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REVIEW

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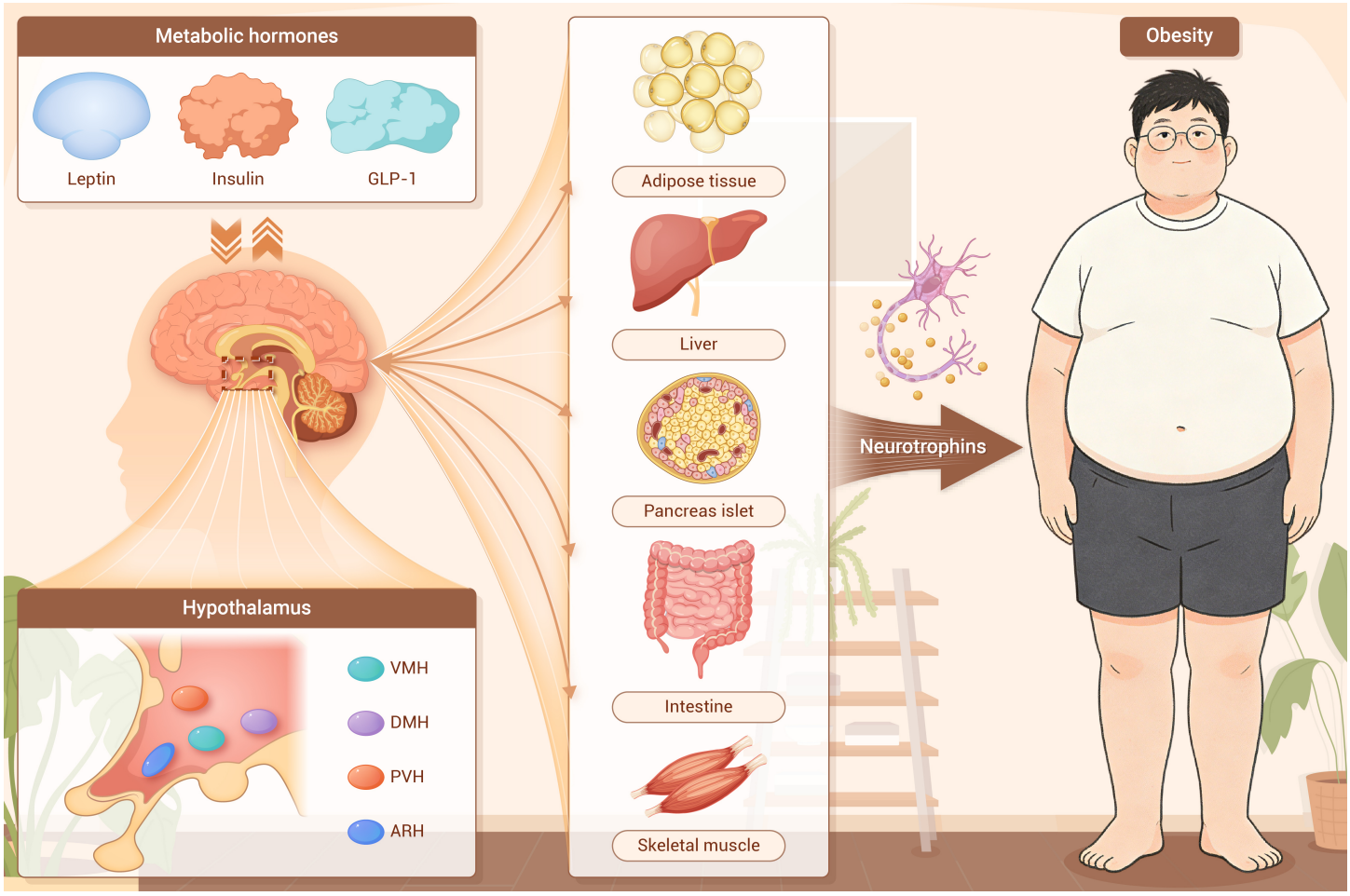
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Neurotrophins form an integrated network linking the central system to peripheral metabolism.
- This network interacts with hypothalamic nuclei involved in nutrient sensing and energy balance.
- Neurotrophins also act on peripheral metabolic organs to regulate energy homeostasis.

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Neurotrophins sensing nutrition: Molecular mechanisms regulating host lipid metabolism and prospects for clinical application

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Obesity arises from dysregulation of central nervous system and peripheral energy homeostasis pathways. To maintain metabolic balance, neural circuits in the brain integrate nutritional signals from central and peripheral systems to correct deviations in energy supply and expenditure. Hence, elucidating the core neurobiological mechanisms of metabolic regulation and how alterations in these pathways contribute to obesity and related metabolic disorders is therefore of critical importance. Notably, neurotrophins not only support neuronal growth, development and function, but also play key roles in sensing nutritional status and regulating energy metabolism. Here, we summarize the potential mechanisms by which neurotrophins in key metabolic organs, including the hypothalamus, adipose tissue, pancreas islet, liver, skeletal muscle and intestine, sense nutritional signals and regulate energy homeostasis. Furthermore, we also further highlight the clinical application prospects and translational strategies for activating, inhibiting and stratifying interventions that target neurotrophins and their receptors. Finally, we outline outstanding issues related to neurotrophins mediated nutritional regulation of lipid metabolism, providing a reference for the design of therapeutic interventions against obesity.

INTRODUCTION

With rising living standards, dietary patterns have changed significantly, particularly with increased consumption of high-energy foods rich in sugar, salt and fat.[1] However, the excess energy is stored as fat, which in turn contributes to various functional disorders and diseases, particularly obesity.[2] Notably, obesity is a global health issue, currently affecting more than 1 billion people worldwide.[3-4] Furthermore, obesity is recognized as a chronic metabolic disorder. It not only increases the risk of cardiovascular disease, diabetes, nonalcoholic fatty liver disease, cancer, neurological, respiratory and digestive disorders, but also contributes to sleep disturbances, reduced mobility and psychological distress.[1,3] Therefore, investigating the pathogenesis of obesity, exploring effective strategies for weight management and conducting in-depth research on the prevalence of obesity-related diseases hold substantial clinical value for enhancing the understanding and treatment of these conditions.

Specifically, obesity is driven by a complex interplay of genetic, environmental (e.g., circadian rhythm disruption), behavioral (e.g., sedentary lifestyle and excessive consumption of energy-dense foods), social, cultural and economic factors.[1,3,5] The physiological and pathological basis of obesity involves multiple aspects of energy metabolism, including appetite regulation, amino acid metabolism and glucose and lipid metabolism homeostasis.[3] Notably, because energy homeostasis and peripheral metabolism are coordinated by the brain through the integration of various hormones, neuronal inputs and nutritional signals, elucidating the fundamental neurobiological mechanisms underlying metabolic regulation is essential for understanding the development and progression of obesity and associated metabolic disorders.[6-7] Current research indicates that dysfunction in central nervous system pathways regulating energy balance may contribute to metabolic disorders and increase the risk of obesity.[8] For instance, an impaired neuronal response to nutritional signals may lead to overeating and obesity.[9] Moreover, this dysfunction often persists even after diet-induced weight loss. Similarly, adipose tissue also interacts with the central nervous system to maintain systemic energy balance.[10] In particular, mammalian adipose tissue is innervated by the sympathetic nervous system. Sympathetic nerve fibers act on β-adrenergic receptors, regulating thermogenesis and lipid metabolism in brown and beige adipose tissue.[10-11] However, the underlying mechanisms are complex and multifaceted, with many aspects remaining unknown and requiring further investigation.

Interestingly, growing evidence indicates that neurotrophins (NTs), a class of small proteins, not only play a crucial regulatory role in neuronal survival, differentiation, axonal growth, synaptic plasticity and repair following injury to the central and peripheral nervous systems,[12-14] but also act as key regulators of cellular metabolism, particularly in modulating host lipid metabolism.[15-17] For instance, NTs enhance the sympathetic innervation of brown and white adipose tissues, thereby promoting thermogenesis in brown adipose tissue and increasing energy expenditure, ultimately helping to prevent diet-induced obesity.[16] Furthermore, NTs play a critical role in regulating cholesterol homeostasis in glial cells and in preserving mitochondrial quality and function.[15,17] These findings indicate that NTs may constitute attractive therapeutic targets for obesity by mediating nutrient sensing and metabolic signal transduction. However, the molecular mechanisms by which NTs regulate lipid metabolism and the roles in obesity remain unclear. Thus, this review primarily focuses on the potential mechanisms by which NTs sense nutritional signals and regulate lipid metabolism. Furthermore, we also emphasize the potential clinical value of NTs in obesity intervention.

NEUROTROPHINS AND NEUROTROPHINS RECEPTORS

Neurotrophins

NTs are small proteins that dimerize to form biologically active species. The NTs possess a highly conserved structure. Among all NTs, nerve growth factor (NGF) has been the most thoroughly studied since its discovery in 1951. The NGF molecule consists of three subunits-α, β and γ-and plays a crucial regulatory role in the development, differentiation, growth, regeneration and functional maintenance of both central and peripheral neurons.[13] Furthermore, key NTs also include brain-derived neurotrophic factor (BDNF), NT-3, NT-4 (also known as NT-5), NT-6 and NT-7.[13] Interestingly, NT-6 and NT-7 have so far only been identified in fish species[18-19] and are therefore not discussed further in this review.

