Deciphering the Role of Glycogen Synthase Kinase-3β in High-Fat Diet-Induced Obesity: Mechanistic Insights and the Therapeutic Potential of Naltrexone and Metformin Combination Therapy

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1. Abstract

Obesity, primarily driven by the prolonged consumption of energy-dense high-fat diets, represents a significant global health crisis linked to severe metabolic complications such as type 2 diabetes and cardiovascular disease. Central to its pathogenesis is the dysregulation of Glycogen Synthase Kinase-3 beta (GSK-3β), a multi-functional kinase that negatively regulates insulin signaling and energy homeostasis. In states of chronic overnutrition, GSK-3β becomes hyperactive due to reduced inhibitory phosphorylation, leading to the aberrant phosphorylation of insulin receptor substrate-1. This molecular defect impairs the PI3K/Akt pathway, causing systemic insulin resistance and abnormal lipid accumulation. Furthermore, high-fat diets trigger rapid neuroinflammation and reactive gliosis in the hypothalamus, which disrupts the delicate balance of appetite-regulating neurons and further blunts hormone sensitivity.

This research highlights the therapeutic potential of a multi-targeted combination therapy involving naltrexone and metformin to counteract these complex metabolic perturbations. Naltrexone, an opioid receptor antagonist, modulates reward-based eating behaviors and enhances anorexigenic signaling by preventing autoinhibition within hypothalamic pro-opiomelanocortin neurons. Complementarily, metformin acts as a potent peripheral insulin sensitizer by activating the AMP-activated protein kinase pathway, suppressing hepatic gluconeogenesis, and improving lipid metabolism. Experimental and clinical evidence suggests that the dual administration of these agents produces a synergistic effect, resulting in significant weight reduction, decreased visceral adiposity, and normalized fasting blood glucose levels. This combination successfully restores the inhibitory phosphorylation of GSK-3β, thereby stabilizing the insulin signaling cascade and attenuating hypothalamic inflammation. By simultaneously addressing central appetite regulation and peripheral molecular defects, the naltrexone-metformin strategy provides a robust framework for the effective management of high-fat diet-induced obesity.

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2. Introduction to Obesity and High-Fat Diets

The consumption of energy-dense, high-fat diets acts as a primary catalyst for systemic metabolic dysfunction, precipitating chronic insulin resistance and hypothalamic signaling abnormalities [1,2]. In these models, increased hypothalamic GSK-3β expression specifically exacerbates hyperphagia and impairs glucose tolerance [3]. Furthermore, recent evidence suggests that this dietary-induced chronic hyperinsulinemia fosters significant functional shifts in ventromedial hypothalamic neurons, effectively decoupling metabolic signals from the regulation of energy homeostasis [4]. This pathological state is exacerbated by high-fat dietary patterns that impair the anorexigenic signaling of insulin within the central nervous system, effectively preventing the brain from properly adjusting food intake in response to energy status [5]. Emerging research indicates that the therapeutic potential of metformin extends beyond glycemic control, as it demonstrates efficacy in mitigating weight gain and metabolic dysregulation by modulating central neural control and adipose tissue physiology [6]. Concurrently, naltrexone functions as an opioid receptor antagonist to suppress the reward-seeking behaviors associated with hyperpalatable foods, thereby reducing overall caloric intake [7]. Furthermore, metformin has been shown to restore leptin sensitivity in obese subjects by enhancing hypothalamic pro-opiomelanocortin expression, effectively correcting the leptin resistance typically observed in high-fat diet models [8]. By concurrently targeting these neuroendocrine circuits, the combination of naltrexone and metformin addresses the multifaceted nature of obesity, moving beyond simple caloric restriction to rectify the underlying signaling defects [9,10]. Furthermore, the persistent activation of GSK-3β in hypothalamic regions serves as a bottleneck that prevents effective weight management, as this kinase directly suppresses pathways involved in glucose metabolism and energy expenditure [11,12]. Targeting this specific kinase activity offers a promising therapeutic avenue to break the cycle of chronic metabolic dysfunction by re-sensitizing insulin signaling cascades and attenuating hypothalamic inflammatory responses [13,14]. By inhibiting the constitutive activity of GSK-3β, this dual approach effectively restores the insulin-mediated activation of metabolic pathways,

counteracting the hypothalamic signaling failures triggered by obesogenic diets [15].

2.1 Definition, Classification, and Epidemiology of Obesity

Obesity is clinically defined by an excess of adipose tissue, typically indexed by a body mass index of 30 kg/m² or higher, which correlates with an increased risk of chronic morbidities such as diabetes and cardiovascular disease [16].

Classification	BMI Range ()	Risk of Comorbidities
Underweight	< 18.5	Low (but high risk of other issues)
Normal Range	18.5 – 24.9	Average
Overweight	25.0 – 29.9	Increased
Obese Class I	30.0 – 34.9	Moderate
Obese Class II	35.0 – 39.9	Severe
Obese Class III	≥ 40.0	Very Severe

Table 1: WHO Classification of Weight Status by BMI

The global escalation of this condition persists despite the presence of evolutionarily conserved homeostatic mechanisms, underscoring the complexity of the current epidemic [17]. Driven by diverse genetic, behavioral, and environmental determinants, this multifactorial crisis now affects over 650 million adults worldwide [18]. Recent data suggests that the prevalence of obesity is linked to modern environmental conditions where the abundance of highly palatable, calorie-dense foods overrides homeostatic signals that evolved to function in periods of caloric scarcity [19,20]. This persistent caloric surplus disrupts the negative feedback loops responsible for maintaining stable body fat stores, thereby facilitating the transition from physiological regulation to a state of pathological allostasis [21]. This chronic state of energy excess effectively shifts the body's homeostatic set-point toward higher levels of adiposity, establishing a defended state of weight gain that becomes increasingly resistant to traditional lifestyle interventions [22,23]. Consequently, the systemic accumulation of excess adipose tissue functions as a primary driver for secondary pathologies, including nonalcoholic fatty liver disease and cardiovascular dysfunction, which substantially shorten life expectancy [24,25].

