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Review

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Neuro–immune Interactions in Metabolic Regulation: Brain and Adipose Tissue Crosstalk

Chan Hee Lee*

Department of Biomedical Science, Hallym University, Chuncheon, Korea

The global obesity epidemic underscores the urgent need to elucidate the mechanisms underlying metabolic disorders. Although excessive caloric intake and sedentary lifestyles have traditionally been viewed as primary contributors, recent evidence highlights significant roles for genetic, environmental, and immunological factors. Notably, dysfunction within the central nervous system (CNS), particularly the hypothalamus, has emerged as a crucial regulator of metabolic homeostasis through CNS–peripheral interactions. Hypothalamic inflammation is primarily mediated by microgliosis, which disrupts systemic homeostasis. This review discusses the detrimental effects of hypothalamic microgliosis on energy metabolism and highlights emerging evidence suggesting paradoxically beneficial roles of hypothalamic microgliosis in metabolic regulation. Within adipose tissue, immune cells, including adipose tissue macrophages (ATMs), T cells, and B cells, exert significant influence over systemic metabolism. Short-term activation of the sympathetic nervous system (SNS) promotes the anti-inflammatory polarization of ATMs and enhances the induction of regulatory T cells; thereby, improving insulin sensitivity. In contrast, chronic SNS activation may exacerbate inflammation due to β-adrenergic receptor desensitization and catecholamine resistance. Parasympathetic acetylcholine signaling is also known to suppress inflammation through activation of α7 nicotinic receptors on macrophages; however, parasympathetic innervation within white adipose tissue is considerably limited. Despite the critical role of the nervous system in systemic metabolism, comprehensive insight into neuro-immune interactions remains lacking. In-depth studies using advanced technologies are needed to deepen knowledge in this field and to cover novel therapeutic targets for obesity and related metabolic disorders.

Key words: Hypothalamus, Adipose tissue, Metabolic diseases, Autonomic nervous system, Hypothalamo-hypophyseal system

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*Corresponding author
Chan Hee Lee

https://orcid.org/0000-0001-8791-817X

Department of Biomedical Science, Hallym University, 1 Hallimdaehak-gil, Chuncheon 24252, Korea
Tel: +82-33-248-2117
E-mail: chl22@hallym.ac.kr

INTRODUCTION

According to the World Health Organization, more than 890 million adults are obese, and over 40% of the global population is estimated to be overweight. The global epidemic of obesity has led to a surge in severe, life-threatening conditions such as type 2 diabetes mellitus (T2DM), cardiovascular diseases, neurodegenerative diseases, and cancer.[1] Recently, growing interest has emerged in 'Medicine 3.0,' a proactive, preventive, and personalized approach aimed at managing disease risk before the onset of major illnesses by controlling metabolic disorders. Traditionally, metabolic disorders have been attributed primarily to excessive caloric intake and sedentary lifestyles; however, emerging evidence suggests that synergistic mediators such as genetic, environmental, and immunological factors contribute to the development of obesity.[2] Among these factors, increasing evidence indicates that dysfunctions within the central nervous system (CNS) can lead to the development of various metabolic disorders.[3] Consequently, a paradigm shift has emerged that highlights the critical role of CNS–periphery communication in the pathogenesis of metabolic diseases.

Both genetic and environmental dysfunctions within the CNS contribute to the pathogenesis of obesity and metabolic disorders. Genetic syndromes such as Prader-Willi syndrome and monogenic mutations in key hypothalamic signaling pathways, including melanocortin 4 receptor (MC4R), leptin, and leptin receptor (LEPR), result in impaired satiety regulation and uncontrolled hyperphagia, leading to early-onset obesity.[4-6] Environmental insults such as hypothalamic injury from surgery, tumors, or trauma disrupt critical neural circuits involved in appetite control, contributing to 'hypothalamic syndrome.'[7] Furthermore, chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis due to persistent psychosocial stress elevates glucocorticoid levels, promoting visceral fat accumulation and insulin resistance.[8] These clinical and mechanistic insights collectively underscore the importance of CNS integrity in maintaining metabolic homeostasis. This review aimed to provide an integrated perspective on the neuroendocrine regulation involving the CNS and peripheral metabolic tissues.

