

Emerging and Novel Molecular Targets in Obesity: Advances Toward Precision Anti-Obesity Pharmacotherapy

Ansh Tripathi, Avijit Mazumder*, Priyanka Bansal

Noida Institute of Engineering and Technology (Pharmacy Institute), Knowledge Park-II, Greater Noida, Uttar Pradesh 201306, India.

*Corresponding author: Dr. Avijit Mazumder, Phone Number: 9871773644, E-mail: avijitmazum@gmail.com, ORCID: 0000-0002-3053-8106

Abstract

Obesity persists to be a major global public health issue, with its prevalence and related comorbidities increasing substantially over the world. This review systematically analyzes the molecular pathophysiology of obesity, emphasizing essential targets involved in disease processes and therapeutic strategies. The main molecular systems talked about are G-protein coupled receptors (GPCRs), including incretin (GLP-1, GIP), melanocortin, and serotonin receptors. Other important systems are nuclear receptors like PPARs, LXRs, and FXR, and transcriptional regulators like SREBPs. This review goes into great detail about how central metabolic enzymes (AMPK, ACC, FAS) and pathways related to energy balance, adipogenesis, and inflammation (NLRP3 inflammasome, NF- κ B, JNK, TLR4) play a role in abnormal lipid and glucose metabolism. Recent clinical and translational research is used to look at new developments in precision medicine, multi-targeted and combination therapy, and new drugs, such as dual or triple receptor agonists and new targets like GDF15 and FGF21. The review focuses on integrated therapy techniques customized to individual molecular profiles, incorporating multi-omics analytics and tissue-selective targeting to enhance efficacy and safety. The molecular insights and translational strategies discussed establish a basis for the future generation of individualized anti-obesity therapies designed to interrupt the pathophysiological connections between obesity and its severe comorbidities.

Keywords: Obesity, G-protein coupled receptors (GPCRs), GLP-1 receptor agonists, Molecular targets, nuclear receptors (PPARs, LXRs, FXR), AMPK and metabolic enzymes, Inflammation and NLRP3 inflammasome
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1. Introduction

1.1. Global Epidemiology of Obesity

Obesity has emerged as the foremost community health issues of twenty-first century which is currently at an all-time high worldwide. The WHO estimates that over two third of a million individuals globally were suffering from obesity in 2022, almost triple as of it was in 1990, while juvenile and adolescent obesity has quadrupled within the same time frame [1]. The number of overweight adults globally is predicted to more than double from 524 million in 2010 to over 1.13 billion by 2030, according to the World Obesity Atlas 2025 [2]. Current trends suggest that the worldwide prevalence of obesity is anticipated to reach around 18% in males and surpasses 21% in females by 2025, with many countries facing significantly higher rates [1]. Obesity is a serious health problem that is spreading quickly over the world. It is a complicated illness that happens when the amount of energy you take in is not equal to the amount of

energy you utilize [3]. The worldwide distribution of obesity shows significant spatial disparities. Traditionally, obesity has been concentrated in economically mature nations yet, the most significant increases and the highest absolute numbers of such cases are now observed in nations with low or middle incomes experiencing rapid socioeconomic transitions [4].

Specific regions, especially the Middle East, exhibit adult obesity rates exceeding 60% in certain populations [5]. The economic consequences are huge, it is estimated that worldwide expenses will amount to US\$4.32 trillion yearly by 2035, which is almost 3% of the world's GDP and is equivalent to the COVID-19 economic impact in 2020 [6].

Obesity greatly raises the chance of many life-threatening comorbidities, which are a group of diseases that affect each other and cause illness and death around the world. Type 2 diabetes mellitus

(T2DM) is intensely linked to obesity. Individuals who are obese have a 3.5- to 4.6-fold higher chance of getting diabetes than people who are of a healthy weight [7]. Prevalence studies show that 58 to 90% of population with T2DM are obese, and 81.84% of diabetics are abdominally obese [8].

1.2. Scope and Organization of This Review

This comprehensive review offers an organised review of molecular targets in obesity, categorised by target classification and therapeutic potential. A thorough look at each major target category, including how it works, clinical evidence, and what it means for treatment. The review focusses on translational aspects that connect basic molecular knowledge with clinical uses, giving both researchers and doctors who work with obesity treatment useful information. The fundamental aim of this review is to establish a framework for the ongoing advancement of effective, safe, and individualised obesity treatments capable of tackling the molecular intricacies associated with this debilitating condition. By comprehending the various molecular targets accessible for therapeutic intervention, the field can persist in progressing towards precision medicine strategies that optimise treatment efficacy while reducing adverse effects. The molecular insights provided herein establish the basis for the development of next-generation obesity therapeutics capable of significantly influencing the global obesity epidemic.

1.3. Molecular Targets associated with Inflammatory Pathways

To understand how modern anti-obesity pharmacotherapies are designed, it is essential to examine the key molecular pathways that regulate appetite, adipogenesis, glucose and lipid metabolism, inflammation, and energy expenditure. The following sections categorize these pathways into major therapeutic target classes, beginning with G-protein coupled receptors (GPCRs) and extending through nuclear receptors, metabolic enzymes, inflammatory signalling networks, epigenetic regulators, gut-brain axis components, and emerging novel targets. Together, these interconnected molecular systems form the mechanistic foundation for precision anti-obesity drug development.