In addition to NTs family, several other peptides or small proteins exhibiting neurotrophic activity have been identified, including members of the fibroblast growth factor (FGF) family, the glial cell line-derived neurotrophic factor (GDNF) family, the ciliary neurotrophic factor (CNTF) family and insulin-like growth factors I and II (IGF-I and IGF-II).[12,20] However, we primarily focus on the role of the NTs family and its cognate receptors in regulating lipid metabolism. (Figure 1) Consequently, other polypeptides or small proteins with neurotrophic activity will not be further discussed.

Neurotrophins receptors

The binding of NTs to neurons involves two types of receptors: high-affinity and low-affinity NTs receptors. (Figure 2) Specifically, NTs exert their effects by binding with high affinity to specific cell surface receptors, known as tropomyosin receptor kinases (Trks), which include TrkA, TrkB and TrkC.[21] For instance, TrkA exhibits high affinity for NGF; TrkB selectively binds BDNF and NT-4; and TrkC has a high affinity for NT-3. Moreover, NT-3 can also bind to TrkA and TrkB, although with relatively low affinity.[13,21] Notably, upon ligand binding, the Trks dimerize and undergo transmembrane phosphorylation, leading to the phosphorylation of their intracellular kinase domains and

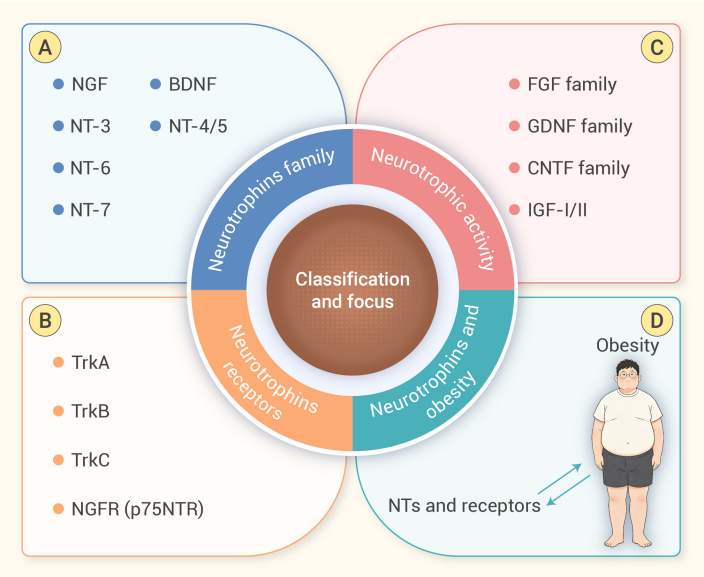

Figure 1. The neurotrophins family and their receptors

subsequent activation of downstream intracellular effectors.[21] On the other hand, both non-processed NTs or precursor form NTs (pro-NTs) and the mature fully processed NTs can bind to the low-affinity NTs receptor (p75), also known as NGFR or p75NTR.[21] Interestingly, all NTs are capable of binding to the p75NTR. Notably, the structure and expression of NTs receptors have been extensively described in previous reviews;[12-13,21] therefore, we will not discuss them in detail.

NEUROTROPHINS AND OBESITY

In the brain, hypothalamic neurons encoded by molecules receive information about the body's energy state through the hormones and cytokines secreted by the circulatory organs and coordinate appropriate responses to maintain internal balance.[22] For instance, the melanocortin circuitry is centered in two neuronal populations within the arcuate nucleus of the hypothalamus, which play a critical role in regulating feeding behavior, energy expenditure and fuel metabolism.[6] However, obesity disrupts endocrine and neuronally mediated feedback signals to the brain, impairing the function of both the peripheral and central nervous systems.[22] Therefore, regulating neuronal signal transmission and restoring nervous system function are particularly important for effective obesity intervention. Interestingly, because NTs promote neuronal differentiation, survival and nervous system repair, their roles in lipid metabolism and obesity intervention have attracted increasing attention in recent years.

Notably, population-based cohort studies suggest that NTs levels are associated with obesity and related metabolic disorders. For instance, in one study, 132 volunteers were stratified into obese and non-obese groups according to body mass index (BMI).[23] Serum BDNF concentrations were significantly lower in the obese group and BDNF levels were negatively correlated with BMI and triglyceride levels.[23] Furthermore, among Korean adult women, serum BDNF levels are significantly lower in overweight individuals than in their normal weight counterparts, whereas no significant difference is observed between obese and normal weight women.[24] However, the salivary concentrations of BDNF and NGF are significantly higher in obese children compared to those with normal weight.[25] Importantly, decreased, unchanged, or increased levels of NTs in individuals with obesity and related metabolic disorders, likely reflecting the combined influence of methodological differences and biological heterogeneity. Specifically, serum BDNF levels are largely determined by platelet release during coagulation, whereas plasma BDNF reflects a distinct biological pool.[26] Accordingly, preanalytical variables, including sample matrix, coagulation time, storage conditions, and centrifugation strategy, are sufficient to influence measured BDNF concentrations and consequently, their clinical interpretation.[26] In addition, age, developmental stage, sex, and hormonal status can all influence peripheral BDNF levels.[27] Therefore, the reduction in serum BDNF observed in adults with obesity does not necessarily conflict with the elevated salivary BDNF and NGF levels reported in children with obesity. Rather, these differences are more likely to reflect the combined effects of developmental stage, sample type, and tissue source. Interestingly, from the perspective of disease progression, BDNF may exhibit compensatory upregulation during the early stages of metabolic dysfunction, followed by a subsequent decline as chronic inflammation, insulin resistance, and metabolic imbalance progressively worsen.[28] Notably, different NTs may also reflect distinct pathological and physiological dimensions. In population-based studies, NGF appears to be more closely associated with obesity, metabolic syndrome and inflammatory markers, whereas NT-3 and BDNF may show stronger associations with lipid profile characteristics.[29] These observations suggest that individual NTs levels may correspond to different biological processes, such as inflammatory responses, lipid remodeling, and tissue adaptation, rather than constituting a uniform group of biomarkers that change in the same direction. Interestingly, mutations in the NTs receptor *TrkB* have been closely linked to human obesity.[30] Overall, NTs and their receptors are closely associated with obesity (Table 1-2). However, their roles in the development and progression of obesity remain incompletely understood. Therefore, it is essential to elucidate the mechanisms by which NTs regulate lipid metabolism, thereby identifying potential targets for clinical intervention.

MOLECULAR MECHANISMS UNDERLYING NEUROTROPHINS MEDIATED REGULATION OF LIPID METABOLISM

NTs and their receptors are broadly expressed throughout the body (Table 3) and function not only as neuroprotective mediators, but also as key regulators of energy metabolism and nutrient sensing. Specifically, they respond to alterations in the body's nutritional status and participate in the precise regulation of energy balance within both the central and peripheral nervous systems through interactions with metabolic signaling pathways. Moreover, peripheral nutrient cues, hormones and gut microbiota derived metabolites modulate the transcription and secretion of NTs, thereby contributing to the regulation of lipid homeostasis. Overall, NTs act as sensors and transducers of nutritional state, underscoring the tight coupling between the nervous and metabolic systems. Hence, elucidating NTs mediated nutrient sensing mechanisms will enhance understanding of the neural control of energy homeostasis and may reveal therapeutic targets for obesity.

Neurotrophins mediated nutrient sensing and energy allocation in hypothalamus

The hypothalamus senses fluctuations in peripheral nutritional signals and via its neuronal circuits, regulates food intake, energy expenditure and peripheral metabolism.[31-33] For example, excessive energy intake or obesity markedly reduces the expression of BDNF in the hypothalamus,[34-35] fasting or caloric restriction can also modulate the expression levels of BDNF.[36-38] Moreover, as the central regulator of energy balance, hypothalamus also integrates peripheral metabolic cues with central NTs signaling.[32,39] In recent years, interactions between NTs and neurons in the ventromedial (VMH), dorsomedial (DMH), paraventricular (PVH) and arcuate (ARH) of the hypothalamus have been extensively investigated.[7,33,40-41] In particular, BDNF functions as a metabolic signal integrator within the energy regulatory network of key hypothalamic regions. (Figure 3A)

Specifically, BDNF is thought to exert an anorexigenic effect in the VMH.[42] In obese model animals, the expression of BDNF in the VMH significantly decreases and this change is closely related to increased energy intake and metabolic disorders.[38,43] Notably, analyses of VMH tissue from human autopsies show that the C allele of the BDNF rs12291063 single nucleotide polymorphism is associated with lower BDNF expression in the VMH and a higher prevalence of obesity.[44] In adult mice, the deletion of BDNF from VMH induces hyperphagia and obesity.[45] By contrast, BDNF deletion in the VMH during embryogenesis does not affect body weight, presumably due to compensatory developmental remodeling of VMH circuits that mitigates the deficit.[45] Interestingly, BDNF also interact with two principal neuronal populations in the ARH: the orexigenic neurons expressing agouti-related protein (AgRP) and neuropeptide Y (NPY) and the anorexigenic neurons expressing proopiomelanocortin (POMC).[46] These ARH neurons receive peripheral energy status signals and in turn drive appropriate metabolic responses to fluctua-

