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Review Article

Cross-regulation between adipose tissue innervation and metaflammation: a potential therapeutic target for obesity

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Abstract: Obesity, marked by adipose tissue dysfunction and systemic metaflammation, poses a major global health burden. Emerging evidence underscores a critical interplay between neural regulation and immune-metabolic crosstalk in obesity pathogenesis. This review highlights the dynamic roles of sympathetic and sensory nerves in lipid metabolism, as well as metaflammation involving macrophage polarization, inflammatory cytokine cascades, and mitochondrial dysfunction. In obesity, decreased sympathetic nerve density and impaired adrenergic receptor signaling compromise lipolysis and thermogenesis, while sensory neuropeptides worsen metabolic dysregulation through immune cell interactions. Adipose tissue macrophages adopt pro-inflammatory phenotypes, releasing cytokines that inhibit insulin signaling - forming pathological crown-like structures. Mitochondrial dysfunction, characterized by excessive fission and reduced fusion, disrupts energy homeostasis and increases oxidative stress. Therapeutic approaches targeting neuropeptide signaling, inflammasome activation, and mitochondrial dynamics show promise in restoring metabolic balance. The neuro-immune-metabolic axis thus represents a novel therapeutic frontier for obesity, supporting integrated strategies targeting neural, inflammatory, and mitochondrial pathways.

Keywords: Adipose tissue innervation, metaflammation, obesity, neuro-immune crosstalk, mitochondrial dynamics

Introduction

Obesity and its associated metabolic disorders-including type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVDs), and non-alcoholic fatty liver disease (NAFLD) have become a global public health crisis. According to the World Health Organization (WHO), the global prevalence of obesity has nearly tripled since 1975. In 2016, over 1.9 billion adults were classified as overweight, and 650 million met the criteria for obesity (body mass index [BMI] ≥30 kg/m^2). Projections estimate that by 2030, 1 billion individuals will be affected by obesity [1].

Obesity is not merely a result of energy intake and expenditure imbalance but is also closely associated with adipose tissue dysfunction. This condition is characterized by chronic low-grade systemic inflammation and metabolic dysregulation, significantly contributing to increased all-cause mortality and healthcare burdens [2].

Recent research has shown that adipose tissue functions not only as an energy reservoir but also as an active endocrine and immunomodulatory organ. Through the secretion of leptin, adiponectin, and pro-inflammatory cytokines, it directly influences insulin sensitivity, glucose and lipid metabolism, and immune homeostasis [3, 4]. For example, alterations in adipose tissue macrophage (ATM) polarization states can promote localized inflammation [5].

The functional regulation of adipose tissue critically depends on the balance between neural innervation and the immune microenvironment. The sympathetic nervous system (SNS) promotes lipolysis and thermogenesis via norepinephrine-mediated activation of β3-adrenergic receptors (β3-ARs) on adipocytes, while the parasympathetic nervous system (PNS) may

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counteract these effects through cholinergic signaling [6, 7]. In obesity, reduced sympathetic nerve fiber density and dysregulated neurotransmitter release contribute to adipose tissue "neuro-remodeling", further aggravating metabolic dysfunction [8].

Concurrently, immune cells infiltrating adipose tissue and nerve terminals form a bidirectional communication network through cytokines and neuropeptides [9, 10]. Disruption of this cross-regulatory mechanism is now recognized as a central pathological feature of obesity-related metaflammation, although its precise molecular underpinnings and therapeutic potential remain incompletely understood [11].

This review examines the crosstalk between adipose tissue innervation and metaflammation, with a focus on its implications for obesity treatment. We systematically explore the regulation of lipid metabolism by the SNS and PNS, the role of metaflammation-including ATM polarization imbalance, cytokine cascades, and mitochondrial dynamic dysregulation in systemic metabolic disturbances, and the integration of neuro-immune interactions. By elucidating how neurotransmitters and inflammatory mediators co-regulate metabolic homeostasis, this review aims to establish a theoretical foundation for precision therapeutic strategies.

Neural innervation of adipose tissue

Neural distribution in adipose tissue

Adipose tissue innervation exhibits substantial anatomical and functional heterogeneity. Both brown adipose tissue (BAT) and white adipose tissue (WAT) are primarily innervated by sympathetic and sensory nerves. Sympathetic nerves regulate mitochondrial uncoupling protein 1 (UCP1)-mediated thermogenesis and lipolysis via norepinephrine (NE) activation of β3-ARs on adipocytes [12]. In rodents, sympathetic fibers (tyrosine hydroxylase-positive [TH+]) in BAT are primarily associated with vasculature and form neuro-adipose nexuses with multilocular adipocytes [13], whereas WAT contains fewer sympathetic fibers, mainly localized around blood vessels [14]. Viral tracing studies using adeno-associated virus (AAV)-mediated labeling demonstrate that obesity and aging reduce sympathetic nerve density in adipose tissue [15], while aberrant proliferation of sensory nerves may contribute to metabolic dysfunction [16].