HYPOTHALAMIC STRUCTURAL SPECIALIZATIONS IN SENSING PERIPHERAL SIGNALS

Among various regions of the CNS, the hypothalamus is considered a key therapeutic target for combating obesity and metabolic disorders.[9,10] This functional importance largely stems from its unique structural features, enabling the sensing and integration of peripheral signals and the coordination of neuroendocrine outputs.[11] Notably, the median eminence (ME), one of the circumventricular organs within the hypothalamus, contains fenestrated capillaries rather than a typical blood-brain barrier.[12] This specialized vascular structure permits real-time detection of circulating metabolic or inflammatory signals and enables the secretion of hypothalamic hormones into the pituitary gland via the hypophyseal portal system.[13]

The vascular permeability of ME can be modulated by metabolic challenges. For instance, fasting for 24 hours elevates vascular endothelial growth factor-A (VEGFA) expression in tanycytes within the ME, leading to an increased number of fenestrated vessels.[14] This structural change enhances the access of circulating ghrelin into the hypothalamus; thereby, promoting appetite.[14] Chronic exposure to a high-fat diet (HFD) also increases vascular permeability and the number of fenestrated vessels in the ME, facilitating elevated entry of circulating free fatty acids.[15] This alteration induces proliferation of perivascular macrophages and disrupts neuronal circuitry.[16,17] These structural adaptations collectively establish the hypothalamus as a dynamic interface between the CNS and peripheral metabolic states.

Within the hypothalamus, distinct neuronal populations in the arcuate nucleus (ARH) play central roles in regulating systemic energy homeostasis. Pro-opiomelanocortin (POMC) neurons exert anorexigenic effects via the release of α-melanocyte-stimulating hormone (α-MSH).[18] α-MSH activates MC4R in the paraventricular hypothalamus (PVH) to suppress appetite and enhance energy expenditure.[18] POMC neurons also project to the dorsomedial hypothalamus and lateral hypothalamus, contributing to sympathetic outflow and thermogenic regulation.[18] In contrast, agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons antagonize MC4R signaling and inhibit PVH activity; thereby, promoting orexigenic responses and reducing energy expenditure.[19] These neurons also send direct gamma-aminobutyric acid (GABA)-ergic projections to POMC neurons.[19] The activity of these hypothalamic neurons is primarily regulated by circulating signals that enter the brain through the ME.

HYPOTHALAMIC INFLAMMATION AND METABOLIC DISORDERS

Under HFD conditions or during chronic inflammation, circulating signals, including metabolic and inflammatory mediators such as saturated fatty acids (e.g., palmitate) and proinflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF-α] and interleukin-6 [IL-6]), enter the hypothalamus and accumulate in the ARH.[14,15] Notably, this influx occurs within hours to days following HFD exposure (before the onset of obesity) and results in the activation of resident glial cells, including microglia and astrocytes (Fig. 1).[14,15,20] Microglia adopt a proinflammatory phenotype characterized by the release of cytokines such as IL-1β, IL-6, and TNF-α, which initiate and sustain hypothalamic inflammation.[9] Astrocytes respond to hypothalamic inflammation with histological changes such as somatic hypertrophy and increased expression of glial fibrillary acidic protein (GFAP).[9] Moreover, astrocytes contribute to neuro-