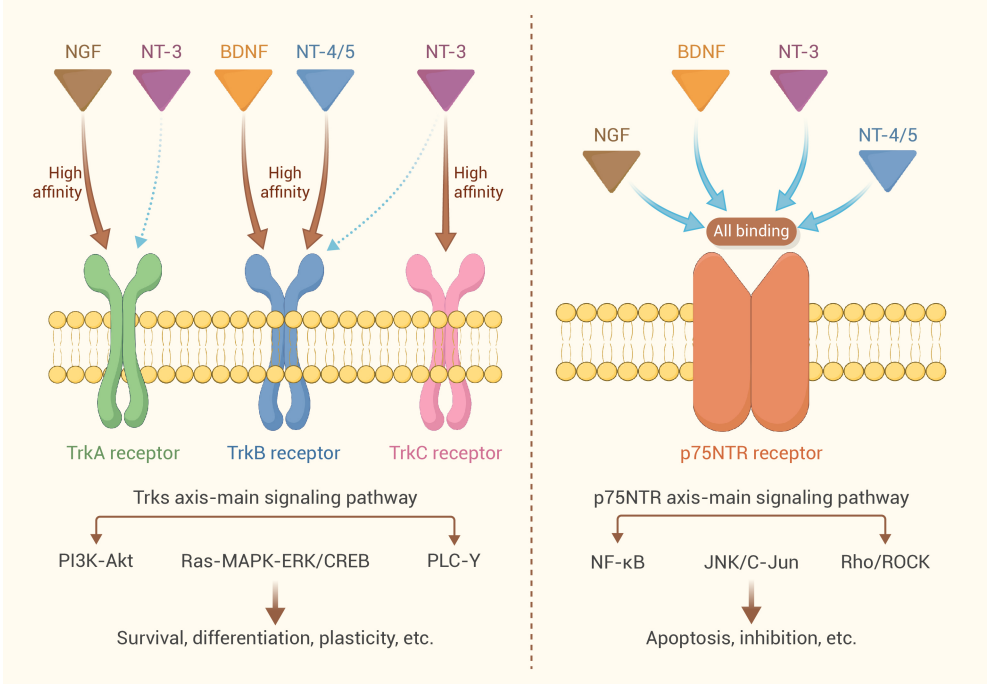

Figure 2. Types of interactions between neurotrophins and their receptors

tions in energy demand. Specifically, the deletion of BDNF also disrupts the projection patterns of AgRP and POMC expressing neurons to the PVH and DMH, respectively and alters the balance of excitatory and inhibitory inputs onto these neuronal populations, ultimately leading to weight gain.[40,46] However, the deletion of the BDNF results in increased excitatory input to POMC neurons and decreased excitatory input to NPY neurons in ARH.[46] Notably, this pattern may reflect a compensatory response to the marked hyperphagia observed in the mutant mice.[46]

Furthermore, BDNF neurons in the medial and posterior PVH project to the spinal cord and establish multisynaptic connections with brown adipose tissue to drive thermogenesis, whereas BDNF neurons in the anterior PVH regulate energy intake and locomotor activity.[47] Notably, ablation of BDNF in the PVH results in atrophy of sympathetic ganglion preferred neurons.[47] Thus, BDNF help maintain the activity and axonal integrity of PVH sympathetic-related neurons, thereby facilitating peripheral fat mobilization and limiting lipid accumulation. For example, administration of BDNF into PVH not only suppresses food intake and energy expenditure but also reverses high-fat diet induced obesity.[48] Conversely, insufficient NTs signaling reduces sympathetic outflow and energy expenditure, predisposing to obesity. This has been confirmed in PVH where the deletion of the *BDNF* gene leads to overeating and obesity.[47]

Notably, activation of TrkB expressing DMH neurons suppresses food intake and helps maintain physiological satiety.[49] Conversely, deletion of TrkB in these neurons increases appetite and decreases energy expenditure.[49] However, the effects of DMH TrkB neuron activity on food intake and thermogenesis are mediated by distinct neural circuits.[50] Activation of DMH TrkB neurons projecting to the raphe pallidus (RPa) stimulates thermogenesis and increases energy expenditure, whereas activation of DMH TrkB neurons that send collateral projections to the PVH and preoptic area (POA) suppresses feeding.[50] Notably, although p75NTR expression in the DMH is the highest among hypothalamic nuclei, its functional significance has not yet been elucidated.[40]

Apart from the BDNF/TrkB signaling, other NTs and their receptors may also participate in nutrient sensing and the central regulation of energy allocation. For example, NGF/p75NTR participate in the hypothalamic integration of nutritional signals, thereby dynamically regulating energy balance.[51] Furthermore, NT-4 can activate the phosphoinositide 3-kinase (PI3K) signaling pathway through a TrkB receptor dependent mechanism, thereby regulating norepinephrine uptake and release in the hypothalamus.[52] This finding suggests distinct NTs may indirectly modulate sympathetic activity and brown adipose tissue energy expenditure by acting on specific hypothalamic regions. However, the underlying mechanism remains to be elucidated.

Bidirectional crosstalk between neurotrophins and metabolic hormones

The hypothalamus constitutes a critical network that integrates peripheral nutritional and metabolic hormone signals and converts them into sympathetic and endocrine outputs. Notably, metabolic hormone signals also remodel NTs at transcriptional and secretory levels across hypothalamus and periphery. (Figure 3B) Specifically, leptin is an adipocyte-derived hormone that reduces food intake by modulating orexigenic and anorexigenic pathways in the hypothalamus.[53-54] Notably, exogenous leptin selectively increases BDNF mRNA and protein levels in VMH and this effect occurs in phosphorylated signal transducer and activator of transcription 3 (STAT3) positive neurons, indicating the presence of a leptin/STAT3/BDNF signaling pathway.[55] Furthermore, leptin also regulates the exon-specific transcription of the *BDNF* gene through epigenetic modifications mediated by the protein kinase B (AKT)/histone acetyltransferase p300 (p300 HAT) signaling cascade.[56] Mechanistically, leptin enhances methylation of the BDNF exon IV promoter and upregulates upstream transcriptional regulators, including *peroxisome proliferator-activated receptor gamma coactivator-1-alpha* (*PGC-1α*) and *fibronectin type III domain-containing protein 5* (*Fndc5*), particularly the Sirtuin-1/PGC-1α/FNDC5 pathway, which may account for the observed increase in hypothalamic *BDNF* expression.[57] Notably, this further demonstrates that metabolic hormones can precisely regulate NTs at the transcriptional level.

Interestingly, insulin not only plays a vital role in neuronal survival, memory formation and energy homeostasis, but recent studies have also demonstrated that insulin receptors regulate the transcriptional levels of NTs (NGF and BDNF) and their receptors (TrkA, TrkB and p75NTR), as well as the secretion of BDNF by neural stem cells.[58] For example, insulin can upregulate hypothalamic BDNF under specific metabolic conditions.[59] However, this effect is region specific and metabolism dependent, indicating that the central nutritional signal of insulin may be integrated with the host's energy status to be effectively transmitted to the level of NTs regulation.[59] Similarly, incretin hormones regulate the expression of BDNF and NGF in microglia through phosphorylated phosphoinositide 3-kinase (PI3K) and protein kinase A (PKA) dependent mechanisms,[60] whereas glucagon-like peptide-1 (GLP-1) modulates BDNF secretion by activating the cAMP response element-binding protein (CREB)-BDNF signaling pathway via the GLP-1 receptor.[61] These findings suggest a close interconnection between metabolic hormone and NTs.

In addition, metabolic hormone induced NTs may act as key mediators that enable the hypothalamus to transform metabolic information into neural signals and to transmit energy related outputs. For example, when NTs binds to its receptor Trks/p75NTR, it activates classic downstream signaling cascades (i.e., PI3K/Akt, MAPK/ERK and PLCγ) in the ARC, VMH and PVH, thereby maintaining the excitability, synaptic efficacy and axonal integrity of target neurons.[62-63] This, in turn, ensures stable amplification of metabolic hormone actions within these nuclei. For example, the BDNF/TrkB signaling in the VMH is an important downstream target of melanocortin-4 receptor (MC4R)-mediated signaling, participates in the central regulation of energy balance and feeding behavior and remains sensitive to peripheral nutritional status.[42]

Notably, signals from metabolic hormones may first be transduced into NTs dependent changes in neuronal plasticity and excitability within the hypothalamus; these NTs amplified neurons then transmit metabolic commands to the sympathetic and endocrine axes to regulate energy metabolism. For instance, in diabetic and obese mice, administration of BDNF

Table 1. Neurotrophins levels are associated with obesity and related metabolic disorders