The presence of parasympathetic innervation in adipose tissue remains controversial. Histochemical analyses have failed to detect classical parasympathetic markers such as acetylcholinesterase and vesicular acetylcholine transporter (VAChT) in mouse subcutaneous (scWAT) and epididymal WAT [17, 18]. Similarly, retrograde transsynaptic viral tracing of vagal nerves has not identified direct parasympathetic innervation of adipose tissue. However, recent studies have identified cholinergic macrophages (choline acetyltransferase-positive [ChAT+]) within the stromal vascular fraction of mouse scWAT. These cells release acetylcholine, which activates nicotinic receptors in beige adipocytes to promote thermogenesis [19, 20]. These findings suggest that immune cells may partially mimic parasympathetic signaling via paracrine mechanisms, though their physiological relevance remains to be fully elucidated.

Sensory innervation of adipose tissue has been increasingly characterized. Peptidergic sensory nerves derived from dorsal root ganglia (DRG), including calcitonin gene-related peptide-positive (CGRP+) and substance P-positive (SP+) fibers, directly influence adipocyte function via neuropeptide release. For instance, CGRP enhances lipolysis through cAMP-independent pathways [21], while substance P suppresses lipid accumulation and promotes fatty acid efflux [22]. Whole-mount immunofluorescence imaging of mouse scWAT reveals that sensory fibers include myelinated nerves aligned with large vessels and unmyelinated fibers innervating the adipocyte parenchyma [13]. Notably, obesity increases both sensory nerve density and circulating CGRP levels [23], potentially exacerbating local inflammation through activation of neurokinin-1 receptors (NK-1R) on adipose-resident macrophages [24].

Neural regulation of lipid metabolism

Sympathetic signaling exhibits receptor subtype- and tissue-specific regulation of lipid metabolism. In WAT, NE activates the cAMP-PKA signaling cascade via β3-ARs, promoting phosphorylation of key lipolytic enzymes such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase [25]. NE also exhibits

Table 1. Neural regulation of adipose tissue and obesity-related abnormalities

Neural Type	Signaling Molecules/ Receptors	Physiological Functions	Obesity-Related Alterations	References
Sympathetic nerves	β3-AR, NE, FGF21	Promote lipolysis (ATGL/HSL activation), induce thermogenesis (UCP1), regulate mitochondrial biogenesis	Reduced sympathetic nerve density; enhanced α2-AR signaling causing lipolysis resistance; impaired thermogenesis	[6, 8, 12, 15]
Sensory nerves (DRG-derived)	CGRP, SP, NK-1R, PAC-1R	Modulate lipolysis (cAMP-independent pathways), inhibit lipid synthesis (DGAT-1), mediate inflammation (via NK-1R on macrophages)	Abnormal sensory nerve proliferation; elevated CGRP/SP levels exacerbating local inflammation and metabolic dysregulation	[16, 21-24]
Cholinergic immune cells	ACh, VAChT	Mimic parasympathetic functions, activate beige adipocyte thermogenesis via nicotinic receptors	Impaired cholinergic macrophage activity, potentially linked to reduced beige fat activation	[17, 19, 20]

ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase.

dose-dependent effects: low concentrations preferentially activate α2-ARs, suppressing lipolysis, whereas higher concentrations activate β-ARs to promote lipolysis [26]. This biphasic regulation becomes dysregulated in obesity, where enhanced α2-AR signaling contributes to lipolytic resistance [12]. Genetic studies confirm that adipocyte-specific deletion of α2-AR restores lipolysis in high-fat diet-fed mice, while β3-AR knockout abolishes cold-induced thermogenesis [27].

Thermogenic regulation in BAT relies on precise spatiotemporal sympathetic activation. Cold exposure induces synchronized firing of BAT sympathetic nerves via the hypothalamic-spinal axis, rapidly elevating local NE concentrations within minutes. This activates β3-ARs and triggers UCP1-mediated proton leak [28]. Single-cell transcriptomic analyses reveal that sympathetic terminals in BAT form functional units with vascular endothelial cells. NE release increases local blood flow, facilitating substrate delivery for thermogenesis [29]. NE also stimulates BAT adipocytes to secrete fibroblast growth factor 21 (FGF21), which promotes mitochondrial biogenesis in neighboring cells via paracrine signaling [30].