2. G-Protein Coupled Receptor (GPCR) Targets

2.1. Incretin Receptor System

2.1.1. GLP-1 Receptors (GLP-1R)

The glucagon-like peptide-1 receptor is the most scientifically validated GPCR target for treating obesity. GLP-1R is a type B GPCR that is very important for keeping blood sugar levels stable and balancing energy levels [9]. Activating GLP-1R starts a number of good processes, such as increasing insulin secretion, slowing gastric emptying, stopping glucagon release, and lowering the desire to eat in the hypothalamus [10]. The molecular mechanism involves the activation of Gs protein-coupled adenylyl cyclase, which elevates intracellular cAMP levels and activates protein kinase A (PKA) pathways. GLP-1 also turns on PKA and EPAC (Exchange Protein directly Activated by cAMP) through a pathway that depends on cAMP and beta-catenin signalling [11]. When GLP-1R is activated, it boosts glucose-dependent insulin secretion, slows gastric emptying, speeds up the growth of pancreatic β -cells, and lowers glucagon release. All of these things help to lower appetite. Also, GLP-1R's interaction with receptors in the hypothalamus reduces hunger sensations, diminishes food cravings, and amplifies feelings of satiety as mentioned in Table 1 [10].

Target/Process	Effect of GLP-1R Activation
Glucose Homeostasis	↑ Glucose-dependent insulin secretion and ↓ Glucagon release (from the pancreas).
Gastrointestinal	↓ Slows gastric emptying (which reduces post-meal glucose spikes and prolongs fullness).
β -Cell Health	↑ Speeds up the growth (proliferation) and survival of pancreatic β -cells.
Central Nervous System	↓ Lowers appetite, ↓ diminishes food cravings, and ↑ amplifies feelings of satiety via interaction with receptors in the hypothalamus (the

	brain's appetite control center).
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Table 1. Major physiological effects of GLP-1 receptor activation on glucose regulation, appetite control, and metabolic homeostasis

GLP-1 receptor agonists also have anti-inflammatory effects by stopping proinflammatory cytokines like TNF- α , IL-6, and IL-1 β from being made in macrophages, lymphocytes, and monocytes [12]. The molecular mechanisms responsible for GLP-1 receptor-mediated weight loss encompass both central and peripheral pathways. GLP-1RA activates the Wnt/ β -catenin signalling pathway, which inhibits adipogenesis by inhibiting genes associated with de novo lipogenesis, such as DGAT1, SCD1, ApoB, FABP1, and FOXA1 [13]. Recent research indicates that signalling bias is strongly associated with GLP-1R agonist-mediated weight loss in diet-induced obese mice, with cAMP-biased signalling being especially critical [14],

2.1.2. GIP Receptors (GIPR)

Glucose-dependent insulintropic polypeptide receptors function together with GLP-1 receptors to improve metabolic benefits [15]. GIP receptors are found in pancreatic β -cells, bone, adipocytes, brain, and they have a wide range of effects on the body. The dual GLP-1R/GIPR agonist tirzepatide shows better results, with weight loss of 15.0–20.9% that depends on the dose. This is due to different ways it affects glucose homeostasis, appetite control, and energy expenditure. Tirzepatide is a synthetic peptide made up of 39 amino acids. It is based on the native GIP sequence, but it has been changed to make it more stable and better at binding to receptors. The drug's biological effect on the GIP receptor is five times stronger than its effect on the GLP-1 receptor [16,17]. In the SURMOUNT obesity trials, tirzepatide resulted in dose-dependent weight reductions averaging 15-22%, nearing outcomes previously associated solely with bariatric surgery. The SURMOUNT-1 trial specifically showed that people lost between 15% and almost 21% of their body weight after 72 weeks of treatment. The SURMOUNT-3 trial showed that tirzepatide helped adults with obesity lose clinically

significant amounts of body weight after intensive lifestyle changes [18]. The synergistic effect occurs when GLP-1 and GIP are infused together, which leads to a much stronger insulin response and glucagonostatic response than when each hormone is given separately [19]. In the SURMOUNT-1 to -4 trials, tirzepatide caused a significant and clinically meaningful weight loss at all doses compared to placebo [20]. Meta-analyses have validated the dose-dependent safety and effectiveness of tirzepatide for weight reduction in non-diabetic adults with obesity, likely elucidated by its dual-incretin mechanism accounting for the significant weight-loss outcomes [21].

2.1.3. Glucagon Receptors (GCGR)

Even though it seems strange that glucagon receptor activation raises blood sugar levels, it actually helps the body burn more energy by making the liver make more FGF21 and stimulating brown adipose tissue [22][23]. Glucagon facilitates hepatic ketogenesis, improves insulin sensitivity, and activates brown adipose tissue, concurrently engaging with GLP-1 and GIP pathways that minimise hyperglycaemic effects [24]. Retatrutide, an example of a triple receptor agonist that targets GLP-1R/GIPR/GCGR, can help people lose more weight up to 24.2% by activating multiple metabolic pathways at once [25]. Retatrutide is a weekly single-agent peptide drug made up of a 39-amino acid peptide linked to a C20 fatty diacid moiety that works as an agonist for GIP, glucagon, and GLP-1 receptors [26]. In phase 2 clinical trials, retatrutide exhibited exceptional weight reduction efficacy, as participants administered the 12 mg dose achieved an average weight reduction of 24.2% after 48 weeks, without any indication of a plateau [25]. Retatrutide showed big drops in body mass index (-5.38), waist circumference (-10.51 cm), fasting plasma glucose (-23.51 mg/dL), haemoglobin A1c (-0.91%), and systolic and diastolic blood pressure (-9.88 mm Hg and -3.88 mm Hg, respectively). The occurrence of attaining $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ weight loss was markedly elevated in the retatrutide groups relative to placebo [27]. Balanced GLP-1R/GCGR dual agonists such as survodutide, and pemvidutide exhibit substantial weight loss in clinical trials via this integrated multi-pathway strategy [28,29]. In preclinical models, retatrutide assisted weight loss by decreasing food consumption and raising energy expenditure relative to calorie intake-matched counterparts, while glucagon activity decreased liver

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fat by enhancing hepatic fatty acid oxidation and inhibiting hepatic lipogenesis as shown in Fig. 1. [30].