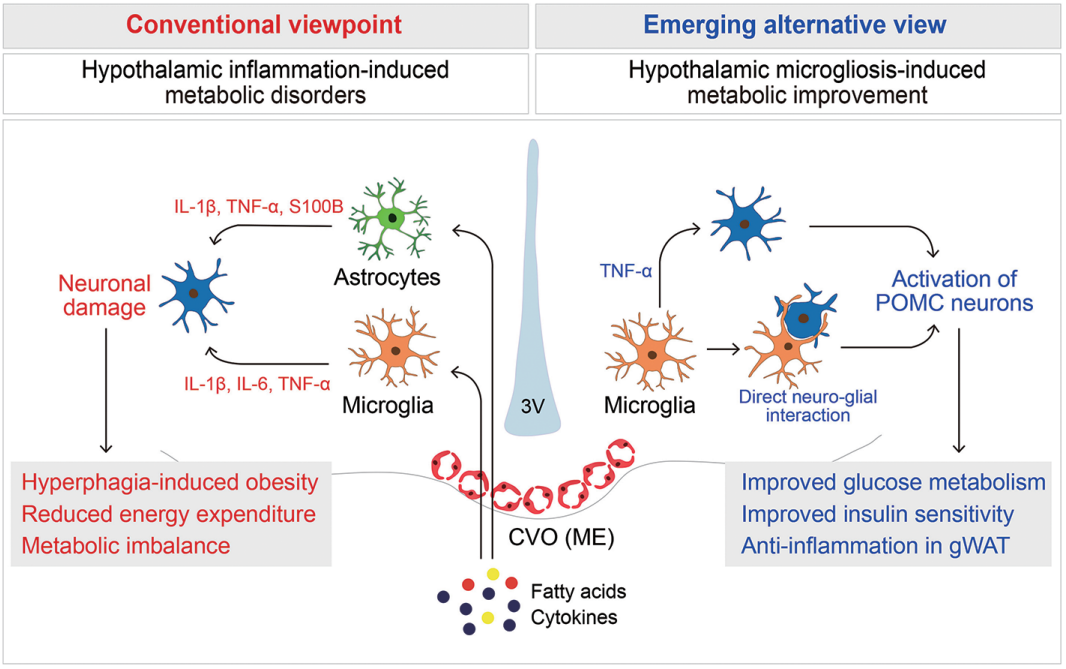

Figure 1. Conventional and emerging views on hypothalamic inflammation. Traditional perspectives link hypothalamic inflammation to metabolic disorders (left panel), whereas recent findings suggest hypothalamic microgliosis can improve metabolic function via pro-opiomelanocortin (POMC) neuron activation (right panel). IL, interleukin; TNF-α, tumor necrosis factor-alpha; S100B, calcium-binding protein B; 3V, third ventricle; CVO, circumventricular organ; ME, median eminence; gWAT, gonadal white adipose tissue.

inflammation by disrupting synaptic coverage, impairing metabolic support to neurons, and releasing proinflammatory mediators, including IL-1β, TNF-α, and calcium-binding protein B (S100B).[21] As a consequence of this glial cell-mediated inflammation, hypothalamic neurons such as POMC and AgRP neurons exhibit impaired leptin and insulin signaling, partially mediated by the upregulation of suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B).[22-24] These neurons may display reduced synaptic plasticity and altered electrophysiological properties, underscoring the essential role of hypothalamic neuronal integrity in maintaining systemic energy balance and metabolic homeostasis.

HYPOTHALAMIC MICROGLIOSIS AND METABOLIC IMPROVEMENT

Paradoxically, recent findings have revealed that hypothalamic microglial activation can exert unexpectedly beneficial effects on systemic energy metabolism (Fig. 1).[25] Specifically, the absence of microglial nuclear factor-kappa B (NF-κB) signaling under HFD conditions leads to impaired glucose and insulin metabolism, highlighting the beneficial role of microglial inflammatory pathways in maintaining metabolic homeostasis.[25] In contrast, chemogenetic activation of microglia significantly improves both glucose tolerance and insulin sensitivity. These metabolic improvements are mediated through microglial TNF-α signaling and POMC neuron-driven parasympathetic output.[25]

Consistent with this, we recently demonstrated that hypothalamic microgliosis induced by IL-2 reverses HFD-induced insulin resistance through hypothalamic-adipose interaction.[26] In the study, central administration of IL-2 suppressed food intake and enhanced systemic insulin sensitivity. Hypothalamic microglia express IL-2 receptor subunits, including IL-2Rα, IL-2Rβ, and IL-2Rγ, and are activated by central IL-2 administration. Once activated, the microglia may stimulate adjacent POMC neurons, leading to enhanced sympathetic activity innervating gonadal white adipose tissue (gWAT).[26] This signaling cascade promotes the differentiation of regulatory T cells (Tregs) and establishes an anti-inflammatory milieu within the gWAT.[26] Notably, these immunometabolic effects occur independently of IL-2's anorexigenic properties. However,

these findings still have several limitations. First, the precise role of the three IL-2R chains expressed in microglia in regulating microglial polarization remains unknown. Second, the current study represents pharmacological rather than physiological conditions, given that endogenous IL-2 levels are significantly lower compared to those in peripheral tissues.[27] Therefore, further in-depth investigations on microglial differentiation and activation are required, considering potential differences according to disease type and duration of inflammation.