Sensory nerves modulate metabolic homeostasis through neuropeptides. Ablation of DRG-derived CGRP+ sensory fibers leads to hyperactivation of β3-AR signaling in scWAT, accompanied by upregulation of lipolytic and thermogenic (UCP1, Dio2) genes [16]. Mechanistically, CGRP enhances β-AR-cAMP signaling by inhibiting protein phosphatase 2A (PP2A) in adipocytes [31], while substance P suppresses insulin-induced expression of the lipid synthesis enzyme diacylglycerol acyltransferase-1 (DGAT-1) via NK-1R [22]. Interestingly, cold exposure increases BAT sensory nerve activity, which downregulates pituitary adenylate cyclase-activating polypeptide receptor (PAC-1R) to suppress thermogenesis, while upregulating PAC-1R in scWAT to promote browning [30], indicating tissue-specific neuropeptide regulation.

Orexin also modulates BAT sensory nerve function. It acts via orexin receptor type 2 (OX2R) on sensory terminals to suppress TH expression and NE release, forming a negative feedback loop [32]. Orexin-deficient mice exhibit impaired mitochondrial function and reduced UCP1 expression in BAT, while exogenous orexin restores PGC-1α-mediated thermogenesis [33]. This central-peripheral feedback axis offers new therapeutic opportunities. For instance, CGRP monoclonal antibodies improve diabetic metabolic phenotypes by enhancing energy expenditure [31], and the NK-1R antagonist CJ-12,255 mitigates obesity by inhibiting adipogenesis and inflammation [34] (**Table 1**).

The role of metaflammation in obesity

Metaflammation and mitochondrial dysfunction

Origins and central propagation of metaflammation: In obesity, adipose tissue expansion reshapes the immune microenvironment, marked by increased macrophage infiltration and elevated secretion of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), establishing chronic low-grade systemic inflammation [35-37]. This peripheral inflammation influences the central nervous

system (CNS) through multiple mechanisms. First, activation of the nuclear factor kappa B (NF-κB) pathway compromises blood-brain barrier integrity by reducing tight junction protein expression, allowing peripheral cytokines and pathogen-associated molecules to enter the brain parenchyma [38, 39]. Second, saturated fatty acids bind to Toll-like receptor 4 (TLR4), activating NF-κB and activator protein-1 (AP-1) signaling in the hypothalamus and microglia, thereby amplifying neuroinflammation [40, 41]. Clinical studies have reported increased levels of pro-inflammatory cytokines in the hippocampus and prefrontal cortex of obese individuals, which are significantly correlated with cognitive decline [42, 43].

Mitochondrial dynamics imbalance and energy metabolism dysregulation: Mitochondria, as central regulators of energy metabolism, exhibit impaired dynamics and function in obesity-related neurodegeneration. High-fat diets (HFD) suppress the expression of mitochondrial fusion proteins, mitofusin 1 (Mfn1), mitofusin 2 (Mfn2), and optic atrophy 1 (Opa1), while promoting cytoplasmic translocation of the fission protein dynamin-related protein 1 (Drp1) to the mitochondrial outer membrane, leading to excessive mitochondrial fragmentation [44-46]. This imbalance reduces respiratory efficiency, evidenced by decreased activity of complexes I and IV, reduced adenosine triphosphate (ATP) production, and elevated reactive oxygen species (ROS) levels [47-49]. In animal models, 12 weeks of HFD feeding results in decreased mitochondrial membrane potential (ΔΨm), mitochondrial swelling, and impaired calcium (Ca^{2+}) retention in the hippocampus, directly impairing synaptic plasticity [50, 51]. Additionally, Mfn2 deficiency in hypothalamic pro-opiomelanocortin (POMC) neurons disrupts endoplasmic reticulum (ER)-mitochondria contacts, triggering ER stress and leptin resistance, which further exacerbates metabolic dysregulation [52, 53].

Oxidative stress and the vicious cycle of inflammatory signaling: Mitochondrial dysfunction and metaflammation are interconnected through a bidirectional regulatory loop. On one hand, excessive ROS activates the NLR family pyrin domain-containing 3 (NLRP3) inflammasome, promoting IL-1β maturation and release, which in turn activates microglia and propagates neuroinflammation [49, 54]. On the other hand, TNF-α impairs insulin signaling by downregulating key mitochondrial biogenesis regulators-peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) and sirtuin 1 (SIRT1) thereby inhibiting respiratory complex synthesis [55]. In diabetic animal models, hippocampal mitochondria show increased basal oxygen consumption but reduced ATP production efficiency, indicating oxidative phosphorylation uncoupling [56]. In obese animals, hypothalamic mitochondria exhibit aberrant glucose sensing, with glutathione redox imbalance and ROS accumulation, which may impair systemic insulin sensitivity via dysregulated vagal signaling [57].