Beyond these structural risks, the sustained metabolic stress imposed by chronic adiposity triggers systemic inflammation and alters adipokine secretion, creating a milieu that favors persistent disease progression [26]. Furthermore, the intricate interplay between gut microbiota dysbiosis and endocrine-disrupting agents acts as an additional layer of metabolic complexity, complicating the clinical prognosis for patients with long-standing adiposity [27]. Given these multifactorial origins, obesity is increasingly categorized as a chronic, relapsing disorder that requires targeted pharmacological interventions to address both the biological defense of excess fat mass and the underlying signaling deficiencies [28]. Specifically, pharmacological strategies focusing on the reversal of hypothalamic neuroinflammation and the recalibration of energy-sensing pathways represent a shift toward precision medicine for metabolic management [29,30]. By modulating specific enzymatic targets such as GSK-3β while simultaneously addressing reward-driven pathways, these integrative therapies aim to stabilize neuroendocrine feedback loops that have been chronically dysregulated by energy-dense nutritional inputs [31,32].

2.2 Influence of High-Fat Diet Consumption on Global Health

The proliferation of diets rich in fats and sugars has fundamentally altered human ingestive behavior, often overriding satiety signals and promoting a state of hyperphagia [33,34]. Such dietary patterns disrupt the delicate communication between the gut, brain, and adipose tissue, which is essential for the physiological regulation of metabolism [35]. This nutritional environment triggers chronic systemic inflammation and oxidative stress, which further exacerbate the development of insulin resistance and dyslipidemia in ectopic storage depots [36,37]. Moreover, the intake of high-fat diets promotes intestinal permeability and microbial imbalance, which facilitates the translocation of bacterial endotoxins into systemic circulation, thereby intensifying metaflammation [38,39]. This state of chronic, low-grade inflammation contributes to adipose tissue hypertrophy and dysfunction, which impairs the metabolic homeostasis of tissues such as skeletal muscle and the hypothalamic-pituitary-adrenal axis [40]. Compounding these physiological perturbations, the shift in microbial composition serves as a critical mediator that links excessive caloric consumption to the disruption of hypothalamic energy-sensing circuits [41,42].

These dietary-induced alterations in the microbiota-gut-brain axis are central to the pathogenesis of obesity, as they modulate innate immune responses and inflammasome activity [43]. Specifically, saturated fatty acids within these diets act as potent triggers for the activation of TLR4 and NF-κB inflammatory pathways, which subsequently induce endoplasmic reticulum stress in the hypothalamus [44,45]. This cellular strain further compromises the structural integrity of the arcuate nucleus, where neurofibrosis may serve as a physical barrier that restricts insulin delivery and impairs metabolic sensitivity [46]. In this context, the recruitment of microglia and the resulting pro-inflammatory environment not only inhibit neuronal insulin action but also disrupt leptin signal transduction, effectively blunting the anorexigenic responses essential for weight management [47]. Further investigation reveals that these hypothalamic insults are specifically mediated by the activation of JNK- and IKK-signaling cascades, which establish a persistent state of central leptin resistance [48]. Within this neuroinflammatory cascade, glycogen synthase kinase 3 beta (GSK-3β) emerges as a critical regulatory node that further exacerbates insulin and leptin resistance by impairing downstream signaling and promoting neuronal stress [49,50].

3. High-Fat Diet-Induced Obesity: Mechanisms and Development

The consumption of saturated fats serves as a primary inflammatory trigger, inducing hypothalamic gliosis and structural damage within the arcuate nucleus within days of exposure [51]. This rapid onset of neuroinflammation, characterized by microglial activation and astrogliosis, occurs well before detectable weight gain or peripheral metabolic dysregulation [52,53]. This early inflammatory response, mediated by toll-like receptor 4, transactivates NF-κB to induce the expression of proinflammatory cytokines and suppressors of cytokine signaling that chronically impair homeostatic control [54,55]. Specifically, the accumulation of long-chain saturated fatty acids within the hypothalamus facilitates this inflammatory signaling, effectively decoupling nutrient sensing from energy expenditure [56]. Concurrent with these inflammatory processes, the persistent activation of GSK-3β further destabilizes metabolic homeostasis by disrupting insulin-mediated intracellular signaling and exacerbating cellular endoplasmic reticulum stress [57,58]. Consequently, the pharmacological inhibition of GSK-3β, in conjunction with the synergistic effects of naltrexone and metformin, offers a promising therapeutic avenue to suppress these neuroinflammatory pathways and restore hypothalamic sensitivity to peripheral satiety signals [59,60]. This therapeutic combination targets key inflammatory mediators such as JNK and IKK, which are known to sustain leptin and insulin resistance within the arcuate nucleus [61,62].

3.1 Energy Imbalance and Excess Caloric Intake

Chronic overnutrition induces a state of positive energy balance where excess caloric density systematically overrides the hypothalamic anorexigenic signaling driven by leptin and insulin [63]. This metabolic dysregulation is compounded by reduced responsiveness to these circulating adiposity signals, which effectively prevents the brain from accurately gauging energy stores [64]. This feedback deficit is further aggravated by structural damage to the median eminence, where the impairment of tanycytic barriers restricts the transport of systemic hormones into the mediobasal hypothalamus [65]. Furthermore, this neuroanatomical disruption is frequently accompanied by a localized increase in proinflammatory cytokine expression, such as IL-1β and TNF-α, which further precipitates the degradation of energy-sensing neuronal integrity [66]. In this pathological landscape, the sustained activation of IKKβ and NF-κB signaling pathways serves to perpetuate a cycle of hypothalamic inflammation that hinders effective metabolic regulation [67,68].

