue mass, lipid metabolism, food intake, and energy

balance.

In summary, in obesity pharmacotherapy, GLP-1, GIP, and GCG mediate different metabolic regulatory pathways through their specific receptors [Figure 1: see original paper]. The GLP-1 pathway core lies in significantly suppressing appetite through the central nervous system, promoting insulin secretion in a glucose-dependent manner, and stimulating lipolysis. The GIP pathway focuses on energy storage while promoting fat redistribution. The GCG pathway primarily functions to mobilize energy by stimulating hepatic glycogenolysis, gluconeogenesis, and lipolysis to elevate blood glucose and free fatty acid levels, thereby increasing energy expenditure.

3. Clinical Applications of Receptor Agonists

3.1 GLP-1R Single-Target Agonists

GLP-1 receptor agonists (GLP-1RAs) represent one of the core pharmacological agents for obesity and type 2 diabetes treatment. These drugs mimic endogenous GLP-1 effects, enhancing insulin secretion in a glucose-dependent manner, suppressing glucagon release, delaying gastric emptying, and reducing food intake through central appetite suppression, thereby achieving dual goals of glycemic control and weight reduction [**?**]. Multiple studies have demonstrated that GLP-1RAs, beyond metabolic regulation, possess potential protective effects against multi-system diseases, significantly reducing risks of disease progression in the heart [**?**], liver [**?**], and kidneys [**?**]. Furthermore, GLP-1RAs provide new therapeutic approaches for psoriasis [**?**] by modulating inflammatory and metabolic pathways and show potential in Parkinson' s disease treatment [**?**].

However, GLP-1RA application also presents certain complexities. Regarding diabetic retinopathy (DR), GLP-1RAs exhibit dual effects [**?**]: on one hand, they can inhibit Ras homolog gene family member A/Rho-associated coiled-coil kinase (RhoA/ROCK) signaling pathways, upregulate tight junction proteins, suppress microglial activation, reduce neuroinflammation and vascular leakage, and repair the blood-retinal barrier by activating GLP-1R in retinal endothelial and neural cells; on the other hand, during rapid blood glucose reduction, certain GLP-1RAs may also increase DR occurrence and progression risks, such as inducing diabetic macular edema or proliferative DR. Although their use correlates with reduced overall cancer risk in obese or overweight populations [**?**], some studies suggest these agents may be associated with increased risks of kidney cancer [**?**] and colorectal cancer [**?**]. Additional reports indicate potential associations between GLP-1RAs and depression [**?**].

In summary, GLP-1RAs demonstrate multi-organ protective potential beyond glycemic control and weight reduction in metabolic disease treatment. Despite potential risk signals regarding retinopathy, specific cancers, and mental health—and although some observational studies suggest cancer risks may be reversible after drug discontinuation [**?**]—such associations lack sufficient confir-

mation from high-quality clinical evidence. Therefore, the core concept of clinical application lies in individualized decision-making: actively prescribing for populations with clear benefits after full patient disclosure, while strengthening targeted monitoring for potentially high-risk individuals to maximize therapeutic benefits while prudently managing and evaluating uncertainties.

3.2 GLP-1R/GCGR Dual Agonists

Although GLP-1RAs offer significant metabolic benefits, many diabetic patients still fail to achieve glycemic targets. Moreover, their weight loss effects remain far inferior to those achieved by metabolic surgery [**?**]. Consequently, researchers have explored more potent therapeutic strategies, with one important direction being combination of GLP-1RAs with other gastrointestinal hormones (such as glucagon) to synergistically regulate energy metabolism and nutrient-sensing pathways. While combined use of endogenous metabolic hormones offers high flexibility in mechanistic studies, drug development [**?**, **?**] faces challenges in pharmacokinetic matching, formulation complexity, and side effect modulation.

Cotadutide, a well-characterized GLP-1R/GCGR dual agonist, demonstrates enhanced insulin sensitivity in hyperinsulinemic-euglycemic clamp experiments after subchronic administration in diet-induced obese male mice, with phosphoproteomic analysis of Cotadutide-treated livers revealing known and novel phosphorylation modification sites on multiple key signaling proteins associated with improved insulin sensitivity [**?**]. The insulin sensitivity improvement is accompanied by reduced insulin secretion demand, indicating potential for decreasing β-cell workload. Additionally, Cotadutide [**?**] significantly improves non-alcoholic steatohepatitis and hepatic fibrosis by regulating mitochondrial function and inhibiting lipogenesis. In high-fat diet mouse models [**?**], multiparametric MRI combined with histological analysis indicates that GLP-1R/GCGR dual agonists more effectively reduce hepatic fat accumulation.

Mazdutide, a novel GLP-1R/GCGR dual receptor agonist currently in clinical use, has demonstrated clinically meaningful weight loss and beneficial effects on all preset cardiometabolic indices in Phase 3 clinical studies of Chinese adults with overweight or obesity after 32 weeks of weekly administration at 4 mg or 6 mg doses [**?**]. Higher doses (e.g., 16 mg) of Mazdutide [**?**] also show good tolerability and achieve more significant weight reduction. Additional research indicates [**?**] that Mazdutide possesses neuroprotective potential: it can restore neuronal structural integrity (such as increasing Nissl bodies and neuron-specific nuclear antigen-positive cell counts), reduce demyelination, enhance synaptic plasticity, and reconstruct excitatory-inhibitory neurotransmission homeostasis by modulating solute carrier family 17 member 6/vesicular glutamate transporter 2 (Slc17a6/VGLUT2)-mediated glutamatergic balance and N-methyl-D-aspartic acid receptor/γ-aminobutyric acid receptor (NMDA Receptor/GABA Receptor) interactions.