Recent findings reveal that NLRP3 activation not only intensifies IL-1β-driven neuroinflammation but also disrupts sympathetic-adipose communication. Guo et al. reported that ROS-induced NLRP3 activation in hypothalamic microglia downregulates β3-AR expression through NF-κB-dependent transcriptional repression, impairing lipolysis and thermogenesis in adipose tissue [54]. Furthermore, mitochondrial ROS accumulation in ATMs in obese individual reduces TH activity in sympathetic terminals, reducing norepinephrine release [57]. These findings highlight a feedforward loop in which metaflammation-induced oxidative stress undermines neural regulation of metabolism and promotes adipose tissue dysfunction.

Targeted intervention strategies and therapeutic potential: Preclinical studies suggest promising interventions targeting the metaflammation-mitochondrial dysfunction axis. Antioxidant therapies, such as N-acetylcysteine (NAC), reduce hippocampal ROS levels and suppress TLR4/NF-κB signaling by restoring glutathione precursors, thereby mitigating HFD-induced synaptic damage and memory impairment [58-60]. Exercise interventions, such as 12-week voluntary running, enhance mitochondrial respiratory capacity and calcium retention in the hippocampus of obese mice while reducing mitochondrial permeability transition pore (mPTP) sensitivity, thus inhibiting neuronal apoptosis [61]. Modulation of mitochondrial dynamics-through Drp1 inhibition or Mfn2 overexpression-improves insulin sensitivity in hypothalamic neurons; for example, ceramide

reduction reverses mitochondrial fragmentation and restores leptin signaling [62]. Additionally, sirtuin 3 (SIRT3) agonists alleviate obesity-related cerebral metabolic deficits by enhancing fatty acid oxidation and tricarboxylic acid cycle enzyme activity via mitochondrial protein deacetylation [63]. Together, these strategies offer a multifaceted approach to treating obesity-associated metabolic and cognitive impairments by targeting the metaflammation-mitochondria axis.

Recruitment, polarization, and neuro-immune crosstalk of adipose tissue macrophages

Mechanisms of macrophage recruitment in obesity: ATMs originate from both circulating monocytes and tissue-resident macrophages. In obesity, adipocyte hypertrophy induces local hypoxia and lipotoxicity, which stimulate the release of chemokines such as C-C motif chemokine ligand 2 (CCL2) and C-X-C motif chemokine 12 (CXCL12), promoting monocyte infiltration into adipose tissue [64, 65]. The CCL2/CCR2 axis plays a central role in ATM recruitment, with elevated CCL2 expression observed in adipose tissue of obese humans and mice. Genetic deletion of CCL2 or its receptor CCR2 reduces macrophage infiltration and improves metabolic outcomes [66, 67]. The CXCL12/CXCR4 axis similarly regulates monocyte migration, while additional chemokines (e.g., CCL5, CCL7) and complement components (e.g., C3a) further contribute to ATM accumulation [68-70]. Notably, local macrophage proliferation, particularly around crown-like structures (CLSs), exacerbates ATM density in obesity [71-73].

Beyond driving inflammation, these recruitment mechanisms may influence sympathetic nerve function via neuro-immune interactions. Inflammatory cytokines can modulate neurotransmitter release, such as norepinephrine, from local nerve terminals, establishing a positive feedback loop that sustains metaflammation [74, 75].

Macrophage polarization phenotypes and metaflammation: Obese adipose tissue favors ATM polarization toward the pro-inflammatory M1 phenotype. M1 macrophages express CD11c and secrete cytokines including TNF-α, IL-6, and IL-1β, which inhibit insulin signaling in adipocytes [76-78]. These cells often cluster around necrotic adipocytes, forming CLSs, and their abundance correlates with the severity of inflammation [79, 80]. In contrast, lean individuals predominantly harbor anti-inflammatory M2 macrophages ($CD206^+$), which support metabolic homeostasis through apoptotic cell clearance and induction of adipocyte browning [81, 82].

Single-cell transcriptomic analyses reveal ATM heterogeneity, identifying subsets such as metabolically activated macrophages (MMe) and lipid-associated macrophages (LAM). MMe aggravate early-stage inflammation but later aid in insulin sensitivity via lysosomal lipid clearance [83, 84]. LAMs rely on triggering receptor expressed on myeloid cells 2 (TREM2) signaling; TREM2 deficiency worsens metabolic dysfunction [85]. Cold exposure or β3-AR activation induces M2 polarization and prompts macrophage secretion of Slit3 and peroxisome proliferator-activated receptor gamma (PPARγ) ligands, which activate sympathetic-adipocyte signaling and enhance thermogenesis [86, 87]. These findings highlight the integration of neural and metabolic signals in macrophage polarization.