Recent evidence suggests that the hypothalamic astrocytic NAD+ salvage pathway also plays a vital role in this maladaptive process, as fat overload activates CD38 to compromise essential metabolic signaling [69]. By mitigating this NAD+ depletion, researchers have demonstrated that restoring astrocytic function can effectively suppress the neuroinflammatory triggers induced by prolonged HFD intake [70]. Furthermore, the administration of naltrexone and metformin has shown efficacy in modulating these pathways by reducing hypothalamic inflammation and enhancing the sensitivity of POMC neurons to anorexigenic stimuli [71]. By specifically restraining the TNFα/NF-κB signaling axis within these neuronal populations, this pharmacological strategy interrupts the cascade of hypothalamic dysfunction that drives chronic hyperphagia and weight gain [72]. Furthermore, the multifaceted therapeutic integration of naltrexone and metformin acts to re-establish the functional balance between orexigenic NPY/AgRP neurons and anorexigenic POMC neurons, effectively reversing diet-induced energy imbalances [73,74].

3.2 Metabolic Alterations Associated with High-Fat Diet Exposure

Chronic consumption of these diets induces "meta-inflammation," a systemic state characterized by

macrophage-mediated cytokine production across adipose tissue, the liver, and the colon [75]. These peripheral inflammatory markers create a deleterious feedback loop with the central nervous system, as elevated systemic cytokines facilitate the transport of inflammatory signals across the blood-brain barrier, thereby amplifying hypothalamic glial activation [76,77]. Additionally, the localized IKK-β signaling within astrocytes contributes to this pathology by shortening cellular processes and reducing GABAergic reuptake, which suppresses the release of neurotrophic factors and ultimately drives hyperphagia [78]. Moreover, the concomitant activation of glycogen synthase kinase 3 beta within these hypothalamic regions facilitates the deleterious effects of hyperinsulinemia, further impairing the homeostatic control of glucose and energy metabolism [79,80].

By modulating these signaling cascades, the co-administration of naltrexone and metformin promotes a neuroprotective milieu that mitigates glial-driven neurotoxicity [81], [82]. Specifically, this intervention appears to downregulate microglial necroptosis and reduce the accumulation of Iba-1 positive cells within the arcuate nucleus, effectively curbing the neuroinflammatory response [83]. This stabilization of the glial environment prevents the further loss of pro-opiomelanocortin neurons, which are essential for maintaining long-term body weight regulation [84]. Furthermore, this dual pharmacological approach facilitates the restoration of insulin sensitivity within the hypothalamus by attenuating the aberrant activation of the NF-κB signaling cascade [85]. Moreover, this regulatory shift effectively suppresses the expression of proinflammatory factors released by reactive microglia, thereby alleviating the hypothalamic inflammation that frequently precedes significant weight gain [86,87]. In this context, the pharmacological inhibition of GSK-3β represents a critical intervention, as this kinase acts as a molecular bridge between insulin resistance and the persistent microglial activation observed in HFD-fed models [88,89]. Beyond the inhibition of GSK-3β, addressing the underlying reactive gliosis is essential, as prolonged HFD consumption triggers a rapid expansion of microglia and astrocytes that directly impairs arcuate nucleus signaling [90,91]. This morphological remodeling is often characterized by increased glial ensheathment of POMC perikarya, which physically disrupts the synaptic inputs necessary for maintaining normal satiety signaling [92].

4. Molecular Basis of Obesity Pathogenesis

The pathophysiology of obesity is increasingly understood as a failure of hypothalamic integration, wherein the dysregulation of key energy-sensing neurons—specifically those co-expressing neuropeptide Y and agouti-related peptide—promotes persistent hyperphagia and metabolic decay [93]. Concurrently, the anorexigenic signaling from pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript neurons is progressively compromised, reflecting a profound disruption in the arcuate nucleus's capacity to process metabolic cues [94,95]. This homeostatic failure is compounded by the HFD-induced activation of microglial populations, which undergo significant morphological ramification and increase the expression of markers such as CD68 [96]. This microglial activation leads to the sustained release of pro-inflammatory cytokines, which directly activate intracellular pathways that exacerbate insulin resistance and disrupt central energy homeostasis [97]. Specifically, the hyperactivation of hypothalamic microglia facilitates the recruitment of peripheral myeloid cells into the arcuate nucleus, intensifying local neuroinflammation and promoting the subsequent loss of POMC neuronal integrity [98,99]. This deleterious cascade is exacerbated by the disruption of interglial crosstalk, where malfunctioning astrocytes further compromise the neuroprotective microenvironment [100]. Consequently, the integration of naltrexone and metformin serves to counteract these deleterious alterations by suppressing reactive gliosis, thereby preserving the structural and functional plasticity of the hypothalamus [101,102]. Beyond these structural adaptations, the combined therapy targets the underlying cellular stress by inhibiting the GSK-3β-mediated inflammatory responses, which are closely linked to the aberrant microglial morphological changes observed in high-fat diet models [103,104].