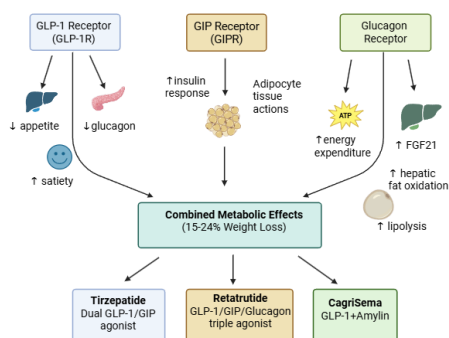


Fig. 1. Multi-receptor agonism targeting GLP-1, GIP, and glucagon pathways in obesity.

The figure depicts the complementary metabolic actions of GLP-1, GIP, and glucagon receptor activation. GLP-1 suppresses appetite and glucagon secretion, GIP enhances insulin response and adipose tissue function, and glucagon increases energy expenditure and fat oxidation. Together, these pathways produce synergistic metabolic effects and substantial weight loss (~15–24%), exemplified by dual- and multi-agonist therapies such as tirzepatide and retatrutide.

2.2. Melanocortin Receptor System

Melanocortin-4 Receptors (MC4R)

MC4R is a very important part of the central nervous system that controls appetite. Pathogenic MC4R variants are the most common cause of monogenic obesity [31]. The highly conserved leptin-melanocortin pathway in the hypothalamus is where MC4R plays a big role in controlling body weight [32]. The MC4R pathway is part of the leptin-melanocortin system that helps keep energy levels stable by sending signals between neurones in the hypothalamus as shown in Fig 2. Biallelic variants in genes that affect the MC4R pathway, such as POMC, LEPR, and PCSK1 deficiencies, can lead to severe obesity that starts early in life [33].

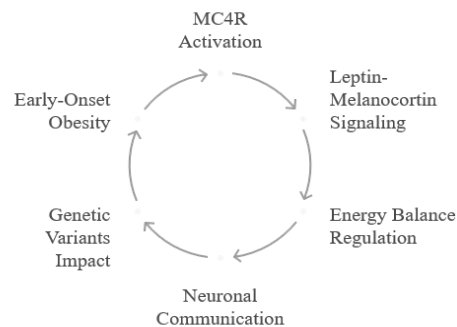


Fig 2. Role of MC4R signaling in central energy homeostasis and obesity.

The schematic illustrates the melanocortin-4 receptor (MC4R) pathway as a core regulator of energy balance, integrating leptin–melanocortin signaling and neuronal communication. Disruption of this pathway by genetic variants impairs energy balance regulation and is strongly associated with early onset obesity.

Setmelanotide (also known as RM-493, BIM-22493, IRC-022493, and Imcivree) is a synthetic cyclic MC4R agonist that binds to MC4R very well and specifically. The drug is very effective for genetic obesity syndromes, causing patients with LEPR, POMC, or PCSK1 deficiency to lose 12.5–25.6% of their body weight [34,35]. The molecular mechanism requires the activation of hypothalamic POMC neurones and downstream appetite suppression pathways [36]. The FDA and the European Medicines Agency have both approved setmelanotide. It has been shown to help people with obesity caused by bi-allelic pathogenic POMC, PCSK1, or LEPR variants lose weight [37]. Clinical trials have shown that the drug works for people of all ages [38]. Phase 3 trials showed that it works for people with POMC or LEPR deficiency obesity who are 6 years old or older. [37] The VENTURE trial assessed efficacy and safety in patients aged 2 to 5 years with POMC or LEPR deficiency or Bardet-Biedl syndrome [39].

There have only been a few studies done, but the results suggest that setmelanotide may help people with heterozygous MC4R variants lose weight. Setmelanotide interestingly caused weight loss in Mc4r heterozygous knockout mice on a high-fat diet, whereas homozygous knockout mice did not respond [40].

2.3. Serotonin Receptor Targets

2.3.1. 5-HT_{2C} Receptors

Serotonin 2C receptors located on hypothalamic POMC neurones facilitate appetite suppression and metabolic regulation. The 5-HT_{2C} receptor is a legitimate target for obesity treatment, as evidenced by studies demonstrating that genetic deletion of 5-HT_{2C} receptor expression in mice resulted in significant hyperphagia and obesity onset in middle age [41]. Preclinical studies involving 5-HT_{2C}CR knockout indicated markedly increased food consumption and weight gain [42] whereas various selective or non-selective 5-HT_{2C}CR agonists produced anorectic effects [43]. The 5-HT_{2C}CRs are seven transmembrane-spanning helices that are coupled to G proteins. They are mostly found in the central nervous system, especially in the epithelial cells of the choroid plexus, limbic areas, hippocampal regions, amygdala, and basal ganglia [44]. The U.S. Food and Drug Administration approved lorcaserin for long-term weight management after three phase-3 clinical trials showed that it worked by lowering body weight and improving metabolic parameters [45]. The overall effect size was small (about 3% change after correcting for placebo), but lorcaserin had a much bigger clinical effect in some people (more than 10% change after correcting for placebo) [46]. The molecular mechanism entails lorcaserin's capacity to diminish glucose consumption by decreasing the frequency of licking behaviour, thereby showing a drug-induced increase in satiety [47]. The 5-HT_{2C}CRs activate phospholipase C β through the G $\alpha_q/11$ protein. They are linked to phospholipase C in neurones and the choroid plexus. When they are activated, inositol 1,4,5-triphosphate and diglyceride build up in the cells [42]. Lorcaserin also reversed the binge-like feeding seen after stimulating the μ -opioid receptors in the nucleus accumbens and blocked the nucleus accumbens. μ -opioid enhancement of fat consumption [48].