Type of disease	BMI	Sex	Age	Sample type	Neurotrophins levels relative to healthy individuals	References
Obesity	25.0-29.9	Both sexes	18-40	Serum	Reduced BDNF levels	[23]
Overweight	23.0-24.9	Women	19-75	Serum	Reduced BDNF levels	[24]
Obesity	≥25.0	Women	19-75	Serum	BDNF levels remained unchanged	[24]
Obesity	36.7±0.7	Both sexes	48.3±1.8	Plasma	Reduced BDNF levels	[64]
Obesity and diabetes	35.5±0.7	Both sexes	58.3±1.4	Plasma	Reduced BDNF levels	[64]
Morbidly obese	47.1±6.5	Women	43.0±10.4	Plasma	Reduced BDNF levels	[29]
Metabolic syndrome	/	Both sexes	/	Plasma	Reduced BDNF levels	[65]
Metabolic syndrome	39.6±1.0	/	45.7±2.2	Plasma	Reduced BDNF levels	[66]
Early stage of metabolic syndrome	39.7±0.9	Women	43.4±1.5	Plasma	BDNF levels were slightly elevated	[67]
Generalized metabolic syndrome	42.1±0.3	Women	45.7±2.2	Plasma	Reduced BDNF levels	[67]
Type 2 diabetes	31.1±6.7	Both sexes	53.5±7.6	Serum	Increased BDNF levels	[68]
Type 2 diabetes	23.5±3.2	Both sexes	56.5±7.9	Serum	Reduced BDNF levels	[69]
Overweight/Obesity	33.7±3.9	Women	48.4±10.3	Plasma	Increased NGF levels	[29]
Obesity	32±5	Women	39±8	Serum	Increased NGF-β levels	[70]
Early stage of metabolic syndrome	39.7±0.9	Women	43.4±1.5	Plasma	Increased NGF levels	[67]
Generalized metabolic syndrome	42.1±0.3	Women	45.7±2.2	Plasma	Reduced NGF levels	[67]
Metabolic syndrome	39.6±1.0	/	45.7±2.2	Plasma	Reduced NGF levels	[66]
Metabolic syndrome	/	Both sexes	/	Plasma	Reduced NGF levels	[65]
Type 2 diabetes	23.5±3.2	Both sexes	56.5±7.9	Serum	Reduced NGF levels	[69]
Type 2 diabetes	31.1±6.7	Both sexes	53.5±7.6	Serum	Reduced NGF levels	[68]
Morbidly obese	47.1±6.5	Women	43.0±10.4	Plasma	Increased NT-3 levels	[29]
Type 2 diabetes	31.1±6.7	Both sexes	53.5±7.6	Serum	Increased NT-3 levels	[68]

into the third ventricle reduces body weight and improves glucose tolerance.[71] Interestingly, these improvements occur independently of changes in appetite, indicating that BDNF activates the sympathetic nervous system via the central nervous system, increases norepinephrine turnover and upregulates uncoupling protein 1 (UCP1) expression in brown adipose tissue, thereby improving systemic metabolic status.[71-72] These findings suggest that BDNF may function as a downstream amplifier of metabolic hormone action: even when hormonal signaling is attenuated by obesity or hormone resistance, NTs levels may remain relatively preserved, allowing energy expenditure to be enhanced. However, under pathological conditions, this system is prone to decoupling, whereby upstream hormonal signals are enhanced but downstream NTs responses are insufficient. Specifically, obesity, high-sugar intake and gestational metabolic load can induce hypothalamic leptin resistance, impair STAT3 phosphorylation and upregulate *suppressor of cytokine signaling 3* (*SOCS3*)/*protein tyrosine phosphatase 1B* (*PTP1B*) expression, thereby directly attenuating leptin induced *BDNF* expression.[73-75] Furthermore, even in the presence of hormonal inputs, alterations in NTs associated MAPK signaling may prevent full activation of NTs signals.[76] Consequently, this results in blunted sympathetic output, reduced thermogenesis and disrupted lipid metabolism.[77-78] Notably, this top-down attenuation may, in turn, further exacerbate peripheral insulin resistance and hyperleptinemia, thereby reinforcing a vicious cycle of disequilibrium between metabolic hormones and NTs.[79-80] In summary, metabolic hormones may induce NTs expression within key hypothalamic nuclei via STAT3, PI3K/Akt and epigenetic mechanisms. Subsequently, via NTs receptors, hormonal signals are converted into stable neural outputs, ensuring that the hypothalamus effectively relays metabolic commands to the sympathetic nervous system, the melanocortin pathway and peripheral tissues. Moreover, reduced sensitivity to hormones or NTs can lead to an imbalance between energy intake and expenditure, diminished lipid mobilization and obesity-related metabolic phenotypes.

Nutrient sensing of neurotrophins in peripheral tissues and regulation of lipid metabolism

The hypothalamus integrates energy-balance signals and relays them via sympathetic and parasympathetic innervation in regulating lipolysis and thermogenesis in white and brown adipose tissue.[16,81-82] Interestingly, adipose tissue also possesses afferent sensory innervation that feeds back to and modulates sympathetic activity.[16,81-82] Recent studies have shown that NTs are also widely expressed in peripheral tissues, including adipose tissue, liver, pancreas and intestine, where they also sense nutritional signals and participate in lipolysis, lipogenesis and thermogenesis. Thus, NTs may as mediators of nutrient sensing and signal transduction in peripheral tissues and are deeply embedded in the bidirectional communication network between the hypothalamus and the periphery.

Adipose tissue and neurotrophins. In adipose tissue, NTs are regarded as key signals linking nutritional status, the inflammatory microenvironment and sympathetic innervation.[81-82] (Figure 4A) NT-3, which is highly expressed in brown and beige adipose tissue, currently has the strongest evidence as an adipose-derived NTs.[16] Notably, NT-3 is critical for maintaining sympathetic innervation and UCP1 expression in both brown and white adipose tissue and attenuation of NT-3 signaling in white adipose tissue reduces sympathetic activity and innervation, leading to the loss of beige adipocytes.[16] This indicates that NT-3 upregulation is associated with enhanced fatty acid oxidation and thermogenic capacity. Moreover, genetic studies have shown that adipose-derived NT-3 acts on sympathetic neurons via TrkC to promote axonal growth and branching and that overexpression or exogenous administration of NT-3 enhances sympathetic innervation of adipose tissue and

Table 2. The effects of neurotrophins or receptor deficiency on host metabolism

Types of neurotrophins deficient mouse	Types of neurotrophins receptor deficient mouse	The metabolic effects of neurotrophins or receptor knockout	References
Sf1-Cre-mediated embryonic deletion of the *BDNF* in the VMH	/	Does not affect energy balance or body weight	45
Adult VMH-specific deletion of *BDNF*	/	Hyperphagia and obesity	45
Sim1-Cre-mediated *BDNF* deletion in the PVH	/	Hyperphagia, impaired thermogenesis and severe obesity	47
Neuron-specific deletion of *BDNF*	/	Hyperphagia and increased body weight	83
PDGFRA^{+} cell-specific deletion of *BDNF*	/	Enhances mitochondrial content and improves insulin sensitivity.	84
Muscle-specific deletion of *BDNF*	/	Impaired energy metabolism and insulin resistance	85
Muscle-specific deletion of *BDNF*	/	Insulin resistance and obesity	17
Muscle-specific deletion of *BDNF*	/	Inflammatory myopathy	86
Vascular-specific deletion of *NGF*	/	Impaired glucose homeostasis	87
BDNF knockout	/	Progresses to non-alcoholic steatohepatitis	88
p75NTR knockout	/	Serum cholesterol and triglyceride levels are decreased.	89
/	*Trkc* +/− or sympathetic neuron-specific deletion of *TRKC*	Exhibit impaired cold-induced thermogenesis and increased susceptibility to diet-induced obesity	16
/	DMH-specific deletion of *Ntrk2*	Hyperphagia, reduced energy expenditure and obesity	49
/	*p75NTR* Knockout	regulates glucose homeostasis and insulin sensitivity	90
/	*p75NTR* Knockout	Promotes energy expenditure and fatty acid oxidation while protecting against HFD-induced obesity	91
/	Adipocyte-specific deletion of *p75NTR*	Protects against HFD-induced obesity and insulin resistance	91
/	Adipocyte-specific deletion of *Ntrk2* (female mice)	Resistance to diet-induced obesity	83
/	*TrkB.T1* knockout	Impairs insulin secretion and glucose tolerance	92
/	Pancreas-specific deletion of *TrkA*	Impaired glucose homeostasis and insulin secretion	87

beige adipogenesis in white adipose tissue, thereby increasing UCP1 mediated energy expenditure and protecting against high fat diet induced obesity.[16]

Compared with NT-3, NGF may more accurately reflects the inflammatory and nutritional load of WAT. For instance, mouse white adipose tissue and human adipocytes both express and secrete NGF and its expression is highly sensitive to inflammatory mediators.[93] Tumor necrosis factor-α (TNF-α) and lipopolysaccharide (LPS) upregulate NGF expression, whereas norepinephrine, interleukin-6 (IL-6) and rosiglitazone (PPARγ agonist) suppress it.[93] These findings indicate that NGF may functions as a prototypical inflammation regulated adipokine that is continuously induced in the context of adipocyte hypertrophy and obesity associated low-grade inflammation. In particular, population-based cohort studies have shown that circulating NGF levels are significantly elevated in individuals with obesity and in women with metabolic syndrome and are positively correlated with BMI, body fat percentage, C-reactive protein (CRP) and IL-6.[29] However, recent studies have shown that NGF also suppresses the inflammatory response of human monocytes through TrkA signaling.[94] Notably, eosinophils produced NGF also promote sympathetic axonal growth in adipose tissue.[95] Moreover, adipocyte-derived nerve growth factor (NGF) can also modulate norepinephrine release and immune cell recruitment.[96] Thus, by acting on sympathetic and local immune cells within adipose tissue, NGF is poised to regulate norepinephrine release and immune infiltration, thereby indirectly influencing lipolysis, browning and lipid mobilization. This suggests that, within the chronic inflammatory milieu associated with obesity, the metabolic outcome may not be determined solely by the presence of NGF, but may instead be shaped by the balance between mature NGF and pro-NGF, as well as by the local inflammatory context.[97] Specifically, mature NGF can enhance macrophage phagocytic activity and growth factor secretion, whereas the precursor form, pro-NGF, may increase the release of neurotoxin.[97] Therefore, NGF may exert anti-inflammatory and tissue-reparative effects during the early stage, but in the later phase of chronic obesity, they may shift toward promoting pathological processes because of altered ligand processing and changes in receptor signaling balance. Interestingly, NTs receptors in adipose tissue, particularly p75NTR and TrkA, also play important roles in sensing peripheral nutritional status. For example, p75NTR upregulation in adipocytes disrupts p75NTR-Rab5 GTPase signals, impairs glucose transporter 4 (GLUT4) trafficking and thereby increases the risk of insulin resistance.[90] In addition, p75NTR upregulation in adipocytes directly inhibits PKA activity, attenuating lipolysis, fatty acid oxidation and thermogenesis, and rendering adipose tissue resistant to catecholamine stimulation.[91] However, blockade of NGF/TrkA signaling inhibits sympathetic neural plasticity within adipose tissue, thereby suppressing cold-induced browning of WAT.[98] This discrepancy may arise because p75NTR in adipose tissue can sense and regulate peripheral metabolism independently of NTs,[90] whereas TrkA is NTs dependent. However, the precise mechanisms remain unclear and require further elucidation.