IMMUNE CELL-MEDIATED REGULATION OF METABOLIC HOMEOSTASIS IN ADIPOSE TISSUES

The inflammatory balance within adipose tissue plays a pivotal role in regulating systemic energy homeostasis.[28] Under HFD conditions, chronic inflammation contributes to the development of metabolic disorders such as hyperlipidemia, atherosclerosis, and T2DM.[28] Both resident and infiltrating immune cells, including adipose tissue macrophages (ATMs), T cells, and B cells, tightly regulate this process.[28,29] The balance between pro-inflammatory and anti-inflammatory immune cell subsets within adipose depots ultimately determines the extent of energy metabolism.

Adipose tissue macrophages

ATMs constitute approximately 5% to 10% of stromal vascular cells in lean adipose tissue, with this proportion increasing up to 40%–50% in obesity.[30,31] These macrophages express F4/80 and CD11b and are broadly classified into two main phenotypes: CD11c and inducible nitric oxide synthase (Nos2)-expressing classically activated macrophages (M1 ATMs) and arginase1 (Arg1) and mannose receptor C-type 1 (Mrc1, CD206)-expressing alternatively activated macrophages (M2 ATMs).[32] In lean adipose tissue, M2-like ATMs are predominant and contribute to tissue homeostasis by limiting adipocyte inflammation and supporting tissue remodeling.[33] In contrast, obesity induces a phenotypic shift toward pro-inflammatory M1-like ATMs.[33] These M1 ATMs secrete pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and monocyte chemoattractant protein-1 (MCP-1, also known as CCL2); thereby, promoting local and systemic insulin resistance by activating serine kinases such as c-Jun N-terminal kinases (JNK) and IκB kinase β (IKKβ).[34]

Previously, clodronate has been employed to suppress the expansion of ATMs under HFD conditions. Clodronate liposomes are widely utilized to selectively deplete macrophages via macrophage-mediated uptake.[35] In a study by Bu et al.[36], long-term administration of clodronate liposomes improved obesity and metabolic parameters in HFD-fed C57BL/6J mice. This treatment reduced the presence of crown-like structures in adipose tissue and significantly suppressed the expression of pro-inflammatory cytokines such as TNF-α and MCP-1.[36] However, contrasting results were reported by Bader et al.[37], where clodronate treatment failed to ameliorate HFD-induced metabolic disorders or obesity and instead induced neutrophilia. These discrepancies may reflect differences in the timing of macrophage depletion. Beneficial effects were observed when long-term depletion was initiated early in the course of HFD feeding, whereas clodronate administration after the establishment of obesity and adipose tissue inflammation failed to improve metabolic outcomes. Another study showed that clodronate liposomes had no beneficial metabolic effects under short-term HFD conditions.[38] These findings highlight the need for further investigation into the specific roles of ATMs in adipose tissue metabolism.

T cells

T cells are essential components of the adaptive immune system and are broadly classified into $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells.[39] They are also found in adipose tissue, where they respond to changes in the metabolic environment. Obesity drives a shift in T cell differentiation toward pro-inflammatory subsets such as T helper 1 (Th1) and $CD8^+$ T cells, along with a concomitant reduction in anti-inflammatory subsets such as Tregs.[40] T cell differentiation is influenced by neighboring immune cells, cytokines, and hormones. Leptin, an adipocyte-derived hormone elevated in obesity, promotes the differentiation of naïve T cells into Th1 cells and inhibits their differentiation into Treg cells.[41,42] This mechanism is closely associated with both hyperleptinemia and the increased Th1 cells commonly observed in obesity. The role of leptin in T cell differentiation and inflammatory regulation is supported by studies demonstrating that *ob/ob* mice, which lack leptin, exhibit resistance to various inflammatory diseases, including mouse mod-

els of multiple sclerosis and arthritis.[43-45] These diverse and complex regulatory processes of T cells contribute to local inflammation and potentially control systemic metabolic homeostasis.[40,46]