2.3.2. 5-HT₆ Receptors

5-HT₆ receptor antagonism is a new target. PRX-07034 has been shown to reduce body weight in diet-induced obesity models by suppressing appetite and increasing satiety signalling [49]. The 5-HT₆ receptor antagonist SB-742457 diminished the frequency of licking behaviour associated with reduced food intake, indicating a drug-induced enhancement of satiety; however, this effect was only observable at the lowest dosage tested (3.0

mg/kg), suggesting an inverted bell-shaped response curve [47]. Results from mechanistic studies implicated the paraventricular nucleus (PVN) within the hypothalamus as a target for hypophagic doses of selective 5-HT₆ receptor antagonists. The arcuate-PVN circuit appears important for mediating hypophagic actions of both 5-HT_{2C} receptor agonists and 5-HT₆ receptor antagonists, with the latter potentially increasing neuronal activity via disinhibition [50]. 5-HT₆ receptor antagonists offer great promise in controlling weight gain and face fewer challenges around benefit to risk ratio compared to 5-HT_{2C} receptor agonists [49].

2.4. Adipocyte GPCR Targets

2.4.1. G α_s -Coupled Receptors in Adipocytes

Activating adipocyte G α_s signalling has good effects on metabolism, such as increased lipolysis, better insulin sensitivity, and higher energy expenditure [51]. The main therapeutic target is β_3 -adrenergic receptors, and selective agonists help activate brown adipose tissue and turn white adipose tissue brown [52]. Brown adipocytes have β_3 -adrenergic receptors, and giving rodents β_3 -selective agonists makes them burn more calories and lose weight. The β_3 -AR is unique because it can uncouple mitochondrial respiration, which is tightly controlled by sympathetic nerve activity [53]. Transgenic mice exhibiting reduced brown adipose tissue develop obesity, highlighting the significance of brown fat in sustaining nutritional homeostasis [54]. In humans, the activation of β_3 -AR by the selective β_3 -AR agonist mirabegron enhances metabolic activity in brown adipose tissue (BAT), increases whole-body energy expenditure, elevates plasma free fatty acids (FFA), and promotes glucose uptake in BAT [55,56]. Obese individuals undergoing chronic treatment with mirabegron exhibit elevated UCP1 expression in subcutaneous white adipose tissue, signifying effective browning of white adipose tissue [57]. Functional studies in human brown/beige adipocytes indicate that β_3 -AR is essential for optimal lipolysis and thermogenesis in these adipocytes. Silencing ADRB3 expression led to a general reduction in the expression of genes pertinent to thermogenesis and fatty acid metabolism, correlated with diminished cAMP production and lipolysis, as well as reduced basal, FCCP, and lipolysis-induced cellular respiration [58].

2.4.2. Gi-Coupled Receptors in Adipocytes

There are many Gi-coupled receptors in adipocytes, such as HCA1/HCA2 (lactate/nicotinic acid receptors), FFAR2 (short-chain fatty acid receptor), and different orphan receptors. These receptors could be used to develop new treatments. Selective regulation of these pathways can enhance lipid and glucose homeostasis without inducing systemic side effects [59]. Adipocyte Gi signalling is critical for sustaining optimal blood glucose homeostasis, as its activation results in significant decreases in plasma free fatty acids, glycerol, and triglyceride levels by inhibiting lipolysis. Acute stimulation of adipocyte Gi signalling leads to major improvement in glucose tolerance and insulin sensitivity, presumably due to decreased plasma free fatty acid concentrations [60]. Mouse adipocytes express numerous GPCRs specifically associated with Gi-type G proteins, including chemokine receptor subtypes, succinate receptor 1, CB1 cannabinoid receptor, HCA receptors 1 and 2, and various orphan receptors [61,62]. Long-term treatment that activated adipocyte Gi signalling led to a big drop in plasma FFA levels and a big rise in insulin sensitivity and glucose tolerance. The heteromerization of FFAR2 and FFAR3 receptors alters short-chain fatty acid signalling and may serve as a new therapeutic target for metabolic disorders. GPR41/FFAR3 and GPR43/FFAR2 function as cosensors for short-chain fatty acids and facilitate the metabolic effects of metabolites derived from gut microbiota [61,63].

2.5. Emerging GPCR Targets

2.5.1. Amylin Receptors

Cagrilintide, a long-acting amylin receptor agonist, induces a 10.8% weight loss as monotherapy and exhibits synergistic effects with semaglutide (CagriSema), resulting in a 17.1% weight reduction [64,65]. Amylin receptor activation controls gastric emptying, satiety, and pancreatic glucagon secretion by using mechanisms that differ from those of GLP-1 [66]. Amylin attaches to heteromeric receptor complexes made up of the calcitonin receptor (CTR) and certain receptor activity-modifying proteins (RAMPs 1-3). These complexes create three different amylin receptor subtypes: AMY1R, AMY2R, and AMY3R as shown in table 2 [67].

Receptor Subtype	Composition
AMY1R	Calcitonin Receptor+RAMP1
AMY2R	Calcitonin Receptor+RAMP2
AMY3R	Calcitonin Receptor+RAMP3

Table 2. Molecular composition of amylin receptor subtypes (AMY1R–AMY3R)

Cagrilintide was created as a long-acting non-fibrillating amylin analogue that still binds to AMY3R [68]. It was made to help people lose weight without causing side effects like nausea and vomiting [69].