4.1 Adipogenesis and Lipid Metabolism Dysregulation

The chronic intake of a high-fat diet drives the abnormal expansion of white adipose tissue, leading to adipocyte hypertrophy and the secretion of proinflammatory adipokines that further dysregulate systemic energy homeostasis [105]. Concurrently, the accumulation of saturated long-chain fatty acids like palmitate in the hypothalamus initiates toll-like receptor 4 signaling, which exacerbates NF-κB-dependent inflammatory cytokine production [106]. This inflammatory stimulus promotes the phosphorylation of cPLA2, which increases the synthesis of prostaglandins—key mediators of brain inflammation that further impair the homeostatic function of the arcuate nucleus [107]. Furthermore,

this localized neuro-inflammation is compounded by the anatomical vulnerability of the arcuate nucleus to systemic stimuli, as its proximity to the median eminence facilitates the infiltration of peripheral inflammatory regulators and free fatty acids [108]. This heightened permeability of the blood-brain barrier under high-fat dietary conditions permits these lipid-derived signals to initiate reactive gliosis, which fundamentally compromises the neurobiological circuitry governing energy balance [109,110]. Crucially, these metabolic and toxic insults induce long-term neuroadaptations that contribute to the maintenance of obesity, even after dietary transition to standard chow [111].

In response, evidence indicates that glial cells in the mediobasal hypothalamus undergo persistent structural modifications, such as altered ensheathment of synaptic inputs, which continue to hinder the physiological regulation of hunger and satiety [112]. The concurrent administration of naltrexone and metformin effectively mitigates these chronic glial adaptations by modulating synaptic plasticity and restoring the inhibitory tone within the hypothalamic circuit [113,114]. This therapeutic synergy not only attenuates the recruitment of peripheral monocytes but also stabilizes the blood-brain barrier permeability, thereby preventing the persistent influx of free fatty acids that sustain pro-inflammatory microglial responses [14]. By curbing this neuroinflammatory cycle, the pharmacological combination effectively restores the responsiveness of arcuate neurons to anorexigenic hormones like leptin [115]. This restoration of leptin sensitivity is critical, as it reverses the state of central metabolic disequilibrium that typically prevents individuals from achieving long-term weight reduction [116]. Furthermore, by inhibiting GSK-3β, this dual-drug regimen suppresses the activation of pathways linked to hypothalamic gliosis, effectively decoupling the chronic exposure to saturated fatty acids from the resulting neuroinflammatory cascade [117,118].

4.2 Oxidative Stress and Chronic Low-Grade Inflammation

High-fat diets catalyze the production of reactive oxygen species within hypothalamic mitochondria, leading to oxidative damage that disrupts energy-sensing neurons and promotes chronic neuroinflammation [119]. This mitochondrial dysfunction further triggers the release of pro-inflammatory cytokines through the activation of the NLRP3 inflammasome, establishing a self-perpetuating feedback loop that impairs insulin-stimulated glucose uptake in the central nervous system [120,121]. The resulting oxidative stress facilitates persistent hypothalamic gliosis and injury, which further desensitizes energy-sensing circuits to peripheral satiety signals [122,123]. The naltrexone-metformin combination targets this mitochondrial impairment by attenuating NLRP3 activation and limiting the production of reactive oxygen species, thereby stabilizing the neuronal microenvironment [23]. Additionally, metformin's modulation of AMPK signaling pathways complements the opioid antagonism of naltrexone in suppressing GSK-3β activity, which otherwise exacerbates metabolic neuroinflammation in the presence of lipid overload [124].

This pharmacological intervention effectively addresses the feedback inhibition that typically limits the therapeutic efficacy of weight-loss strategies, allowing for more sustained regulation of energy intake [125,126]. Moreover, recent findings highlight that suppressing microglial NF-κB-dependent signaling is essential for reversing the hypothalamic inflammatory state induced by excessive saturated fatty acid consumption [127,128]. This mechanism appears particularly relevant given that the disruption of the NSAPP signaling pathway, which is essential for canonical leptin and insulin action, is frequently blunted by high-fat diet consumption [129]. By mitigating these redox-sensitive inflammatory cascades, the therapeutic combination restores the regulatory capacity of Nrf2, which is critical for bolstering the brain's antioxidant defense against fatty acid-induced mitochondrial damage [130]. Furthermore, the upregulation of this antioxidant pathway facilitates the restoration of mitochondrial biogenesis, which helps maintain cellular energy homeostasis despite the persistent metabolic challenges posed by high-fat intake [131].

5. Glycogen Synthase Kinase-3β (GSK-3β): Structure and Biological Functions

GSK-3β is a serine/threonine kinase that exists as two isoforms, α and β, characterized by their constitutive activity in resting cells and their unique regulation through inhibitory phosphorylation at N-terminal residues [3]. Unlike most kinases, GSK-3β remains active under basal conditions, requiring specific inhibitory signaling pathways to modulate its involvement in glucose metabolism and energy homeostasis [132]. The kinase's structural versatility allows it to function as a central signaling hub, with over 100 identified substrates involved in diverse pathways ranging from cell fate determination to bioenergetics [133]. In the context of obesity, the elevated expression and activity of this kinase serve as a negative regulator of insulin-mediated glycogen synthesis and overall glucose homeostasis [134]. Specifically, hypothalamic overexpression of GSK-3β during high-fat feeding promotes leptin resistance by impairing PI3K-mediated signaling,

thereby exacerbating weight gain and suppressing metabolic feedback mechanisms [135,136]. Additionally, the aberrant activity of GSK-3β facilitates the phosphorylation of insulin receptor substrate-1, a modification that directly hinders insulin signaling and compromises the homeostatic regulation of systemic energy balance.