Neuro-Immune crosstalk in macrophage function regulation: The interplay between neural and immune elements in adipose tissue is a growing research focus. Electron microscopy reveals sympathetic nerve terminals (H^+) located within 1 μm of ATMs in mouse subcutaneous white adipose tissue (scWAT), with local norepinephrine (NE) levels sufficient to modulate ATM function via β2-ARs [88]. Sensory nerve-derived neuropeptides, such as CGRP and substance P, can directly stimulate $CD8^+$ T cell proliferation and cytokine release [89]. Optogenetic stimulation of scWAT sympathetic nerves transiently suppresses ATM nuclear factor kappa B (NF-κB) activity, while sensory nerve ablation upregulates pro-inflammatory cytokines such as TNF-α, emphasizing the regulatory potential of neural input on local immune responses [90].

Sympathetic NE release activates β3-AR signaling to induce adipose browning, a process that requires macrophage involvement. β3-AR agonists stimulate M2 macrophages to secrete osteopontin and 9-/13-hydroxyoctadecadienoic acids (9-/13-HODE), promoting recruitment of beige adipocyte precursors and enhancing

Table 2. Core molecules and pathological mechanisms of obesity-associated metaflammation

Category	Key Molecules/ Pathways	Functions/ Mechanisms	Association with Obesity	Intervention Outcomes	References
Macrophage polarization	M1 ($CD11c^+$, TNF-α, IL-1β)	Secrete pro-inflammatory cytokines, suppress insulin signaling, form crown-like structures	M1 dominance in obesity drives adipose inflammation and insulin resistance	NLRP3 inhibitors (e.g., MCC950) reduce IL-1β release and M1 polarization; IL-1β antagonists improve insulin sensitivity	[5, 35-37, 54, 76-78]
	M2 ($CD206^+$, IL-4/IL-13)	Clear apoptotic cells, promote browning (Slit3, PPARγ ligands)	Reduced M2 polarization; cold exposure or β3-AR agonists restore M2 activity	β3-AR agonists or cold exposure restore M2 activity and thermogenesis	[81-83, 86, 87]
Mitochondrial dynamics	Drp1, Mfn1/2, Opa1	Drp1 mediates fission; Mfn1/2 and Opa1 regulate fusion	Drp1 hyperactivation and Mfn1/2 suppression cause mitochondrial fragmentation, ROS accumulation, and energy deficits	Drp1 inhibitors (e.g., Mdivi-1) restore fusion-fission balance; SIRT3 agonists enhance mitochondrial respiration	[44-47, 52, 62, 63]
Neuro-immune crosstalk	β2-AR (macrophages), CGRP (T cells)	NE suppresses macrophage NF-κB via β2-AR; CGRP enhances T cell proliferation	Reduced sympathetic activity weakens immune regulation; CGRP dysregulation amplifies metabolic inflammation	CGRP monoclonal antibodies reduce sensory nerve-driven inflammation; TNF-α blockade restores sympathetic tone	[24, 88-90, 92]

PPARγ, peroxisome proliferator-activated receptor gamma; CGRP, calcitonin gene-related peptide; β3-Ars, β3-adrenergic receptors; ROS, reactive oxygen species.

thermogenesis [87, 91]. Cold exposure induces eosinophil-derived IL-4 and IL-13, which drive M2 polarization and facilitate browning [86]. Conversely, obesity-associated chronic inflammation may impair sympathetic activity via TNF-α signaling, creating an "inflammation-induced neural suppression" cycle [92]. Recent studies have identified macrophage-derived molecules such as Slit3 that modulate sympathetic tone and influence systemic metabolism [93]. Additionally, deletion of circadian clock genes (e.g., Period 1/2 [PER1/PER2]) in macrophages disrupts PPARγ expression, worsening adipose inflammation and insulin resistance [94]. These findings suggest that targeting neuro-immune regulatory nodes, such as β3-AR or PPARγ signaling, could offer promising therapeutic avenues (**Table 2**).

In summary, ATM recruitment and polarization are central to obesity-associated metaflammation, with their function tightly regulated by neural signaling. Elucidating the mechanisms underlying neuro-immune crosstalk may inform the development of macrophage-targeted therapies for obesity.

Therapeutic targeting of neural, metaflammatory, and neuro-immune axes

Emerging therapeutic strategies for obesity increasingly focus on modulating lipid metabolism, metaflammation, and neuro-immune crosstalk through either single or combination approaches. Pharmacological activation of sympathetic signaling using β3-AR agonists, such as Mirabegron, promotes lipolysis and thermogenesis by enhancing cAMP-PKA signaling and upregulating UCP1 expression [12, 87]. In contrast, inhibiting sensory nerve hyperactivity via CGRP antagonism or sensory denervation reduces lipolysis resistance and neuropeptide induced inflammation [16, 31].