2.5.2. Y2 Receptors (Neuropeptide Y)

PYY receptor agonists that target Y2 receptors in the brain lower food intake and make people feel fuller [70]. In phase 1 trials, Y14 peptide caused people to lose 2.9–3.6 kg of weight and eat 38–55% less food [71]. The neuropeptide Y system has demonstrated its significance as a crucial regulator of feeding behaviour and energy homeostasis [72]. Y2 receptors are primarily localised presynaptically, where their activation by NPY, PYY, and N-terminal truncation products results in the inhibition of neurotransmitter release [73]. PYY3-36 decreased feeding in obese rodents and human beings, with pharmacological and genetic methods indicating that the Y2-receptor is responsible for the anorectic effects of PYY3-36 [74]. Mechanistic investigations in rodents have found the hypothalamus, vagus nerve, and brainstem as prospective loci for PYY-mediated appetite regulation [75]. Functional brain imaging techniques in humans revealed that PYY3-36 modulates neuronal activity in the hypothalamus, brainstem, and other brain regions associated with reward processing [76]. Multiple lines of evidence indicate that low circulating PYY concentrations contribute to the development and persistence of obesity, as individuals with diminished after meal PYY release demonstrate reduced satiety, and circulating PYY levels exhibit a negative correlation with markers of adiposity [75].

3. Nuclear Receptor and Transcription Factor Targets

3.1. Peroxisome Proliferator-Activated Receptors (PPARs)

3.1.1. PPAR α

PPAR α activation enhances fatty acid oxidation in the liver and muscle, serving as a crucial molecular target for mitigating lipotoxicity in obesity [77]. PPAR α agonists, including fibrates, augment hepatic and skeletal muscle fatty acid β -oxidation, decrease plasma triglycerides, and increase HDL cholesterol, consequently mitigating ectopic lipid accumulation and adipocyte hypertrophy [78,79]. Animal studies confirm this by demonstrating that PPAR α activation enhances the expression of mitochondrial oxidation genes in skeletal muscle (e.g., CPT-1, MCAD, LCAD, and PGC-1 α), leading to the depletion of fatty acids and the inhibition of triglyceride synthesis [80]. However, continued or excessive PPAR α activation in cardiac tissue, as seen in long-term fibrate therapy or transgenic mouse models, promotes muscle degeneration and lipotoxic cardiomyopathy, accompanied by insulin resistance [81,82]. The status of oestrogen also affects these effects by stopping some of PPAR α 's anti-obesity actions. Selective activation keeps being a challenge for therapeutic targeting.[83]

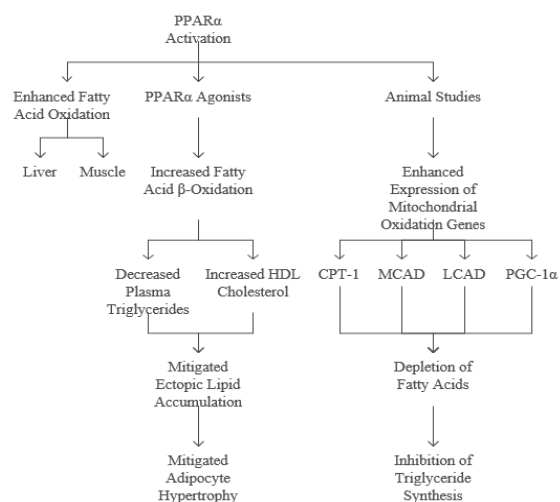


Fig. 3. Role of PPAR α activation in lipid metabolism and fatty acid oxidation.

The figure illustrates how PPAR α activation enhances fatty acid oxidation in liver and muscle through induction of β -oxidation pathways and mitochondrial oxidative genes (e.g., CPT-1, MCAD, LCAD, PGC-1 α). These effects lead to reduced plasma triglycerides, increased HDL cholesterol, depletion of fatty acid stores, inhibition

of triglyceride synthesis, and attenuation of ectopic lipid accumulation and adipocyte hypertrophy, as supported by animal studies.

3.1.2. PPAR γ

PPAR γ is a complicated target for obesity because it has contradictory effects: thiazolidinedione (TZD) agonists greatly increase insulin sensitivity and change how fat cells use energy, yet they usually cause weight gain because they increase fat cell growth.[84]. PPAR γ agonists also promote the development of smaller, insulin-sensitive adipocytes, decrease obesity-induced inflammation, and enhance glucose homeostasis. Genetic and pharmacological models demonstrate positive impacts on adipocyte functionality and inflammatory conditions [85,86]. Still, targeted or partial regulation of PPAR γ (for instance, through natural chemical suppression or selective agonists) may induce insulin sensitivity and anti-inflammatory effects while reducing adipogenic consequences, a strategy currently under rigorous investigation [87]

3.1.3. PPAR δ

PPAR δ activation has become a promising target for metabolic efficiency in obesity, because of its function in improving skeletal muscle fatty acid oxidation, mitochondrial biogenesis, and energy expenditure, all while inhibiting adipogenesis [88,89]. PPAR δ is widely present in metabolic tissues, and its overexpression or pharmacological activation promotes a transition to oxidative muscle fibers, providing resistance to diet-induced obesity and exercise-induced tiredness [90]. Activation promotes the expression of genes involved in mitochondrial β -oxidation, enhances reverse cholesterol transport, and safeguards against obesity-related insulin resistance by promoting anti-inflammatory macrophage polarization [89,91]. PPAR δ agonists like GW501516 have showed promise in animal and early human studies by improving body weight, cholesterol level, and insulin sensitivity. But any harmful consequences associated with pan-PPAR activation require careful tissue selection and dosage techniques [88,92].