5.1 Structural Characteristics and Regulation of GSK-3β

The enzyme's activity is primarily governed by the phosphorylation of its N-terminal serine residues, where inhibitory phosphorylation at Ser9 serves as a critical regulatory switch mediated by upstream kinases such as protein kinase B [137]. This inhibitory mechanism functions by creating a pseudo-substrate that binds to the enzyme's catalytic site, thereby preventing the phosphorylation of key metabolic substrates [138]. Conversely, in the absence of such inhibitory signals, the kinase remains constitutively active, exerting negative regulatory pressure on essential pathways such as glycogen synthesis [139]. Beyond its primary role in glycogen metabolism, GSK-3β also modulates gluconeogenesis by influencing the gene expression of key enzymes like PEPCK and G6P [140]. The phosphorylation of these residues acts as a key signaling checkpoint, where insulin-stimulated activation of the PI3K/Akt pathway effectively suppresses this kinase activity to promote glycogen storage and stabilize glucose production [141,142]. Evidence suggests that this regulatory checkpoint is frequently disrupted in obesity, as the kinase's hyperactivation contributes to the phosphorylation of insulin receptor substrate-1 and subsequent development of insulin resistance [143,144].

Furthermore, the kinase isoforms display distinct localization patterns and functional specificities, which are mediated by their unique N-terminal domains and interactions with scaffold proteins that dictate downstream target selection [145,146]. In particular, phosphorylation of Tyr216 within the activation loop is required for its maximal catalytic potential, representing an essential regulatory level distinct from the inhibitory Ser9 phosphorylation [147]. Such regulatory precision ensures that only specific pools of the kinase are activated in response to physiological stimuli, thereby preventing indiscriminate substrate phosphorylation [148]. Beyond this N-terminal control, the balance of GSK-3β activity is further modulated by phosphatases like protein phosphatase 1 and 2A, which remove the inhibitory Ser9 phosphate to restore catalytic competence [149]. Consequently, the dysregulation of this phosphatase-kinase axis under conditions of chronic nutrient excess shifts the equilibrium toward persistent GSK-3β activation, further impairing insulin-stimulated signaling [150,151].

5.2 Physiological Roles of GSK-3β in Cellular Signaling

The kinase serves as a critical signaling node in the Wnt pathway, where it facilitates the phosphorylation and subsequent degradation of β-catenin, a process essential for regulating cell growth and differentiation [152]. Beyond this developmental role, GSK-3β integrates signals from the PI3K/AKT and AMPK pathways to maintain metabolic equilibrium, particularly in peripheral tissues where it directly phosphorylates glycogen synthase to govern energy storage [153–155]. In this regulatory capacity, GSK-3β remains constitutively active and subject to inhibitory phosphorylation by kinases such as Akt, providing a mechanism by which insulin signaling can modulate glycogen synthesis [156,157]. Consequently, pathological hyperactivation of GSK-3β in obesity disrupts this homeostatic balance, reinforcing the rationale for its pharmacological inhibition to restore metabolic sensitivity [158,159]. By targeting this node with agents like naltrexone and metformin, clinicians can synergistically suppress the enzyme's overactivity and potentially reverse the metabolic deficits induced by chronic high-fat diets [160,161]. This pharmacological strategy leverages the ability of these agents to promote the inhibitory phosphorylation of GSK-3β, thereby preventing the constitutive inactivation of glycogen synthase and restoring normal glucose disposal [162,163]. Furthermore, the integration of these therapeutic agents may mitigate the chronic over-nutrition-induced dysregulation of the PI3K/PDK1/Akt/GSK-3β axis, thereby attenuating the aberrant phosphorylation of key insulin-signaling components [164]. Recent experimental evidence indicates that tissue-specific ablation of this kinase in pancreatic islet cells can paradoxically prevent diet-induced glucose intolerance while enhancing β-cell mass, underscoring its dual role in peripheral insulin sensitivity and endocrine homeostasis [165]. Moreover, studies utilizing selective GSK-3β inhibitors have demonstrated significant improvements in glucose tolerance and peripheral insulin sensitivity without necessarily altering total adipose tissue mass [166].

6. Role of GSK-3β in High-Fat Diet-Induced Obesity

Chronic exposure to high-fat diets leads to increased GSK-3 activity within epididymal adipose tissue, which directly contributes to the exacerbation of metabolic dysregulation [167]. Specifically, proteomics analysis of islets in obese models reveals that this hyperactivation contributes to the suppression of downstream survival pathways and facilitates β-cell failure [24]. Moreover, the inability of insulin to effectively reduce GSK-3 activity in these models serves as a central mechanism in the

development of systemic insulin resistance [168]. Elevated expression and overactivity of this kinase in the skeletal muscle of rodent models have been directly linked to an impaired capacity for insulin-stimulated glucose disposal and glycogen synthesis [169]. Consistent with these findings, genetic studies indicate that mice deficient in specific GSK-3 isoforms exhibit reduced fat mass and improved glucose tolerance when challenged with an obesogenic diet [170,171]. Furthermore, pharmacological modulation of GSK-3β has been shown to ameliorate hepatic steatosis and enhance energy expenditure, providing a promising mechanism to reverse the deleterious metabolic impacts of chronic nutrient excess [172,173]. Specifically, the synergistic use of naltrexone and metformin has been proposed to recalibrate this pathway, as their combined influence likely addresses both the central appetite regulation and the peripheral insulin-sensitizing mechanisms critical for offsetting diet-induced β-cell stress [174,175].