In addition, a high-fat diet increases *BDNF* expression in mouse WAT while decreasing *Ntrk2* (the gene coding for TrkB) expression.[83,99-100] However, adipocyte-specific deletion of *BDNF* does not reduce *BDNF* expression in adipose tissue, suggesting that adipocytes are not the primary source of BDNF.[83] Notably, high-fat diet induced BDNF expression in WAT is abolished following macrophage depletion.[99] Moreover, BDNF expression is higher in the stromal vascular fraction than in isolated adipocytes, indicating that macrophages and stromal cells are the principal sources of BDNF in WAT.[83] Interestingly, *Ntrk2* is expressed in adipocytes and adipocyte-specific deletion of *Ntrk2* under a normal diet has no significant effect on body weight or lipid metabolism.[83] By contrast, under a high-calorie diet, adipocyte-specific Ntrk2 deletion reduces food intake and confers resistance to obesity.[83] Notably, in an aging model, pro-BDNF levels in epididymal white adipose

Table 3. Expression of neurotrophins and their receptors in different cell types and tissues

Cell/tissue type	Neurotrophins	Receptor	References
DMH	BDNF	TrkB, p75NTR	40,43,50
PVH	BDNF	TrkB	41,45
VMH	BDNF	TrkB	43
ARH	/	TrkB, p75NTR	46,51
Hippocampus	BDNF, NT-3	TrkB, TrkC	101
Amygdala	BDNF	TrkB, TrkC	102
Cerebellar external granule layer	NT-3	/	103
Purkinje layer of cerebellar primordia	/	TrkC	103
Astrocytes	NGF, BDNF, NT-3	TrkB, TrkC	104
Pericytes	NGF, BDNF, NT-3	/	104
Retinal ganglion cells	NGF, BDNF, NT-3	TrkA, TrkB, p75NTR	105
Müller cells	NGF, BDNF, NT-3	TrkB, TrkC	106
Pancreatic β cells	NGF	TrkA, p75NTR	87,107
Pancreatic vascular cells	NGF	/	87
White adipocytes	NGF, BDNF, NT-3	TrkA/B, p75NTR	16,108
Brown/beige adipocytes	NGF, BDNF, NT-3	TrkA/B, p75NTR	16,109
Monocytes/macrophages	NGF, BDNF, NT-3/4	TrkA/B/C, p75NTR	110-111
Perivascular adipose tissue	BDNF	TrkB	112
Liver	NGF	p75NTR	89
Myocytes	BDNF	p75NTR	113
Enteric glia cells	NGF	TrkA	114
Epithelial cells/submucosal neurons	NGF	TrkA, p75NTR	115
Airway epithelial cells	NGF, BDNF	/	116
Eosinophils	NGF, BDNF, NT-3	TrkA, TrkB, p75NTR	116-118
Mast cells	NGF, BDNF, NT-3	TrkA/B/C, p75NTR	96,119
Dendritic Cells	/	TrkA/B, p75NTR	120
B cells	NGF	/	121
Oocytes/granulosa cells (ovary)	NGF, BDNF, NT-4	TrkB	96,122
Testis	NGF	TrkA, p75NTR	123

tissue (eWAT) are progressively increased in PDGFRα$^+$ adipose progenitor cells accompanied by reduced sympathetic innervation, diminished mitochondrial content and heightened local inflammation.[84] Selective knockdown of *BDNF* in eWAT progenitor cells enhances sympathetic innervation and mitochondrial content and improves insulin sensitivity.[84] Furthermore, in patients with coronary heart disease, *BDNF* and its receptor *TrkB* are also expressed in perivascular adipose tissue (PVAT) and are associated with vascular dysfunction and local inflammation suggesting that BDNF in WAT/PVAT may be involved in regulating angiogenesis and the vascular inflammatory microenvironment.[112] These findings indicate that BDNF and pro-BDNF are produced primarily by adipose tissue macrophages, adipose progenitor cells and perivascular cells and together contribute to sympathetic innervation, angiogenesis and local inflammatory remodeling within adipose tissue, thereby influencing patterns of adipose expansion and the capacity for lipid mobilization. Furthermore, the NTs/immune cell axis may serve as a regulatory node in obesity related immune metabolic dysfunction by modulating local inflammation, immune cell infiltration and sympathetic nerve remodeling. However, systematic studies of their roles in lipolysis, adipose browning and lipid droplet deposition are still lacking. Therefore, further clarification using tissue-specific or cell lineage specific manipulations is required in future studies.

Skeletal muscle and neurotrophins. Skeletal muscle is not only a major site for glucose and fatty acid utilization but also an important source of various myokines.[124-125] Notably, NTs, particularly BDNF, have been identified as contraction induced myokines and their expression in skeletal muscle is closely linked to exercise status and energy demand.[126-127] (Figure 4B) In vitro experiments have demonstrated that electrically stimulated contractions of L6 myotubes markedly upregulate *BDNF* transcription and protein levels.[127] Interestingly, exogenous BDNF treatment increases phosphorylation of AMP-activated protein kinase (AMPK) at Thr172 and its downstream target acetyl coenzyme A carboxylase β (ACCβ) at Ser79, thereby enhancing the rate of fatty acid oxidation.[127] Moreover, inhibition of AMPK activity almost completely abolishes the BDNF induced increase in fatty acid oxidation.[127] These findings indicate that BDNF in skeletal muscle directly reprograms the substrate utilization pattern of myocytes by activating the AMPK-ACC axis, shifting an energy deficient state toward a metabolic phenotype that relies predominantly on fatty acids as fuel.

Interestingly, under glucose deprivation, phosphorylation of AMPK and

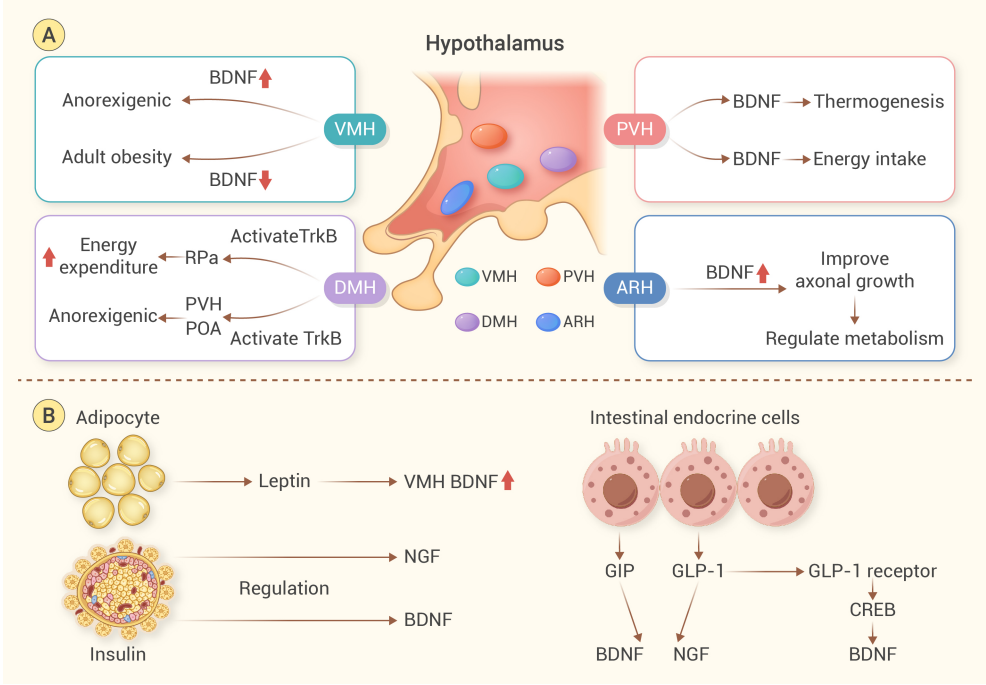

Figure 3. Neurotrophins in the hypothalamus sense nutritional status and interact with metabolic hormones. (A) Neurotrophins sense nutritional cues in key hypothalamic nuclei and regulate host lipid metabolic homeostasis. (B) Metabolic hormones regulate neurotrophins expression/levels.