3.2. Liver X Receptors (LXRs)

LXR α and LXR β are important for controlling how the body uses cholesterol and fatty acids. When they are activated by drugs, they change the expression of

genes that are linked to metabolic problems that cause lipid disorders and obesity. LXR agonists promote reverse cholesterol transport (RCT), elevate HDL-cholesterol levels, and diminish LDL-cholesterol levels[93]. However, typical LXR activation also stimulates hepatic lipogenesis, which restricts therapeutic use due to the potential danger of steatosis of the liver and lipotoxicity. This means that attempts are directed towards the creation of tissue-selective or gene-specific LXR modulators aimed at achieving targeted advantages in obesity and metabolic syndrome[93].

3.3. Farnesoid X Receptor (FXR)

FXR, a nuclear receptor that senses bile acids, improves metabolic parameters in obesity by doing several things, such as speeding up the breakdown of fatty acids, normalizing mitochondrial function, and lowering the amount of fat that builds up in the liver [92,94]. FXR activation safeguards against non-alcoholic fatty liver disease (NAFLD) by inhibiting SREBP-1c-mediated lipogenesis and enhancing the expression of genes involved in fatty acid oxidation [94]. FXR also affects how glucose levels stay stable and how sensitive insulin is in metabolic tissues. This makes FXR a good target for treating metabolic problems connected to obesity, including NAFLD[94].

3.4. Sterol Regulatory Element-Binding Proteins (SREBPs)

SREBPs are the main transcriptional regulators of the synthesis of lipids. SREBP-1c enhances lipogenesis and triglyceride synthesis in hepatic and adipose tissues, leading to ectopic fat accumulation in obesity[95,96]. Blocking SREBP-1c signaling lowers lipogenesis, stops ectopic lipid buildup, and is a way to treat the problems caused by lipotoxicity in people who are overweight [95]. Preclinical models and novel modulators aimed at the SREBP pathway have shown potential in the prevention and management of metabolic syndrome and obesity-related comorbidities [95,97].

4. Enzymatic and Metabolic Pathway Targets

4.1. AMP-Activated Protein Kinase (AMPK)

AMPK is a primary regulator of cellular metabolism that maintains energy homeostasis and activating it has become a key treatment for obesity. AMPK

activation whether through physiological stimuli like exercise and fasting or pharmacological agents facilitates fatty acid oxidation, inhibits lipogenesis and adipogenesis, improves insulin sensitivity, and minimizes inflammatory signaling in metabolic tissues [98,99]. In adipose tissue, the activation of AMPK inhibits lipogenesis predominantly by phosphorylating and deactivating acetyl-CoA carboxylase (ACC), leading to reduced malonyl-CoA levels and enhanced fatty acid oxidation [88,98]. AMPK has strong effects on the growth and differentiation of preadipocytes. Many studies have shown that it stops the expression of C/EBP β , PPAR γ , C/EBP α , SREBP-1c, and late adipogenic markers like fatty acid synthase (FAS) and adipocyte protein aP2, which stops adipogenesis[100]. Mechanistic connections between AMPK and the WNT/ β -catenin pathway explain its anti-adipogenic activities. [101] AMPK also helps white adipose tissue to brown, encourages the growth of mitochondria, and supports adaptive thermogenesis. This makes it an important molecular switch for metabolic flexibility and anti-obesity treatments [99].

Metformin, the most common anti-diabetic drug, helps people lose weight by activating AMPK and stopping NLRP3 inflammasome activation, which lowers inflammation linked to obesity and improves metabolic parameters [102][103]. Natural AMPK activators, such as dietary polyphenols like resveratrol and plant-derived berberine, are the subject of extensive investigation for their potential for reducing obesity, due to their diverse impacts on adipose tissue, liver, skeletal muscle, and inflammation [104,105].

4.2. Acetyl-CoA Carboxylase (ACC)

ACC is the enzyme that slows down the manufacture of fatty acids. It catalyzes the carboxylation of acetyl-CoA to make malonyl-CoA, which is a precursor for de novo lipogenesis and an inhibitor of carnitine palmitoyltransferase I (CPT1) [98,106]. AMPK directly phosphorylates ACC, which stops it from working and lowers the production of malonyl-CoA. This speeds up the breakdown of fatty acids and slows down the formation of new lipids and the storage of lipids in places where they shouldn't be [107,108]. Mouse models with ACC mutations show more triglyceride buildup, although drugs or genetic changes that block ACC lead to less fat [109]. Direct ACC inhibitors are being developed for therapeutic use in treating obesity and metabolic

syndrome, taking advantage of the fact that ACC is at the center of regulating both lipid synthesis and breakdown [110].

4.3. Fatty Acid Synthase (FAS)

FAS is a protein with many enzymes that helps the last steps of de novo lipogenesis by turning acetyl-CoA and malonyl-CoA into long-chain fatty acids [111]. FAS expression is elevated in obesity and metabolic diseases, leading to enhanced triglyceride production and ectopic lipid buildup. Inhibition of FAS such as with cerulenin or C75 has shown strong anti-obesity benefits in preclinical models by blocking fat production, which lowers body weight, adipose mass, and hepatic lipid storage. However, toxicity concerns have hindered the move to clinical application, and the search of safer FAS inhibitors continues to be a priority for obesity therapies [112].

4.4. Sodium-Glucose Cotransporter 2 (SGLT2)

SGLT2 inhibitors, first designed for diabetic management, exhibit unexpected anti-obesity benefits via various mechanisms. In addition to their main function of causing glycosuria-induced caloric loss, SGLT2 inhibitors bring back phosphorylated AMPK levels, encourage autophagy, and stop NLRP3 inflammasome activation, which lowers inflammation and improves metabolic outcomes [113]. These medicines offer supplementary cardiovascular and weight reduction advantages, supporting their use as multipurpose medications for obesity and associated comorbidities [114].