In adipose tissue, naïve $CD4^+$ T cells differentiate into specific effector subsets in response to antigen presentation by local antigen-presenting cells (APCs) and the surrounding cytokine milieu.[47,48] In obesity, APCs such as dendritic cells and macrophages become activated and enhance their antigen-presenting efficiency through upregulation of costimulatory molecules (e.g., CD80/CD86) and major histocompatibility complex class II expression.[49] These factors promote $CD4^+$ T cell activation and polarization into inflammatory subsets.[49] Specifically, obesity-associated APCs preferentially secrete cytokines like IL-12 and IL-23, driving the polarization of $CD4^+$ T cells toward a Th1 phenotype characterized by interferon-gamma (IFN-γ) production, which subsequently enhances pro-inflammatory macrophage activation.[50-52] Similarly, the adipose tissue microenvironment in obesity promotes differentiation of $CD4^+$ T cells into Th17 cells, further amplifying tissue inflammation through secretion of IL-17.[50] This dysregulated interplay between APCs and $CD4^+$ T cells perpetuates chronic inflammation in adipose tissue and contributes significantly to obesity-associated metabolic dysfunction.

In contrast, a subset of $CD4^+$ T cells differentiates into Tregs in response to IL-2 and transforming growth factor beta (TGF-β).[53] $CD4^+CD25^+$forkhead box P3 $(FoxP3)^+$ Tregs actively suppress inflammation by inhibiting the activation of both macrophages and effector T cells.[53] Depletion of Tregs using anti-CD25 antibody exacerbated inflammation and insulin resistance in *db/db* (LEPR-deficient) mice, whereas adoptive transfer of $CD4^+FoxP3^+$ Tregs improved glucose metabolism.[54] In a separate study using *ob/ob* (leptin-deficient) mice, administration of anti-CD3 antibody together with β-glucosylceramide induced $CD4^+$latency-associated peptide $(LAP)^+$ Tregs, resulting in reduced inflammation and improved glycemic control.[55]

However, conflicting reports also suggest that adoptive Treg transfer may not always yield metabolic benefits and could even be detrimental. Van Herck et al.[56] demonstrated that the adoptive transfer of $CD4^+CD25^+FoxP3^+$ Tregs failed to expand within visceral adipose tissue and aggravated liver pathology in mice fed a high-fat, high-sucrose diet. These findings may reflect obesity-induced reductions in peroxisome proliferator-activated receptor-gamma (PPARγ) expression, which impairs long-term Treg maintenance.[56] In another study, adipose tissue-specific knockout (KO) of Tregs improved glucose and insulin metabolism in aged mice.[57] These findings suggest that the metabolic roles of Tregs may vary depending on the temporal context or the surrounding microenvironment, presenting critical limitations for the therapeutic application of Tregs in metabolic disorders.

HFD feeding leads to a marked increase in $CD8^+$ T cell numbers within adipose tissue.[58] These activated $CD8^+$ T cells produce IFN-γ and CCL5, which contribute to local inflammation and monocyte recruitment.[58] These cytokines promote the polarization of adipose-resident macrophages toward a classically activated phenotype, thereby sustaining the inflammatory state of adipose tissue.[59] Notably, systemic administration of anti-CD8 antibodies significantly reduced HFD-induced adipose tissue inflammation and macrophage infiltration compared to immunoglobulin G (IgG)-treated controls.[58] Moreover, improvements in glucose metabolism and insulin sensitivity were also observed.[58] These effects were further confirmed in CD8α KO mice. In CD8α KO mice, the adoptive transfer of splenic $CD8^+$ T cells re-established adipose inflammation and M1 macrophage infiltration.[58] Collectively, these findings highlight the critical role of $CD8^+$ T cells in initiating and sustaining adipose tissue inflammation.

B cells

Adipose-resident B cells include multiple subsets, such as anti-inflammatory B1 cells and regulatory B cells (Bregs), as well as pro-inflammatory B2 cells and memory-like B cells.[60] Each subset possesses distinct immunological functions during the progression of metabolic disorders. B cells, which are increased in adipose tissue during HFD feeding, promote insulin resistance through modulation of T cells and the production of pathogenic IgG antibodies.[61] B cell-deficient mice exhibit improved glucose metabolism and insulin sensitivity, along with reduced M1 macrophage polarization and adipose tissue inflammation.[61,62] These effects occur independently of changes in body weight, suggesting that B cells specifically contribute to inflammatory responses and metabolic dysfunction.[61,62]

However, anti-inflammatory B cell subsets exert beneficial effects on adipose tissue inflammation and metabolic homeostasis. Expan-

sion of B1 B cells, one of the anti-inflammatory subsets, alleviates HFD-induced obesity, adipose tissue inflammation, and insulin resistance in B cell-specific Id3 KO mice.[62,63] Similar to Tregs, Bregs exhibit immunosuppressive properties and play a crucial role in mitigating HFD-induced chronic inflammation. Studies have reported a reduction in Breg cell numbers within the adipose tissue of individuals with obesity, suggesting a potential link between Breg deficiency and the development of metabolic dysfunction.[64,65]