CREB is markedly increased in C2C12 myotubes, accompanied by upregulation of *BDNF* and *PGC-1α* expression.[85] Overexpression of *CREB* further augments *BDNF* expression in C2C12 cells.[85] Notably, in female mice with muscle-specific *BDNF* knockout, fasting reduces *PGC-1α* expression, mitochondrial content and fatty acid oxidation-related gene expression in skeletal muscle, leading to decreased energy expenditure and suggesting that the BDNF-AMPK-CREB-PGC-1α axis functions as a transcriptional switch coupling metabolic demand to gene expression.[85] By contrast, muscle-specific *BDNF* deletion has no significant effect on body weight in male mice.[85] Thus, muscle derived BDNF appears to act as a female-specific myokine that regulates metabolic reprogramming during fasting. In addition, during the post-exercise recovery period, *BDNF* expression in skeletal muscle is increased and induces PPARδ transcription via the Ca^{2+}/calmodulin-dependent protein kinase kinase 2 (CaMKK2)-AMPK pathway, thereby promoting metabolic reprogramming, mitochondrial remodeling and muscle recovery.[128] Thus, BDNF reprograms skeletal muscle lipid metabolism through the AMPK-CREB-PGC-1α/PPARδ axis.

Notably, under conditions of chronic lipid overload or high-fat diet feeding, muscle derived BDNF can further optimize skeletal muscle lipid handling by regulating mitochondrial quality control.[17] For instance, BDNF promotes mitochondrial fission and clearance in skeletal muscle.[17] By contrast, *BDNF* deletion in myotubes attenuates fatty acid induced mitochondrial fission and mitophagy, leading to mitochondrial elongation and impaired lipid handling.[17] Consistently, in female muscle-specific BDNF knockout mice, high-fat diet feeding results in defective mitochondrial fission and mitophagy in skeletal muscle, accumulation of damaged mitochondria, reduced energy expenditure and exacerbated insulin resistance.[17] Conversely, administration of the BDNF mimetic 7,8-dihydroxyflavone increases mitochondrial content and enhances mitochondrial fission and mitophagy in skeletal muscle.[17] Thus, BDNF acts as an important myokine for maintaining mitochondrial quality and function and its suppression in obesity may contribute to metabolic impairment.

Pancreas islet and neurotrophins. Within the pancreatic islets, β cells are not only the primary source of insulin but also both a source and a target of NTs, among which the roles of NGF and BDNF are the best characterized.[92,96,129-130] (Figure 4C) For example, under conditions of elevated glucose or membrane depolarization, endogenous NGF secretion from β cells is markedly increased, indicating that its release is regulated by nutrient status and electrical activity.[131-132] Interestingly, short-term NGF treatment enhances the insulin secretion index under both low and high glucose conditions, whereas anti-NGF antibodies or the Trk receptor inhibitor K252a significantly suppress glucose-stimulated insulin secretion (GSIS).[132] Mechanistically, NGF increases voltage-dependent Ca^{2+} channel current density in β cells and prolongs Ca^{2+} influx during the action potential plateau, thereby amplifying exocytotic responses to a given glucose stimulus.[132] Furthermore, during development and functional maturation, NGF promotes the transition of β cells from an immature, lipid-preferring phenotype to a mature, glucose-responsive phenotype by increasing GLUT2 expression and its membrane localization, thereby enhancing glucose uptake and glucokinase activity.[130] Thus, the endogenous NGF/TrkA autocrine circuit in β cells, by coordinately regulating Ca^{2+} channels and nutrient-sensing components such as GLUT2 and glucokinase, enhances β-cell sensitivity to glucose load and secretory efficiency and constitutes one of the core mechanisms underlying the fine tuning of GSIS.

In addition to the β-cell autocrine loop, islet vascular smooth muscle cells and intra-islet pericytes are also important sources of NGF.[87] Tissue-specific deletion of NGF or TrkA in islets or blockade of TrkA signaling impairs glucose tolerance and insulin secretion in mice.[87] However, glucose stimulation induces NGF release from vascular smooth muscle cells, which activates TrkA on β cells, triggers F-actin remodeling and promotes recruitment of insulin granules to the submembrane region, constituting a key step in stimulus secretion coupling.[87] Moreover, glucose stimulation elicits a transient burst of NGF release from islets and inhibition of TrkA/p75NTR increases basal insulin secretion while blunting the GSIS response, suggesting that endogenous NGF restrains basal secretion while amplifying signaling for stimulated secretion.[133] Thus, glucose functions not only as a metabolic substrate for β cells but also as a signal that recruit islet vascular smooth muscle cells and pericytes to provide NGF, thereby activating TrkA signaling, remodeling the cytoskeleton and granule distribution and ultimately regulating insulin secretion.[87,133]

Interestingly, in parallel with NGF/TrkA signaling, BDNF-TrkB signaling provides a second NTs input to β cells. For instance, mouse and human pancreatic β cells almost exclusively express the *TrkB.T1* (a TrkB receptor lacking kinase activity), but not the *TrkB.FL* (a full-length receptor with an extracellular ligand binding domain and an intracellular kinase domain used for signaling).[92] Under low glucose conditions, BDNF alone can induce intracellular Ca^{2+} signaling and insulin release in β cells and in the presence of glucose it synergistically amplifies GSIS.[92] Conversely, *TrkB.T1* KO results in attenuated GSIS and impaired glucose tolerance, while insulin sensitivity remains largely normal, further supporting the notion that BDNF-TrkB.T1 signaling functions as a second NTs input that fine-tunes nutrient sensing and Ca^{2+} dependent secretion in β cells.[92] Moreover, mice with skeletal muscle-specific *BDNF* deletion exhibit GSIS attenuation and impaired glucose tolerance similar to those observed in *TrkB.T1* KO during glucose loading, whereas exogenous BDNF partially improve glucose control and islet function.[92] These findings suggest that skeletal muscle derived BDNF and islet TrkB.T1 may together form a cross-organ axis that relays nutritional and physical activity status to coordinate insulin secretory responses.

Liver and neurotrophins. The liver is not only a central hub for lipid, bile acid and cholesterol metabolism but also expresses NTs and their receptors. Notably, NTs expression is markedly remodeled under conditions such as lipotoxicity and cholestasis, suggesting may a functional coupling between lipid and bile acid load and NTs signaling.[134-136] (Figure 4D) For instance, treatment of AML-12 mouse hepatocytes with BDNF activates AMPK, upreg-

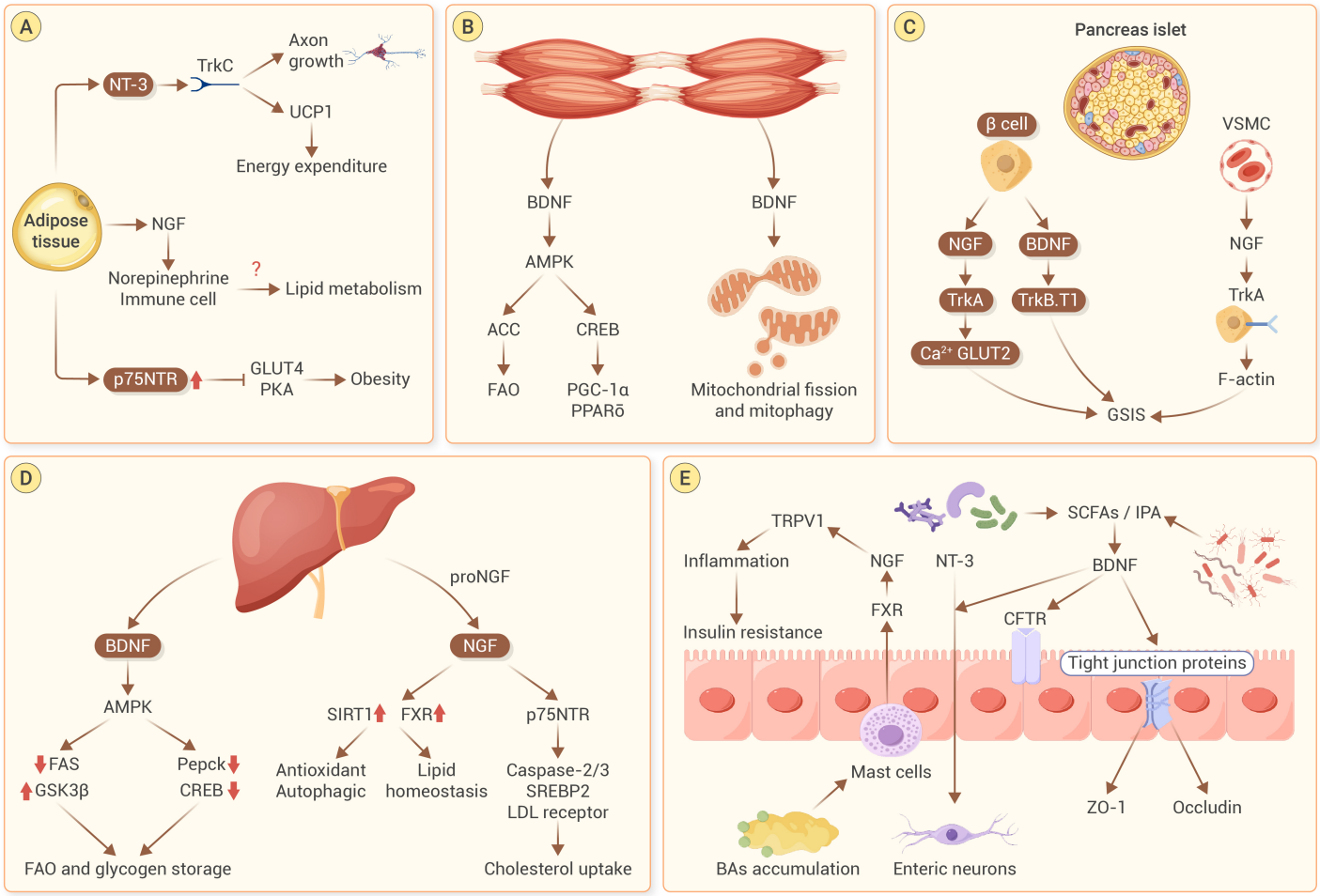

Figure 4. Neurotrophins sense nutritional cues in peripheral tissues and regulate host lipid homeostasis. (A) Adipose tissue mediates lipid metabolic regulation through NT-3/TrkC, p75NTR and NGF signaling. (B) Skeletal muscle mediates BDNF induced activation of AMPK signaling and enhances mitochondrial quality. (C) BDNF and NGF sense glucose levels and regulate insulin secretion in pancreatic islets. (D) BDNF activates hepatic AMPK signaling, whereas NGF exerts dual effects on hepatic lipid metabolism. (E) Neurotrophins regulate intestinal lipid metabolism, while the gut microbiota also modulates neurotrophins levels.