6.1 GSK-3β in Insulin Resistance and Glucose Homeostasis

In these models, heightened GSK-3 activity in skeletal muscle and liver tissues correlates strongly with enhanced insulin receptor substrate-1 serine phosphorylation, which prevents normal downstream insulin signal transduction [176]. Concurrently, clinical investigations reveal that inhibiting this kinase effectively restores glucose infusion rates and enhances glycogen synthase activity, thereby reversing the metabolic bottlenecks characteristic of high-fat diet-induced diabetes [177]. This restorative effect appears to be particularly pronounced in models where GSK-3β expression is modulated through targeted interventions, as elevated baseline activity in adipose tissue has been identified as a driver of diet-induced obesity [178]. Furthermore, the pharmacological inhibition of GSK-3β has been shown to counteract the deleterious effects of chronic hyperglycemia on pancreatic β-cell function, potentially preserving secretory capacity in the face of metabolic stress [179,180]. By promoting the phosphorylation of GSK-3β at Ser9, this combinatorial pharmacological approach effectively mimics the protective regulatory mechanisms lost during the development of diet-induced insulin resistance [181,182]. Such therapeutic interventions essentially reprogram the cellular milieu, restoring the inhibitory control of GSK-3β necessary for robust glycogen storage and the mitigation of systemic insulin resistance [183,184]. Additionally, research indicates that the therapeutic efficacy of such interventions is linked to improved adiponectin levels, which further safeguard against diet-induced metabolic syndrome by bolstering insulin-dependent PI3K/Akt signaling pathways [185]. Furthermore, the ability of metformin to activate AMP-activated protein kinase provides a secondary regulatory layer that suppresses the downstream pathological consequences of hyperactive GSK-3β, including diminished glucose transporter expression [186]. Ultimately, the interplay between AMPK-mediated signaling and GSK-3β inhibition addresses both the suppression of hepatic gluconeogenic enzymes, such as PEPCK and glucose-6-phosphatase, and the reinforcement of peripheral glucose uptake mechanisms [187,188]. In this context, the combined administration of naltrexone and metformin acts to optimize the phosphorylation status of metabolic regulators, ensuring that GSK-3β remains in its inactive state to facilitate glycogen synthesis [189]. Furthermore, the reduction of oxidative stress facilitated by this dual treatment prevents the pathological blockage of glycogen synthase, which is often exacerbated in insulin-resistant hepatocytes [190].

6.2 GSK-3β-Mediated Signaling Pathways in Obesity Development

The hyperactivation of GSK-3β within metabolic tissues functions as a critical node in disrupting insulin signaling, primarily by modulating the activity of key transcription factors and metabolic enzymes [191,192]. Specifically, increased kinase activity promotes the nuclear translocation of FoxO proteins, which in turn upregulates the transcription of genes governing hepatic gluconeogenesis, such as PEPCK and G6P [193]. Concurrently, this enzymatic dysregulation impairs the IRS/AKT pathway, preventing the phosphorylation-mediated inactivation of GSK-3β required for efficient glucose uptake and glycogen storage [194,195]. Moreover, the inhibitory action of insulin on GSK-3 activity is essential for hormonal regulation of glucose homeostasis, as inactivation via phosphorylation at specific serine residues is required to permit unimpeded glycogen synthase function [196]. Beyond these regulatory effects, the non-canonical Wnt signaling pathway also intersects with these cascades, acting in an antagonistic manner to the canonical Wnt/β-catenin axis to modulate cellular transcriptional responses and metabolic homeostasis [12].

Furthermore, recent investigations demonstrate that the suppression of GSK-3β activity restores the stability of β-catenin, thereby mitigating lipid accumulation and inflammation within adipose tissue [197]. This interaction suggests that targeted inhibition of the kinase not only redirects metabolic flux away from adipogenesis but also facilitates the transcription of genes that promote healthy energy storage [198]. Moreover, the therapeutic modulation of these pathways mitigates the pro-inflammatory environment characteristic of visceral adipose tissue dysfunction, effectively reducing the hypertrophy

and hypoxia associated with metabolic syndrome [199]. Additionally, the depletion or pharmacological downregulation of β-catenin has been associated with enhanced insulin sensitivity and reduced basal activity of key signaling kinases, indicating that stabilizing this protein through GSK-3β inhibition is a viable strategy to reverse diet-induced metabolic failure [200]. Consequently, the synergistic potential of naltrexone and metformin in modulating these molecular nodes underscores a promising strategy for stabilizing metabolic signaling and preventing the progression of obesity-related comorbidities [201].

7. Therapeutic Role of Naltrexone and Metformin

The administration of naltrexone in conjunction with metformin addresses the dual challenge of obesity-related neuroendocrine dysregulation and hepatic insulin resistance. By attenuating GSK-3β-mediated interference in insulin signaling, this combination enhances the overall efficacy of glycemic control and adipose tissue homeostasis [202]. Moreover, metformin's ability to suppress adipogenesis via AMPK-dependent pathways complements naltrexone's modulation of central satiety signals, creating a multifaceted therapeutic approach that effectively recalibrates energy metabolism [203]. This integrated strategy leverages the crosstalk between pro-opiomelanocortin activation and AMPK signaling to mitigate the compensatory mechanisms that typically limit long-term weight reduction [204]. Specifically, naltrexone facilitates weight loss by acting as an opioid receptor antagonist to prevent the autoinhibition of β-endorphin on POMC neurons, while metformin reduces hepatic glucose production by suppressing the gluconeogenesis pathway [205]. Additionally, evidence suggests that the drug combination produces a synergistic effect on food intake by influencing reward-based consumption, further enhancing the metabolic benefits observed in clinical settings. Beyond these neuroendocrine and hepatic effects, this combination may also modulate systemic inflammation by alleviating lipotoxicity-induced cellular stress, which is essential for protecting the integrity of signaling pathways prone to insulin resistance [206,207].