Beyond metabolic disorders, Bregs ameliorate several inflammatory conditions, including experimental autoimmune encephalomyelitis, transplantation tolerance, and sepsis, highlighting their immunosuppressive effects.[66-69] These immunoregulatory effects are primarily mediated through the production of IL-10.[70] Although Bregs have not been studied as extensively as Tregs, emerging evidence supports the potential of targeting Breg function as a therapeutic strategy for metabolic disorders.

CONTRIBUTION OF THE NERVOUS SYSTEM TO IMMUNOMETABOLIC FUNCTIONS

Sympathetic nervous system

The sympathetic nervous system (SNS) plays a critical role in regulating metabolic homeostasis, particularly through the modulation of adipose tissue function.[71] Sympathetic nerve terminals densely innervate adipose depots and release neurotransmitters such as norepinephrine (NE), which profoundly influence adipocyte lipolysis and thermogenesis.[72] Importantly, SNS activation in adipose tissues exhibits distinct, depot-specific patterns among brown adipose tissue (BAT), inguinal WAT (iWAT), and gWAT. Distinct sympathetic stimuli, such as cold exposure, food deprivation, glucoprivation, and MC4R activation, induce unique SNS activation patterns across various adipose tissues.[73-75] This phenomenon has been described as a 'Sympathetic fingerprint.'

Beyond its classical role in lipid mobilization, recent studies have revealed that SNS activation and subsequent NE release significantly affect immune cell polarization (Fig. 2A).[76,77] These neuro-immune interactions contribute to obesity-associated inflammation and insulin resistance. A recent study demonstrated that hypothalamic microgliosis and chemogenetic activation of POMC neurons induce SNS activation, resulting in enhanced lipolysis and thermogenesis in BAT and iWAT while concurrently modulating immune cell activity and insulin sensitivity in gWAT.[26,71] Sympathetic activation predominantly promotes anti-inflammatory M2 macrophage polarization and suppresses the expression of macrophage-derived

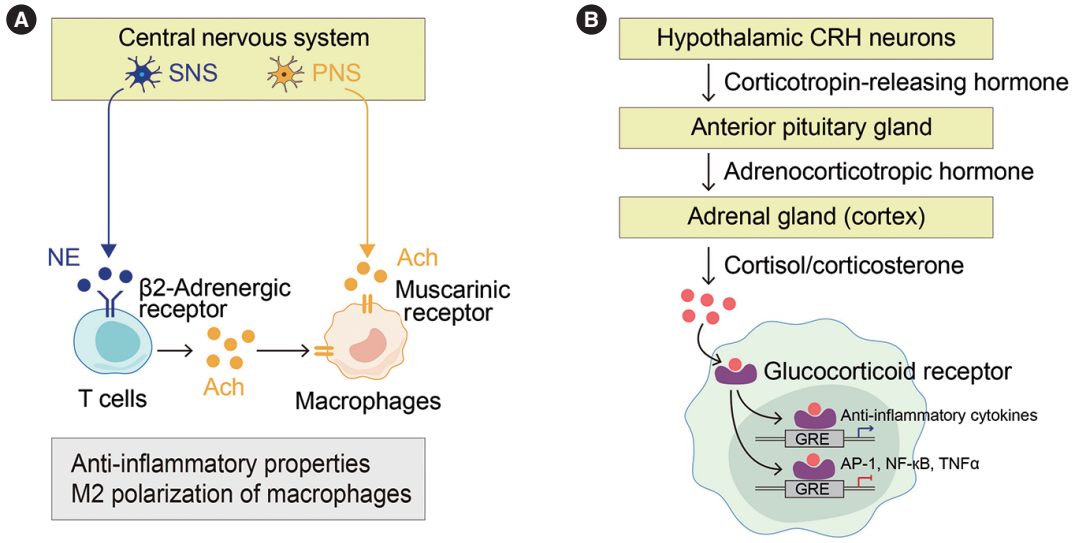

Figure 2. Autonomic and endocrine regulation of immune cell polarization. (A) The sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) regulate immune cell responses through neurotransmitters norepinephrine (NE) and acetylcholine (Ach), respectively. (B) The hypothalamic-pituitary-adrenal axis modulates inflammation and metabolic responses via glucocorticoid receptor signaling pathways. CRH, corticotropin-releasing hormone; GRE, glucocorticoid response element; AP-1, activator protein-1; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor-alpha.