Targeting metaflammation includes approaches such as inhibition of the NLRP3 inflammasome using agents like MCC950, which suppress interleukin-1β (IL-1β) release and limit mitochondrial ROS accumulation, thereby mitigating adipose inflammation [54, 58]. Promoting anti-inflammatory M2 macrophage polarization, either through β3-AR stimulation or cold exposure, enhances IL-4/IL-13 secretion and facilitates beige adipocyte recruitment [86, 87].

Neuro-immune crosstalk represents another promising therapeutic node. Blocking TNF-α or CGRP signaling interrupts pathological feedback between macrophages and neurons, restoring sympathetic tone and improving insulin sensitivity [24, 92]. For instance, TNF-α inhibition reverses sympathetic dysfunction, while CGRP neutralizing antibodies attenuate sensory neuropeptide driven immune activation [24, 31].

Combination therapies have demonstrated enhanced efficacy by simultaneously targeting multiple mechanistic pathways. Co-administration of β3-AR agonists with NLRP3 inhibitors synergistically restores sympathetic activity and suppresses inflammasome-mediated metaflammation [12, 54]. Likewise, combining

Table 3. Advantages and disadvantages of therapeutic strategies targeting the neuro-immune-metabolic axis

Target Category	Advantages	Disadvantages	References
Neural Signaling	Restores lipolysis/thermogenesis; Enhances UCP1	Risk of sympathetic overactivation; Sensory nerve hypersensitivity	[12, 16, 31, 87]
Inflammatory Pathways	Reduces metaflammation; Improves insulin sensitivity	Systemic immunosuppression; Cytokine rebound	[54, 58]
Mitochondrial Regulators	Improves energy metabolism; Reduces ROS	Disrupts mitochondrial adaptability; Limited tissue specificity	[44, 62, 63]
Combination Therapy	Synergistic efficacy; Multi-pathway targeting	Increased side effects; Pharmacokinetic challenges	[12, 54, 58]

Drp1 inhibitors (e.g., Mdivi-1) with SIRT3 agonists reduces mitochondrial fission and oxidative stress while enhancing fatty acid oxidation, thereby improving overall energy metabolism [44, 62, 63]. Concurrent inhibition of CGRP and IL-1β signaling also disrupts neuro-immune-metabolic amplification loops, underscoring the potential of multi-targeted therapeutic regimens [31, 54].

These strategies highlight the importance of addressing the multifactorial nature of obesity through integrated interventions. Future research should prioritize validating combination therapies in preclinical models that reflect metabolic heterogeneity, with a particular focus on neural plasticity, macrophage-nerve interactions, and mitochondrial dynamics as key mechanistic targets. **Table 3** summarizes the advantages and limitations of therapeutic strategies targeting the neuro-immune-metabolic axis. While monotherapies have shown promise in experimental models, combination strategies may offer broader benefits but require careful optimization to minimize potential risks.

Summary and perspectives

The pathogenesis of obesity is driven by complex interactions between adipose tissue innervation and metaflammation. Sympathetic nerves regulate lipolysis and thermogenesis via β3-ARs; however, obesity leads to reduced sympathetic nerve density and aberrant α2-AR signaling, contributing to lipolysis resistance. Although parasympathetic nerves do not directly innervate adipose tissue, cholinergic macrophages can modulate beige adipocyte function through paracrine acetylcholine signaling. Sensory nerves dynamically regulate lipid metabolism and inflammation via neuropeptides such as CGRP and substance P, whose dysregulated activation promotes metabolic dysfunction.

An imbalance in ATM polarization fosters local inflammation, with pro-inflammatory cytokines such as TNF-α and IL-1β impairing insulin signaling and exacerbating systemic metabolic dysregulation. Mitochondrial dynamics are disrupted, with downregulation of fusion proteins (Mfn1, Mfn2) and hyperactivation of the fission protein Drp1, leading to increased ROS, impaired ATP production, and uncoupling of oxidative phosphorylation. This creates a vicious cycle of inflammation and mitochondrial dysfunction. Within the central nervous system, mitochondrial impairment in the hypothalamus and hippocampus has been linked to cognitive decline. Meanwhile, the neuro-immune axis modulates macrophage polarization through norepinephrine and cytokines, further influencing systemic metabolic homeostasis (**Table 4**; **Figure 1**).