Recent studies have found that GLP-1R/GCGR dual receptor agonists exhibit

multiple pharmacological potentials beyond glycemic control and weight reduction. For example, these agents can alleviate renal allograft fibrosis after transplantation by modulating lipid metabolism [**?**]; S3-2, a novel long-lasting oxyntomodulin derivative, can improve diabetes and renal injury [**?**]; another representative drug, LM06, demonstrates extended half-life and superior metabolic characteristics in pharmacokinetic studies in rats and monkeys [**?**]. In db/db mice, 8-week treatment significantly improved glycemic control, body weight, pancreatic function, and lipogenesis. Moreover, LM06 combined with low-intensity ultrasound can accelerate diabetic skin wound healing.

3.3 GLP-1R/GIPR Dual Agonists

With continuous development of multi-receptor synergistic agonist strategies in metabolic disease treatment, GLP-1R/GIPR dual agonists have become a notable novel therapy. GIP enhances postprandial insulin release and may promote nutrient storage in white adipose tissue, but its monotherapy shows limited effects on weight and glucose improvement. GIP and GLP-1 belong to the incretin hormone family, exhibiting complementary roles in promoting insulin secretion and regulating energy homeostasis [**?**].

Tirzepatide [**?**], a representative drug in this class, demonstrates superior metabolic improvement compared to GLP-1 mono-agonists (liraglutide 3.0 mg) at 10 mg or 15 mg doses, though with higher risks of severe hypoglycemia and injection site reactions. Another prospective, single-arm, open-label single-center study [**?**] showed that Tirzepatide significantly improved insulin sensitivity after 12 weeks of treatment in obese patients with type 2 diabetes, suggesting early metabolic benefits beyond weight reduction. Recent research found that Tirzepatide can alleviate metabolic dysfunction-associated steatotic liver disease by downregulating CD36 and OBP2A expression [**?**], and exerts beneficial effects on cardiomyocytes through positive modulation of β-adrenergic receptor signaling and glucose metabolism rather than direct receptor targeting [**?**]. It can even reduce left ventricular mass and paracardiac adipose tissue volume in patients with obesity-related heart failure [**?**].

3.4 GLP-1R/GIPR/GCGR Triple Agonists

With deepening research on dual receptor agonists, triple agonists simultaneously targeting GLP-1R, GIPR, and GCGR have become a new focus in metabolic disease treatment. These agents demonstrate broader pharmacological potential in glycemic control, weight management, liver health, and energy expenditure through synergistic activation of multiple metabolic pathways.

Retatrutide [**?**], the first GLP-1/GIP/GCG triple agonist to complete Phase 2 clinical trials, is currently undergoing Phase 3 studies for obesity and/or type 2 diabetes management. Its mechanism includes not only enhanced insulin sensitivity and promoted insulin secretion but also increased energy expenditure and fat oxidation through GCGR activation, thereby more effectively reducing

fat mass and improving hepatic lipid metabolism.

Functional experiments based on cAMP accumulation [**?**] show Retatrutide' s efficacy across different receptors: strongest potency for GIPR at 8.9 times human GIP (EC50: 0.0643 nM vs. 0.574 nM); relatively lower potency for GLP-1R and GCGR at 40% of human GLP-1 (EC50: 0.775 nM vs. 0.312 nM) and 34% of human glucagon (EC50: 5.79 nM vs. 1.97 nM), respectively.

In a Phase 2 randomized controlled trial of 281 participants with type 2 diabetes [**?**], body composition subgroup analysis of 189 participants via dual-energy X-ray absorptiometry revealed dose-dependent reductions in total body fat mass after 36 weeks: -4.9% in the 0.5 mg group, -15.2% in the 4 mg group, -26.1% in the 8 mg group, and -23.2% in the 12 mg group, compared with placebo and dulaglutide (1.5 mg). The 8 mg and 12 mg groups showed statistically significant fat mass reductions. Safety profiles were similar across groups, with gastrointestinal events predominating and no deaths reported. These findings indicate that Retatrutide effectively reduces fat without causing abnormal lean mass proportion decline, with superior fat reduction effects compared to dulaglutide, suggesting potential advantages in body composition improvement.

Additionally, research found that circulating angiopoietin-like protein 3/8 (ANGPTL3/8) concentrations decreased following Retatrutide treatment, paralleling improvements in lipid profiles [**?**]. ANGPTL3/8 is a key atypical unfoldase regulating intravascular lipolysis by catalyzing lipoprotein lipase unfolding [**?**]. Studies show ANGPTL3/8 concentrations correlate closely with atherogenic lipoprotein profiles [**?**], characterized by elevated triglycerides and low-density lipoprotein cholesterol and reduced high-density lipoprotein cholesterol. Beyond lipid metabolism regulation [**?**], cardiovascular protective effects of ANGPTL3 and ANGPTL3/8 inhibitors are also thought to involve improved vascular inflammatory states.

4. Conclusion and Outlook

Obesity, as a complex chronic disease, has seen treatment strategies evolve from traditional lifestyle interventions and single-target agents toward a new era of multi-target synergistic regulation. Multi-target agonist drugs will undoubtedly become the mainstream of research and development, with core advantages in simultaneously regulating appetite, modulating glucose-lipid metabolism, and improving chronic inflammatory states, thereby achieving synergistic efficacy. However, long-term safety data for such innovative drugs remain relatively limited. Therefore, while actively advancing formulation technology innovation, large-scale, long-term real-world studies should be conducted to continuously monitor and evaluate long-term medication risks. Moreover, with advances in machine learning-assisted obesity subtyping and biomarker research, future treatment strategies will become more precise, promising to weigh benefits against risks and select optimal drugs for patients based on genetic background, metabolic phenotype, and complication risk.

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