Feature	Naltrexone	Metformin
Primary Target	Opioid Receptors (μ-opioid antagonist)	AMPK Activation / Mitochondria
Primary Site	Central Nervous System	Peripheral
Action on Appetite	Reduces reward-driven/hedonic eating	Minor appetite suppression
Action on Glucose	Indirectly improves metabolic drive	Decreases hepatic glucose production
Effect on Weight	Modest reduction in food intake	Modest reduction in body mass

Table 2: Comparative Pharmacological Profile

7.1 Mechanism of Action of Naltrexone in Appetite Regulation

Naltrexone functions by antagonizing the mu-opioid receptors on hypothalamic pro-opiomelanocortin neurons, thereby disrupting the negative feedback loop typically mediated by $beta$-endorphin [208,209]. This blockade facilitates the sustained activation of POMC neurons, which promotes anorexigenic signaling and reduces the motivational drive associated with hedonic eating [24]. By mitigating these reinforcing properties of food stimuli, naltrexone modulates the mesolimbic reward pathways that contribute to compulsive eating behavior [210]. By diminishing the perceived reward of caloric-dense foods, this mechanism directly addresses the neurobiological drivers of overconsumption that often undermine weight loss efforts [211]. Concurrently, this pharmacological intervention effectively counteracts the opioid-dependent feedback mechanisms that would otherwise attenuate the efficacy of neuroendocrine satiety signals [212]. Furthermore, the integration of metformin with this pharmacological approach leverages AMPK activation to inhibit the downstream signaling nodes that typically promote adipogenesis and hepatic gluconeogenesis [213]. By stabilizing metabolic fluxes and tempering central reward-seeking behavior, this dual-agent strategy addresses both the peripheral insulin resistance and central neuroendocrine dysregulation inherent in obesity [214,215]. Furthermore, this combination has been shown to reduce cravings and grazing behaviors, which are critical drivers of weight regain in patients with binge eating tendencies [216].

Moreover, the clinical efficacy of this approach is likely enhanced by the reduction of systemic inflammatory markers, which are intrinsically linked to the pathophysiology of high-fat diet-induced metabolic dysfunction [217]. Beyond these metabolic considerations, preclinical models suggest that the therapeutic efficacy of such combined pharmacotherapy might be further refined by considering sex-dependent hormonal modulation

of hypothalamic signaling [218]. Additionally, naltrexone's ability to augment POMC neuronal activity by preventing $beta$-endorphin-mediated autoinhibition suggests a targeted approach to restoring satiety, particularly in subjects whose hedonic eating patterns are exacerbated by high-fat diet consumption [219,220]. In this context, the integration of metformin provides a complementary mechanism by stabilizing glucose homeostasis and inhibiting the cellular stress responses that typically impair metabolic flexibility [221,222].

7.2 Metformin and Its Effects on Energy and Metabolic Regulation

Metformin primarily enhances metabolic regulation by activating AMP-activated protein kinase, a critical cellular energy sensor that promotes fatty acid oxidation and inhibits lipogenesis in the liver and skeletal muscle [223]. By modulating the duodenal AMPK-GLP-1R-PKA axis, metformin further optimizes systemic glucose utilization and diminishes hepatic glucose production [224]. In addition to these glycemic benefits, metformin has been shown to mitigate weight gain in high-fat diet models, acting as a multifaceted agent to correct the metabolic imbalances associated with obesity [6]. Furthermore, research indicates that metformin improves fatty liver disease by reversing hepatic steatosis, a condition frequently exacerbated by high-fat diet consumption through the stimulation of hepatic fatty acid oxidation [225]. Furthermore, the combined administration of these agents serves to synchronize central appetite suppression with peripheral metabolic stabilization, effectively overriding the homeostatic mechanisms that resist sustained weight loss. Recent investigations have specifically identified that metformin alleviates hypothalamic inflammation by inhibiting microglial necroptosis, a critical process that otherwise propagates cytokine-mediated metabolic dysregulation in obese subjects [83].

Furthermore, the inhibition of this inflammatory pathway works in tandem with metformin's ability to modulate hypothalamic AMPK, which directly suppresses food intake by decreasing NPY expression [226]. This modulation of hypothalamic signaling underscores the drug's capacity to restore leptin sensitivity, which is typically compromised in high-fat diet-induced obesity [8]. In addition to these hypothalamic effects, the interplay between metformin and GSK-3$beta$ signaling appears to represent a pivotal intersection in mitigating diet-induced metabolic dysfunction, as the suppression of GSK-3$beta$ activity often synergizes with AMPK activation to enhance cellular insulin sensitivity and glucose uptake [227,228]. Specifically, by restraining GSK-3$beta$ phosphorylation of insulin receptor substrate-1, this pharmacological synergy preserves insulin signaling cascades and prevents the deleterious metabolic consequences of chronic nutrient excess [229]. By concurrently modulating these pathways, the combination therapy effectively lowers the threshold for insulin-stimulated glucose transport in peripheral tissues [230,231].

8. Combination Therapy with Naltrexone and Metformin

8.1 Mechanistic Basis of Combined Drug Action

The synergistic interaction between naltrexone and metformin targets the convergence of reward-driven overeating and impaired glucose homeostasis by simultaneously optimizing central POMC activity and peripheral AMPK-dependent metabolic flux [125,232]. This dual-target approach effectively antagonizes the inhibitory feedback loops that typically limit weight loss success, while simultaneously alleviating the systemic metabolic stress induced by chronic caloric excess [124,126]. By dampening GSK-3$beta$ activity, this combination also downregulates pro-inflammatory cytokines that exacerbate hypothalamic dysfunction and neuroendocrine resistance in obese phenotypes [10]. Additionally, recent evidence suggests that this pharmacological modulation of microglial activity is essential for reversing the hypothalamic inflammation that often sustains obesity-related metabolic failures [89,128]. Concurrent to these neuro-inflammatory benefits, metformin directly influences the hypothalamic arcuate nucleus by blocking AMPK phosphorylation, which subsequently limits neuropeptide Y gene expression and its associated hyperphagic response [233]. Simultaneously, the blockade of opioid-mediated reward signaling by naltrexone complements these peripheral shifts, thereby stabilizing the energy balance by preventing the compensatory overconsumption often triggered by high-fat diet-induced neuroendocrine stress [17,234].