ulates glycogen synthase kinase 3β (GSK3β), inhibits the key fatty acid synthase (FAS) and downregulates phosphoenolpyruvate carboxykinase (Pepck) and CREB activity.[134] This indicates that BDNF simultaneously inhibit gluconeogenesis and lipogenesis, promote fatty acid oxidation and glycogen synthesis, and shift hepatocytes from a gluconeogenic/lipogenic state to a postprandial-like state. Notably, this state is characterized by enhanced fatty acid oxidation and increased glycogen storage.[134] Furthermore, BDNF KO mice are more prone to spontaneously develop non-alcoholic steatohepatitis (NASH), accompanied by dysregulated expression of genes involved in hepatic lipid metabolism and inflammation, as well as increased neutrophil infiltration.[88] Notably, clinical cohort studies have also reported elevated serum BDNF levels in patients with non-alcoholic fatty liver disease (NAFLD), which are thought to reflect a compensatory NTs response to metabolic liver injury.[137] These findings further support a key protective role of BDNF in maintaining hepatic lipid homeostasis. Interestingly, BDNF also increases hepatic expression of core circadian clock genes such as *Bmal1* while reducing *Cry1* expression.[134] We therefore speculate that, in addition to reprogramming hepatic energy and lipid metabolism, BDNF may modulate the liver clock, introducing a temporal dimension to its metabolic responses to the feeding-fasting cycle and thereby improving nutrient utilization efficiency and reducing the risk of lipotoxicity.

In contrast, under conditions of cholestasis and elevated bile acid load, NGF expression in hepatic parenchymal cells is markedly upregulated and closely associated with systemic and intrahepatic inflammation.[135] Notably, exogenous NGF administration or endogenous NGF overexpression alleviates liver injury and cholestasis and enhances antioxidant capacity.[135] Mechanistically, NGF upregulates SIRT1 and FXR in hepatocytes, thereby increasing antioxidant capacity and autophagic flux and protecting hepatocytes from injury.[138-139] SIRT1 and FXR also regulate hepatic fatty acid oxidation, cholesterol and bile acid synthesis and represent key nodes in therapeutic strategies for NAFLD.[140] Thus, NGF may improve hepatic lipid homeostasis by enhancing autophagy and anti-inflammatory and antioxidant responses via SIRT1 and FXR, thereby mitigating bile acid and lipotoxicity induced hepatocellular damage. However, the NGF/proNGF-p75NTR signaling axis also directly regulates hepatocellular cholesterol uptake and lipid related gene expression through activation of the caspase-2/3-sterol regulatory element binding protein 2 (SREBP2)-low density lipoprotein receptor (LDLR) pathway.[89] Consistent with this, p75NTR deleted mice exhibit reduced expression of hepatic lipid metabolism genes and decreased serum cholesterol and triglyceride levels,[89] indicating that NGF/p75NTR has a dual role in regulating hepatic lipid homeostasis: on the one hand, it exerts protective effects under stress conditions, whereas on the other, it may promote cholesterol accumulation in chronic metabolic disorders. Overall, the apparently dual roles of p75NTR are not intrinsically contradictory at the molecular level; rather, they underscore its ability to engage distinct signaling modules in adipocytes, hepatocytes, and hepatic stromal cells. For example, p75NTR suppresses cAMP/PKA-dependent lipolysis and thermogenesis in adipose tissue, activates the caspase-2/3-SREBP2-LDLR axis to promote cholesterol metabolism in hepatocytes, and participates in cell differentiation, antioxidant defense and autophagy during liver injury.[89,91,135,138-139,141] Accordingly, p75NTR should be considered a metabolic therapeutic target that requires precise modulation according to tissue context, disease stage, and ligand bias, rather than a receptor amenable to simple systemic activation or inhibition in a unidirectional manner.

The intestine and neurotrophins. The intestine not only serves as a central hub for the digestion and absorption of dietary lipids and the enterohepatic circulation of bile acids, but also expresses multiple NTs, including NGF, BDNF and NT-3,[142-144] thereby playing a critical role in the regulation of nutritional signaling. (Figure 4E) For instance, NT-3 promotes the survival and differentiation of enteric neurons and is critical for maintaining normal intestinal peristalsis.[142] Furthermore, BDNF is also a key NTs within the enteric nervous system that regulates the excitability of excitatory and inhibitory motor neurons innervating intestinal smooth muscle in response to physiological stimuli.[143] Mice with impaired BDNF or TrkB signaling exhibit disordered gastrointestinal motility and impaired cholinergic and nitrergic neurotransmission.[143] Conversely, exogenous BDNF modulates smooth muscle excitability and the activity of enteric neural circuits, thereby finely tuning peristaltic reflexes.[143] These changes influence the residence time of fat emulsions in the intestinal lumen and their contact area with the intestinal mucosa, which are key upstream determinants of lipid absorption efficiency. Notably, BDNF also enhances cystic fibrosis transmembrane conductance regulator (CFTR) dependent bicarbonate and chloride secretion in the intestinal epithelium, promotes mucus release and mucosal hydration and helps maintain an appropriate environment and pH.[143] These changes influence pancreatic lipase activity, the extent of fat emulsification and the contact of lipid droplets with the villous surface, thereby indirectly modulating lipid absorption. Moreover, in mice with epithelial specific deletion of BDNF, tight junction proteins (such as *ZO-1* and *occludin*) are downregulated, barrier function is impaired and susceptibility to inflammation and increased permeability is increased, which in turn contributes to lipid metabolic disorders.[143]

Notably, impaired bile acid absorption can lead to excessive accumulation of bile acids in the colonic lumen. During this process, intestinal mucosal mast cells may serve as primary cellular targets for bile acid signaling.[145] Specifically, bile acids directly stimulate mucosal mast cells, activating the FXR-mitogen activated protein kinase kinase (MKK)3/6-p38MAPK-NF-κB signaling cascade to upregulate NGF expression and promote its secretion.[145] Inhibition of FXR signaling almost completely abolishes this NGF response, indicating that bile acid-FXR-NGF signaling is a key mechanism by which mucosal mast cells sense bile acid load. The resulting increase in intestinal NGF under bile acid overload further acts on transient receptor potential vanilloid 1 (TRPV1), leading to NGF dependent visceral hypersensitivity, as observed in diarrhea-predominant irritable bowel syndrome.[145] Notably, visceral hypersensitivity is frequently accompanied by chronic inflammation, which in turn promotes insulin resistance.[146] Thus, excessive luminal bile acid accumulation may promote systemic inflammation via FXR-NGF signaling and consequently increase the risk of obesity associated insulin resistance.

Furthermore, the gut microbiota comprises trillions of microorganisms residing in the gut. They not only directly participate in the digestion, absorption and transformation of dietary lipids, but also influence systemic metabolism by producing diverse bioactive metabolites, thereby constituting a key factor in the development of obesity and related metabolic diseases.[5,147-148] Interestingly, recent studies have shown that the gut microbiota not only promotes neuronal regeneration and repair but also plays a crucial role in regulating NTs levels (Figure 4E).[149-150] For instance, in germ-free mice or treated with antibiotics mice, *BDNF* expression in the hippocampus, amygdala and cortex is reduced.[151-153] However, administration of probiotics restores *BDNF* expression,[154-155] indicating a reversible regulatory relationship between the gut microbiota and BDNF signaling. Mechanistically, the gut microbiota primarily regulates NTs levels through their metabolites. In particular, microbial short-chain fatty acids (SCFAs), such as butyrate, can stimulate the secretion of BDNF.[156] Interestingly, SCFAs also promote fatty acid oxidation, inhibit lipogenesis and enhance insulin sensitivity.[148] Furthermore, the gut microbiota is a key regulator of tryptophan metabolism and the level of its metabolite indole-3-acetic acid (IPA) is positively correlated with serum BDNF concentrations.[157] This effect may be attributed to the ability of IPA to enhance BDNF secretion in neuronal cells.[157] Interestingly, IPA not only activates PPARα signaling to inhibit lipid synthesis and improve glucose tolerance and insulin sensitivity, but also ameliorates neuronal injury.[158-159] Thus, the gut microbiota-SCFA/IPA-NTs signaling cascade, in concert with lipid metabolic pathways, may represent a key molecular hub through which the gut microbiota interface with neurotrophic networks and concomitantly improve host lipid metabolism. Interestingly, bile acids in patients with depression can suppress BDNF transcription by activating FXR.[160] However, it remains unclear whether this effect is driven by alterations in the bile acid profile secondary to gut microbial dysbiosis. In addition, impaired intestinal bile acid absorption can increase NGF levels, further supporting the notion that disrupted bile acid composition modulates NTs expression. Therefore, future studies are needed to systematically evaluate the effects of distinct bile acid species and bile acid-exposure thresholds on NTs.