Metaflammation and neuro-immune crosstalk form a central axis in obesity development. Pro-inflammatory cytokines such as TNF-α and IL-1β suppress sympathetic signaling by downregulating β3-AR expression and TH activity [54, 92], while sensory neuropeptides like CGRP recruit immune cells and sustain adipose inflammation [24]. In turn, reduced sympathetic tone aggravates mitochondrial dysfunction and ROS accumulation, activating the NLRP3 inflammasome and downstream cytokine cascades [54]. This bidirectional feedback loop perpetuates metabolic dysfunction through reciprocal neural remodeling and immune dysregulation. Therapeutic strategies that target both pathways, such as β3-AR agonists to restore sympathetic tone and inflammasome inhibitors to attenuate metaflammation hold potential for disrupting this cycle [12, 87].

The relationship between obesity and neurological dysfunction is both reciprocal and interdependent. Adipose tissue expansion in obesi-

Table 4. Potential therapeutic strategies targeting the neuro-immune-metabolic axis

Target Category	Intervention	Mechanism of Action	Experimental Evidence	References
Neural signaling	β3-AR agonists (e.g., Mirabegron)	Activate sympathetic signaling to enhance lipolysis and thermogenesis	Restores cold-induced thermogenesis and reduces adiposity in rodent models	[12, 27, 87]
	CGRP monoclonal antibodies	Block CGRP-induced metabolic disturbances and inflammation	Improves glucose homeostasis and energy expenditure in diabetic mice	[31, 89]
Inflammatory pathways	NLRP3 inhibitors (e.g., MCC950)	Suppress inflammasome activation and IL-1β release	Reduces adipose inflammation and systemic insulin resistance	[54, 58, 59]
Mitochondrial regulators	Drp1 inhibitors (e.g., Mdivi-1)	Inhibit excessive mitochondrial fission, restore fusion-fission balance	Improves mitochondrial membrane potential and reduces neuronal oxidative damage	[44, 62]
	SIRT3 agonists	Enhance mitochondrial deacetylation to boost fatty acid oxidation and TCA cycle activity	Alleviates metabolic syndrome-associated energy deficits	[63]
Combination therapy	β3-AR agonist + IL-1β antagonist	Synergistically improve neural signaling and dampen inflammation	Preclinical studies show superior efficacy compared to monotherapy	[58, 87]

CGRP, calcitonin gene-related peptide; NLRP3, NLR family pyrin domain-containing 3; β3-Ars, β3-adrenergic receptors; SIRT3, sirtuin 3; TCA, tricarboxylic acid.