4.5. Dipeptidyl Peptidase-4 (DPP-4)

DPP-4 is a serine protease that cleaves and inhibits incretin hormones (GLP-1, GIP) from working. When it is inhibited, endogenous incretin signaling lasts longer [115]. DPP-4 inhibitors like sitagliptin and vildagliptin only help people lose a little weight on their own, but they are crucial for understanding how they work and for combining them with GLP-1 agonists and SGLT2 inhibitors. DPP-4 blockage positively influences glycemic control and metabolic flexibility, thus helping in weight management in obesity [116].

5. Inflammatory Pathway Targets

5.1. NLRP3 Inflammasome

The NLRP3 inflammasome is an important inflammatory target in obesity. It can be activated by

a variety of danger signals, such as saturated fatty acids, ceramides, and cellular stress. When the NLRP3 inflammasome is turned on, it causes pro-IL-1 β and pro-IL-1 β to be processed by caspase-1. This leads to long-term inflammation and insulin resistance [117,118].

Direct NLRP3 inhibitors, such as MCC950 and other small compounds, exhibit potential in preclinical obesity models. Indirect NLRP3 suppression via AMPK activation (metformin) or SGLT2 inhibition offers clinically verified strategies [119,120]

5.2. Nuclear Factor- κ B (NF- κ B)

Blocking the NF- κ B pathway lowers inflammation linked to obesity and makes insulin more sensitive. IKK β inhibitors and other NF- κ B pathway modulators exhibit anti-obesity benefits by decreasing the production of inflammatory cytokines. GLP-1 receptor agonists exhibit anti-inflammatory effects, by inhibiting the NF- κ B signaling pathway [121,122]

5.3. c-Jun N-terminal Kinase (JNK)

Blocking the JNK pathway makes insulin more effective by stopping IRS-1 serine phosphorylation. JNK1/2 inhibitors have potential for treating insulin resistance that is linked to obesity, although there are problems with selectivity in clinical development [123,124]

5.4. Toll-like Receptor 4 (TLR4)

TLR4 antagonism diminishes obesity-associated inflammation induced by saturated fatty acids and bacterial lipopolysaccharide. TLR4 is a critical player in metabolic endotoxemia, which connects problems in the stomach to inflammation throughout the body [125,126]

6. Epigenetic and Transcriptional Targets

6.1. DNA Methyltransferases (DNMTs)

DNMT inhibitors can change the DNA methylation patterns that are linked to obesity and modify important metabolic genes. 5-azacytidine and other DNMT inhibitors have the ability to reverse epigenetic modifications in genes associated with leptin, adiponectin, and insulin signaling [127,128]

6.2. Histone Deacetylases (HDACs)

HDAC inhibitors change the patterns of histone acetylation, which in turn changes the expression of metabolic genes [129]. Class-specific HDAC inhibitors exhibit anti-obesity effects by promoting mitochondrial biogenesis and fatty acid oxidation. [130]

6.3. MicroRNA Targets

Certain miRNAs control genes that are important for metabolism and are new targets for treatment. Anti-miR treatments aimed at obesity-related miRNAs exhibit potential for reinstating normal metabolic gene expression profile [131]

6.4. Sirtuin Activators

Through PGC-1 α deacetylation, SIRT1 activators, such as olivetol, improve diet-induced insulin resistance and encourage mitochondrial oxidative metabolism [132]. One method of treating obesity that mimics calorie restriction is sirtuin activation [133].

7. Gut-Brain Axis Targets

Recent evidence highlights the significant role of gut microbiota modulation in obesity management, where specific bioactive compounds from medicinal herbs interact with host metabolic and inflammatory pathways, regulate gut microbial composition, and influence energy balance and adiposity. Such integrative approaches underscore the relevance of gut-brain-microbiota axis targets in anti-obesity strategies [134]

7.1. Microbiome-Derived Targets

Short-Chain Fatty Acid Receptors

The advantageous effects of SCFAs generated from microorganisms are mediated via FFAR2 (GPR43) and FFAR3 (GPR41) receptors. Treatments for obesity that target the microbiota may be possible with selective receptor agonists [135,136]

Bile Acid Receptors

Bile acids activate TGR5 (GPBAR1), which leads to the release of GLP-1 and better metabolism. TGR5 agonists are new ways to target the gut-liver-metabolic axis [137]

7.2. Intestinal Barrier Targets

Intestinal permeability regulators and tight junction modulators provide strategies to stop metabolic inflammation. Inflammation originating from the

gut may be addressed by focusing on zonulin and other mediators of barrier function [138]

8. Novel and Emerging Targets

8.1. Growth Differentiation Factor 15 (GDF15)

GDF15 is a potential target for appetite regulation through activation of the brainstem GFRAL receptor. Analogues of GDF15 are being developed as the next generation of appetite suppressants [139]

8.2. Fibroblast Growth Factor 21 (FGF21)

Analogues of FGF21 target metabolic pathways related to fat oxidation and energy expenditure. FGF21 induces the activation of brown adipose tissue, increases insulin sensitivity, and encourages hepatic ketogenesis. [140]

8.3. Activin Receptor Antagonists

Bimagrumab and other activin receptor antagonists help keep muscle mass while losing weight, which is important for body composition. These drugs work on the myostatin/activin pathways to keep lean mass [141]

8.4. Dual Amylin and Calcitonin Receptor Agonists (DACRAs)

DACRAs (specially KBP-066A) are new types of compounds that target both amylin and calcitonin receptors to help people lose weight faster. In preclinical tests, these drugs have been shown to cause a lot of weight loss [142]