pro-inflammatory cytokines such as TNF-α and MCP-1.[78,79] This response is mediated through β-adrenergic receptor signaling pathways.[78] Systemic administration of the β-blocker propranolol, sympathetic denervation, or central administration of AgRP inhibits NE-mediated adrenergic signaling and reduces the expression of TNF-α and MCP-1 in WAT.[78,79] T cells are also sensitive to sympathetic signals. NE released from sympathetic nerve terminals binds to β2-adrenergic receptors (β2-ARs) expressed on choline acetyltransferase (ChAT)$^+$ T cells and stimulates the secretion of acetylcholine by these cells.[80] Subsequently, acetylcholine binds to α7-nicotinic acetylcholine receptors (α7nAChR) on macrophages, promoting M2 polarization and suppressing TNF-α production.[79-82] Additionally, increased sympathetic activity induced by cold exposure or β3-adrenergic receptor activation promotes the induction of FoxP3$^+$ Tregs.[83]

However, prolonged activation of SNS can induce β-adrenergic receptor desensitization and reduced receptor expression (also known as catecholamine resistance) in adipose tissue.[84,85] Moreover, sympathetic axonal degeneration triggered by prolonged metabolic stress may shift adipose tissue toward a pro-inflammatory environment, further exacerbating metabolic disturbance.[86-88] Further elucidation of the molecular and cellular mechanisms underlying SNS-immune cell interactions will enhance the understanding of obesity pathogenesis and support the development of novel immunometabolic therapeutic strategies.

Sympathetic signals influence diverse cell populations within adipose tissue, affecting both immune cells and adipocytes. Specifically, thermogenic adipose tissues, such as BAT or beige adipose tissue, undergo lipolysis through NE-β3-AR signaling.[89,90] Numerous studies have demonstrated that moderate SNS activation can exert anti-obesity effects and improve energy metabolism.[71,90] However, chronic metabolic stress or pandemic-like extreme conditions may lead to intense SNS activation and insulin resistance.[91,92] Elevated levels of free fatty acids induced by excessive lipolysis can enter systemic circulation, contributing to systemic inflammation and inducing insulin resistance in various tissues, including the hypothalamus, liver, and skeletal muscle.[16,93-95] Circulating fatty acids, such as palmitate, can activate Toll-like receptor 4 (TLR4) signaling pathways; thereby, increasing the expression of pro-inflammatory cytokines including IL-6 and TNF-α.[96] Although the direct role of palmitate as a TLR4 agonist remains controversial,[97] prolonged activation of these inflammatory signals ultimately induces insulin resistance. Further studies will need to apply more refined approaches and optimized experimental conditions to delineate the extent of SNS activation and the cell-specific responses mediated via distinct receptor subtypes.

Parasympathetic nervous system

In contrast to the SNS, parasympathetic innervation within WAT remains largely uncharacterized.[98] Nevertheless, parasympathetic acetylcholine signaling is fundamentally recognized for its anti-inflammatory properties and its capacity to attenuate systemic immune responses.[99] This signaling significantly improves systemic metabolism in obesity by reducing adipose tissue inflammation through neuro-immune interactions.[99] In general, parasympathetic acetylcholine acts on the α7nAChR expressed on macrophages, suppressing pro-inflammatory cytokines like TNF-α and IL-6 and promoting polarization of macrophages toward the anti-inflammatory M2 phenotype (Fig. 2A).[79] Genetic ablation or pharmacological inhibition of α7nAChR exacerbates inflammatory responses and insulin resistance, highlighting the critical anti-inflammatory and metabolic properties of the parasympathetic nervous system (PNS).[100] A recent study reported that optogenetic stimulation of the vagus nerve improves diabetes and metabolic dysregulation by promoting pancreatic β-cell proliferation and enhancing insulin secretion.[101] In addition to these beneficial effects on metabolic disorders, vagus nerve stimulation has also been shown to reduce inflammation and endotoxin shock induced by lipopolysaccharide.[100,102,103]