Moreover, by promoting the phosphorylation of GSK3β at Ser9, this therapeutic combination effectively counteracts the obesity-induced overactivity of the kinase that otherwise inhibits insulin receptor substrate-1 [235], [135]. Consequently, this regulatory interplay restores downstream insulin signaling pathways, thereby enhancing peripheral glucose uptake and overcoming the insulin resistance characteristic of high-fat diet-fed models [236]. Furthermore, this pharmacological intervention effectively reverses brain insulin resistance in high-fat diet models by preserving mitochondrial function and augmenting hippocampal signaling [237]. Beyond these neurological benefits, the combined administration of these agents addresses the systemic metabolic dysregulation by inhibiting the excessive activation of hypothalamic AMPK, which otherwise drives

hyperphagia under conditions of chronic nutrient availability [238].

8.2 Experimental and Clinical Evidence Supporting Combination Therapy

Preclinical assessments have demonstrated that this dual-pharmacological approach significantly reduces adipose tissue accumulation and systemic insulin resistance in rodent models exposed to long-term high-fat feeding [1]. Specifically, these studies indicate that the intervention blunts the diet-induced hypothalamic inflammatory response, thereby preventing the microglial activation that typically contributes to persistent neuroendocrine disruption [87]. Moreover, the combined treatment demonstrates an enhanced capacity to modulate hypothalamic plasticity, effectively recalibrating energy expenditure beyond the effects observed with either agent administered in isolation [239,240]. These observations are consistent with existing data regarding opioid antagonists, which have demonstrated a clear capacity to diminish food intake by interfering with hypothalamic signaling pathways [241,242]. Building on this, the opioid system's role as a homeostatic regulator of energy balance confirms that antagonizing these receptors can attenuate the behavioral and metabolic shifts induced by chronic high-fat consumption [243]. This synergy aligns with the growing body of evidence indicating that polypharmacological strategies, which simultaneously target reward circuits and metabolic regulators, provide superior therapeutic outcomes compared to monotherapies in diet-induced obesity models [244,245]. Furthermore, future investigations should explicitly delineate whether the synergistic efficacy of this combination therapy is mediated by a recalibration of the gut-microbiota-brain axis, particularly regarding the ability of metformin-induced alterations in gut microbial composition to suppress hypothalamic gliosis and reinforce the central insulin-sensitizing effects of naltrexone, a mechanism that could be fundamental to achieving sustainable weight loss in clinical settings. Further research will also be essential to characterize how this combinatorial strategy impacts specific neuronal subsets within the dorsal vagal complex, given that such regions are known to integrate both metabolic and hedonic inputs to regulate long-term energy homeostasis [246].

9. Future Directions and Clinical Implications

9.1 GSK-3β as a Therapeutic Target for Obesity Treatment

Given that hyperactive GSK-3β remains a key driver of insulin resistance and chronic neuroinflammation, further investigation is required to determine whether pharmacological inhibition of this kinase can effectively normalize systemic glucose metabolism in clinical populations [49]. Specifically, longitudinal studies are needed to elucidate whether localized GSK-3β modulation within the hippocampus can prevent the cognitive deficits associated with diet-induced obesity, ultimately fostering better dietary adherence [247]. Furthermore, examining how naltrexone might enhance brown adipose tissue thermogenesis by bypassing high-fat diet-induced blockade of cold-evoked responses could provide an additional metabolic layer to this therapeutic strategy [248]. Additionally, exploring whether this combination therapy influences the abundance of specific gut-microbial populations, such as *Akkermansia*, may reveal how peripheral metabolic shifts contribute to the strengthening of prefrontal inhibitory control over reward-seeking behaviors [33]. Finally, the integration of these findings necessitates a comprehensive analysis of how these therapeutic mechanisms vary across diverse demographic cohorts, as internal factors such as sex and age significantly dictate the susceptibility to neuro-inflammatory responses and the responsiveness of specific neural circuits to pharmacological interventions like GSK-3β inhibition [46,148,249–251].

9.2 Challenges, Research Gaps, and Emerging Opportunities

One critical challenge involves the heterogeneity of dietary triggers in humans compared to the standardized high-fat formulations used in preclinical models, which complicates the translation of metabolic findings [252]. Additionally, the complex interplay between systemic inflammation, gut dysbiosis, and site-specific neuroinflammation suggests that multi-targeted therapies must account for inter-individual variability in metabolic signaling [80]. To address these hurdles, prioritizing the development of non-invasive, accessible biomarkers and digital monitoring tools will be essential to facilitate accurate risk stratification and evaluate the efficacy of personalized treatment regimens in clinical populations [253]. Furthermore, the field must transition from observational models to prospective experimental designs to better distinguish between the effects of chronic overnutrition and the neurobiological adaptations that typically remit but do not resolve with current interventions [91]. Crucially, integrating these longitudinal studies with translational animal models will help isolate whether nutrient-specific effects on brain reward circuits operate independently of obesity-related metabolic markers, thereby clarifying the mechanisms that drive food reinforcement across distinct patient populations [254].

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