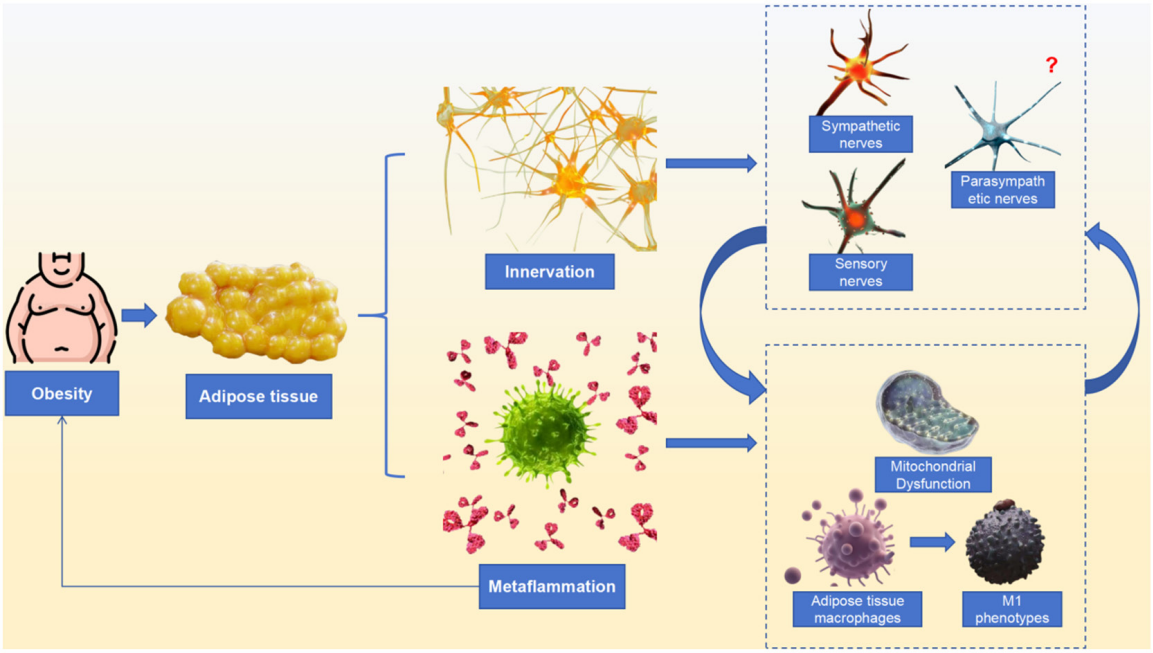

Figure 1. Obesity alters adipose tissue homeostasis through dual mechanisms involving innervation and metaflammation. Obesity-induced adipose tissue expansion leads to altered neural regulation (innervation), involving sympathetic, sensory, and possibly parasympathetic nerves (indicated by the question mark), and triggers metaflammation characterized by immune cell activation. This includes mitochondrial dysfunction in adipose tissue macrophages and polarization toward pro-inflammatory M1 phenotypes. These changes contribute to a feedback loop that exacerbates adipose tissue dysfunction and impairs neural regulation.

ty triggers sympathetic nerve degeneration and aberrant sensory nerve sprouting, impairing lipolysis and thermogenesis while promoting neuropeptide-mediated inflammation [8, 16]. In turn, diminished β3-AR signaling and α2-AR hyperactivity in adipocytes further exacerbate metabolic disturbances [12, 27]. Neuro-immune crosstalk intensifies this interplay: macrophages polarized by inflammatory cytokines inhibit sympathetic activity via TNF-α, while CGRP recruits immune cells to sustain metaflammation [24, 88]. Collectively, these

mechanisms support a model in which neural remodeling and adipose dysfunction mutually reinforce obesity progression. Targeting neuro-immune-metabolic interfaces may offer a strategy to restore bidirectional homeostasis.

Despite promising advances, current therapies targeting the neuro-immune-metabolic axis face significant limitations. Neural interventions may risk sympathetic overstimulation or sensory hypersensitivity; anti-inflammatory therapies may lead to systemic immunosuppression or cytokine rebound. Mitochondrial-targeted agents struggle with tissue specificity and adaptability. Combination therapies, while synergistic, are complicated by pharmacokinetic challenges and the potential for increased side effects. Furthermore, much of the current evidence is derived from preclinical models, revealing a translational gap in addressing human obesity heterogeneity.

Future directions include elucidating the molecular interplay between neurotransmitters and cytokines, developing nanotechnology-based delivery systems to improve tissue targeting, and designing combination regimens, such as β3-AR agonists paired with inflammasome inhibitors to modulate neuro-immune nodes. Clinical translation will require personalized therapeutic approaches that account for individual variation in obesity phenotypes, potentially advancing precision medicine strategies for metabolic disorders.

Disclosure of conflict of interest

None.

Abbreviations

AAV, adeno-associated virus; AP-1, activator protein-1; AR, adrenergic receptor; ATGL, adipose triglyceride lipase; ATM, adipose tissue macrophage; ATP, adenosine triphosphate; BAT, brown adipose tissue; BBB, blood-brain barrier; BMI, body mass index; CGRP, calcitonin gene-related peptide; ChAT, choline acetyltransferase; CLS, crown-like structures; CNS, central nervous system; CVD, cardiovascular disease; CXCL12, C-X-C motif chemokine 12; CXCR4, C-X-C chemokine receptor type 4; DGAT-1, diacylglycerol acyltransferase-1; Dio2, iodothyronine deiodinase 2; DRG, dorsal root ganglion; Drp1, dynamin-related protein 1; ER, endoplasmic reticulum; FGF21, fibroblast growth factor 21; HFD, high-fat diet; HSL, hormone-sensitive lipase; IL, interleukin; LAM, lipid-associated macrophages; Mfn1, mitofusin 1; Mfn2, mitofusin 2; MMe, metabolically activated macrophages; mPTP, mitochondrial permeability transition pore; NAFLD, non-alcoholic fatty liver disease; NE, norepinephrine; NF-κB, nuclear factor kappa B; NK-1R, neurokinin-1 receptor; NLRP3, NLR family pyrin domain-containing 3; NAC, N-acetylcysteine; Opa1, optic atrophy 1; OX2R, orexin receptor type 2; PAC-1R, pituitary adenylate cyclase-activating polypeptide receptor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PNS, parasympathetic nervous system; PP2A, protein phosphatase 2A; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; scWAT, subcutaneous white adipose tissue; SIRT1, sirtuin 1; SIRT3, sirtuin 3; SNS, sympathetic nervous system; SP, substance P; SVF, stromal vascular fraction; T2DM, type 2 diabetes mellitus; TCA, tricarboxylic acid; TH, tyrosine hydroxylase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; TREM2, triggering receptor expressed on myeloid cells 2; UCP1, uncoupling protein 1; VAChT, vesicular acetylcholine transporter; WAT, white adipose tissue.

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