The anti-inflammatory functions of the parasympathetic cholinergic signaling can be attributed to interactions between the PNS and secondary lymphoid organs, such as the spleen and lymph nodes. The spleen serves as a crucial reservoir for immune cells, including monocytes, and exerts anti-inflammatory effects by mobilizing these cells during inflammatory conditions.[104] Specifically, undifferentiated monocytes within the subcapsular red pulp region of the spleen rapidly mobilized to inflammatory sites, effectively mitigating inflammation in a myocardial infarction model.[104] This protective effect was abolished in splenectomized mice.[104] Another study identified the spleen as a key reservoir and source of innate-like B cells within visceral adipose tissue.[105] These innate-like B cells

produce IL-10; thereby, suppressing adipose tissue inflammation and ultimately improving insulin resistance.[105] Although direct neural circuits connecting the PNS to secondary lymphoid organs have yet to be fully elucidated, further research is essential for a comprehensive understanding of immune cell regulation within the proposed PNS-lymphoid organ-adipose tissue network.

Hypothalamic-pituitary-adrenal gland axis

The HPA axis plays a critical role in coordinating physiological stress responses and intricately modulates peripheral immune activity and metabolic processes (Fig. 2B).[106] Under acute stress conditions, the hypothalamic secretion of corticotropin-releasing hormone (CRH) rapidly stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), triggering glucocorticoid (cortisol/corticosterone) secretion from the adrenal cortex.[107] Corticosterone exerts context-dependent immunomodulatory effects, demonstrating both anti-inflammatory and pro-inflammatory properties depending on exposure duration and physiological conditions.

Research has provided substantial mechanistic insights into the anti-inflammatory effects of the HPA axis.[108-110] Glucocorticoids rapidly modulate gene expression through the activation of glucocorticoid receptors (GRs) by inhibiting NF-κB and activator protein-1 (AP-1)—two key transcription factors that drive the production of inflammatory cytokines, including TNF-α and IL-1β.[111-113] Recent research further demonstrated that GR activation in macrophages promotes their polarization towards an anti-inflammatory M2 phenotype; thereby, conferring protection against insulin resistance.[114] This protective effect depends on cooperative interactions with signal transducer and activator of transcription 6 (STAT6), highlighting the critical role of GR signaling in modulating both inflammatory and metabolic responses in adipose tissue.[114]

Despite the intrinsic anti-inflammatory function of corticosterone, prolonged activation of the HPA axis paradoxically induces inflammation. Although the specific molecular mechanisms remain incompletely understood, one possible explanation involves SNS activation, which enhances lipolysis and increases circulating levels of free fatty acids.[115,116] Elevated free fatty acids or catecholamine-induced adipocyte death elicit the infiltration of pro-inflammatory M1 macrophages; thereby, enhancing the expression of inflammatory cytokines.[117] Another potential mechanism involves glucocorticoid-driven upregulation of 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in adipose tissue.[118,119] 11β-HSD1 is well-known to induce insulin resistance.[118] Mice deficient in 11β-HSD1 exhibit reduced levels of circulating fatty acids and are protected against metabolic disorders, including insulin resistance, hepatic steatosis, and obesity.[119] Furthermore, administration of an 11β-HSD1 inhibitor in *ob/ob* mice resulted in improved blood glucose levels, reduced serum lipids, and enhanced insulin sensitivity.[120] However, these results do not directly demonstrate that immune cells undergo pro-inflammatory differentiation following long-term exposure to corticosterone. Future studies utilizing *in vivo* techniques such as chemogenetics or optogenetics are necessary to conclusively establish this link.

CONCLUSION

Despite growing evidence underscoring the importance of neuro-immune interactions in metabolic regulation, the current understanding of the underlying mechanisms remains limited. This review comprehensively describes how the CNS modulates peripheral immune cell functions and how immune cells in adipose tissue contribute to metabolic disorders. Nonetheless, several key research directions require further investigation, including (1) identification of the specific neuronal populations involved in this network, (2) clarification of depot-specific differences across various adipose tissues, and (3) delineation of the distinct effects of short-term versus long-term autonomic stimulation. Continued advancements in diverse methodologies, expanded use of various animal models, and the application of emerging tools such as adeno-associated viruses are expected to enable more in-depth studies of neuro-immune interactions in the near future.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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