9. Multi-Target and Combination Approaches

9.1. Rational Combination Strategies

The pathophysiology of obesity is marked by interconnected and redundant pathways of inflammatory and metabolic dysregulation, requiring multi-target treatment approaches for effective disease management. Because of compensatory mechanisms and pathway overlap, single-agent therapy frequently fails to provide a sufficient or long-lasting benefit [143]. When incretin-based medicines (GLP-1, GIP, and glucagon receptor agonists) are used alongside anti-inflammatory drugs like NLRP3 or NF- κ B inhibitors, they can target both metabolic and inflammatory axes at the same time [144]. These combinations have demonstrated additive or synergistic effectiveness for weight reduction and

enhancement of insulin sensitivity in both preclinical and clinical investigations. For instance, combining AMPK activators (such as metformin and resveratrol) with NLRP3 inhibitors (such as MCC950 and SGLT2 inhibitors) produces synergistic anti-inflammatory and metabolic benefits, mitigating both chronic systemic inflammation and lipotoxicity induced metabolic dysfunction [145]. Current trials are examining additional rational combinations, such as dual incretin receptor agonists, SGLT2 inhibitors, and selective modulators of nuclear receptor pathways, with the objective of enhancing efficacy while reducing toxicity [146]

9.2. Precision Medicine Approaches

The growing use of molecular endotyping changes the way we treat obesity from a one-size-fits-all approach to personalized, biomarker-driven methods that take into account each person's inflammatory, metabolic, and genetic profiles. Multi-omics methods, which include genomes, transcriptomics, metabolomics, proteomics, and epigenomic evaluation, provide comprehensive characterization of obesity's heterogeneous endotypes and the prediction of therapy response [147]. For instance, classifying patients based on their inflammatory cytokine profile, adipokine patterns, metabolite signatures, or insulin action helps choose the best treatment. For example, anti-inflammatory drugs are best for people with dominant metaflammation, and incretin-based drugs are best for people with severe appetite dysregulation and beta-cell dysfunction [148,149]. Utilizing companion diagnostics and pharmacogenomic data enhances the optimization of drug selection and dose, facilitating rational combination therapy designed to mitigate adverse effects and enhance efficacy [150]. Alterations in gut-brain signalling and intestinal function have been implicated in obesity pathophysiology, including low-grade systemic inflammation and changes in microbiome composition that influence energy balance and metabolic regulation. Functional gastrointestinal disorders such as irritable bowel syndrome exhibit bidirectional associations with obesity and share common mechanistic features including gut permeability, chronic inflammation, and altered neurotransmitter signalling, reinforcing the importance of gut-brain and microbiome-derived targets in anti-obesity strategies [151]

10. Future Directions and Challenges

Next-Generation Target Discovery

New technologies like single-cell sequencing, spatial proteomics, and high-resolution metabolomics are quickly finding new therapeutic targets, cell populations, and inter-organ signaling axes that were not known before in the study of obesity pathogenesis. Integrating multiple omics layers, such as genotype, phenotype, and functional regulatory levels, could reveal distinct causal cascades and molecular "hubs" for targeted intervention [152,153]. Genome-wide CRISPR screens, high-content transcriptome profiling, and functional metabolic network analysis facilitate the identification of molecular drivers and quick prioritization of druggable targets. Integrative methodologies enhance biomarker creation for risk categorization and treatment monitoring [154,155]

Tissue-Selective Targeting

Designing modulators that only affect certain tissues (such as adipose-selective PPAR γ agonists and liver-specific LXR modulators) could make them work better while reducing side effects and general toxicity [156]. These strategies use different receptor expression and tissue-specific signaling to get the most out of the desired effects (like better lipid oxidation, more insulin sensitivity, and less lipogenesis) where they are most needed and lower the risks (like cardiovascular events and hepatic steatosis) in organs that are at risk. Preclinical investigations utilizing tissue-targeted variations of traditional nuclear receptor agonists and ligand-directed gene expression methodologies provide proof-of-concept for the subsequent phase in therapeutic enhancement [157]

Personalized Target Selection

Molecular profiling and pharmacogenomic strategies are progressively facilitating personalized target selection and drug dosing, enhancing the accuracy and dependability of obesity therapies. Algorithms that combine genetic variants, methylation signatures, transcriptome landscapes, microbiome composition, and environmental exposures create a personalized "molecular passport" that can be used to improve treatment. Adaptive trial designs and real-world data registries will facilitate the rapid integration of individualized treatment algorithms into mainstream obesity management [158,159]

11. Conclusions

The molecular landscape of obesity is characterized by diversity, complexity, and dynamic interactions among GPCRs, nuclear receptors, metabolic enzymes, inflammatory mediators, transcription factors, and epigenetic regulators. Recent clinical results, especially with multi-target incretin-based therapies and rational combination strategies, underscore the significance of integrated molecular targeting in obesity therapy. AMPK consistently functions as a metabolic "master switch," whereas NLRP3 and other anti-inflammatory pathways are becoming increasingly essential in disease modification. Tissue-selective nuclear receptor modulators and tailored pharmacogenomic approaches have additional potential for optimizing efficacy and reducing undesirable effects. The interconnectedness of obesity pathogenesis necessitates therapeutic strategies that include this complexity, including combinations, precision medicine, and systemic network regulation. Future obesity treatments will probably include a combination of targeting different molecular processes, based on each patient's profile and real-time biomarkers. The combination of next-generation molecular technologies, drug discovery platforms, and precision medicine infrastructure makes it possible to create fully tailored, effective, and long-lasting treatments for obesity. To turn

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mechanistic insights into real clinical benefits and break the link between obesity and its terrible comorbidities, we need to keep putting money into molecular target validation, multi-omics biomarker discovery, and translational research.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: data collection: SJ; study conception and design: AM; analysis and interpretation: BP and MC; draft manuscript: all authors. All authors reviewed the findings and approved the final version of the manuscript.

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