NEUROTROPHINS SIGNALING AND GLUCAGON-LIKE PEPTIDE-1 IN METABOLIC REGULATION: DISTINCTION, CONVERGENCE AND INTEGRATION

GLP-1 is an endocrine hormone primarily produced by enteroendocrine L cells in the intestinal mucosa, pancreatic α-cells and neurons in the nucleus tractus solitarius, secreted in response to nutrient intake and neuroendocrine stimulation.[161-162] Notably, GLP-1-based therapy is currently a highly effective treatment option for patients with type 2 diabetes and obesity, as it effectively improves glycemic control and promotes weight loss.[162] Mechanistically, GLP-1 primarily exerts its effects by activating the GLP-1 receptor, a class B1 G protein-coupled receptor (GPCR), thereby triggering the intracellular cAMP signaling cascade, and regulates insulin secretion, gastric emptying, appetite and energy metabolism.[161-162] Classical NTs, including BDNF, NGF and NT-3, primarily mediate signal transduction through the Trks receptor family and p75NTR. Therefore, they belong to a molecular signaling system distinct from that of GLP-1.

Although GLP-1 is not classical NTs, accumulating evidence indicates that GLP-1 exhibits distinct neurotrophic-like effects, enabling the translation of nutrient sensing into adaptive remodeling of neural circuits and thereby influencing metabolic homeostasis. For example, GLP-1 receptor activation can engage intracellular programs that overlap with those of NTs, including the cAMP/PKA/CREB and PI3K/AKT signaling pathways,[61,163] thereby linking nutrient-derived signals to more sustained changes in neuronal excitability, synaptic plasticity, and behavioral output. Specifically, GLP-1 exerts neuroprotective effects in mouse hippocampal HT22 cells through the cAMP/CREB/BDNF signaling pathway.[61] Notably, activation of central GLP-1 receptors enhances sympathetic nerve activity and brown adipose tissue thermogenesis in mice.[164] Similarly, BDNF and NT-3 exert comparable effects.[16,165] These further suggest that GLP-1 and neurotrophic factor signaling pathways may functionally converge at the levels of sympathetic output, adipose tissue innervation and thermogenesis/fatty acid oxidation. Furthermore, BDNF cells in the medial nucleus tractus solitarius lie downstream of GLP-1 receptor signaling and constitute a critical node mediating the anorectic and weight-reducing effects of GLP-1 receptor agonists.[166] These findings suggest that the anti-obesity effects of GLP-1 are mediated, not only through GPCR signaling but also through recruitment of BDNF centered neurotrophic module, which may translate endocrine input into more sustained satiety, enhanced fatty acid oxidation, and reprogramming of energy balance.

By contrast, other NTs, such as NGF and NT-3, appear to extend this framework primarily through parallel or peripheral mechanisms, including pancreatic regulation, adipose sympathetic innervation and thermogenesis,[16,96] rather than serving as equally well-established direct downstream mediators of GLP-1 signaling. Therefore, GLP-1 should also be regarded a metabolic hormone with neurotrophic-like effects that partially converges on BDNF centered neurotrophic network to regulate energy balance.

CLINICAL APPLICATION PROSPECTS AND TRANSLATIONAL STRATEGIES FOR NEUROTROPHINS

NTs and their receptors play critical roles in mediating the transmission of nutritional signals between the central nervous system and peripheral tissues, as well as in regulating lipid metabolism. (Figure 5) In particular, TrkB/TrkC mediated signaling by BDNF and NT-3 promotes energy expenditure, fat mobilization and lipid oxidation, whereas p75NTR exerts inhibitory effects on lipolysis and thermogenesis, thereby constituting a potential interventional signaling axis. Notably, although GLP-1 receptor agonists have substantially advanced the treatment of human obesity, they still present

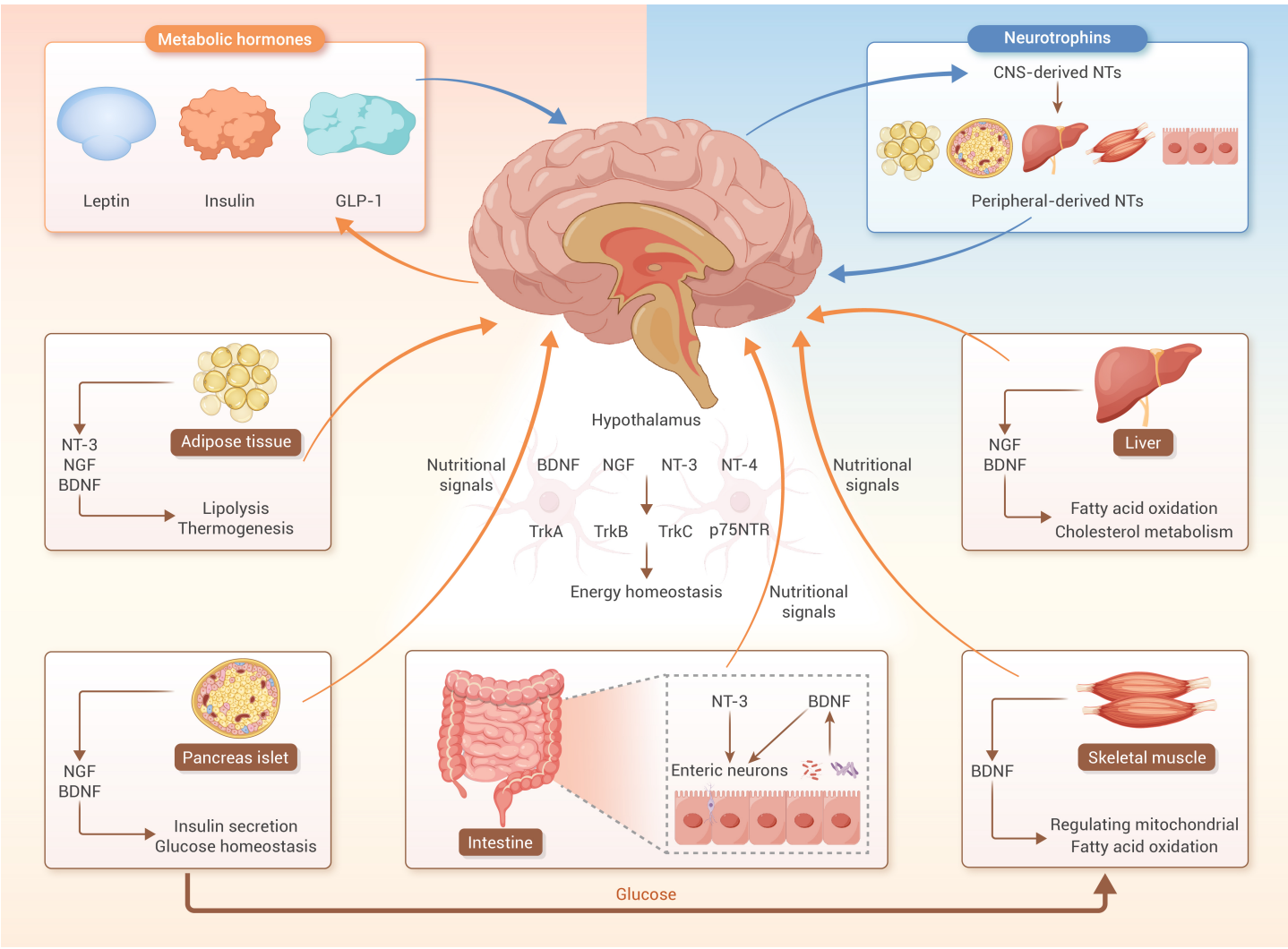

Figure 5. Neurotrophins mediate nutritional signaling between the central nervous system and peripheral tissues

important clinical limitations.[167-168] Moreover, combination strategies involving GLP-1-based agents may improve therapeutic efficacy in individuals with poor treatment responsiveness and in patients with complex metabolic phenotypes.

Particularly, from a translational perspective, NTs targeted strategies may be more appropriately positioned as complementary, rather than competing, approaches to GLP-1 receptor agonist-based therapies. In the current clinical landscape, GLP-1 centered interventions remain the most extensively validated pharmacological framework for obesity treatment, particularly with respect to reducing food intake and body weight. By contrast, modulation of NTs pathways may offer additional therapeutic value in domains that are less comprehensively addressed by GLP-1 alone, including the enhancement of energy expenditure, reinforcement of adipose sympathetic innervation, promotion of adipose neuroplastic remodeling, and improvement of metabolic responsiveness in partial responders or non-responders. Within this framework, TrkB/TrkC activation or p75NTR inhibition should be regarded not primarily as stand-alone alternatives, but rather as candidate adjunctive strategies that could expand the therapeutic ceiling of existing GLP-1 based treatments. Such a complementary model is likely to be more clinically realistic and may help guide the development of future precision combination therapies for obesity and related metabolic disorders. Thus, targeting NTs mediated regulation of lipid metabolism may have important clinical value for the prevention and treatment of obesity (Figure 6).

Activation and delivery targeting Trk receptors

Mechanistically, Trk receptors (particularly TrkB and TrkC) occupy key nodes at the interface between neurotrophic signaling, sympathetic outflow and thermogenesis in adipose tissue and skeletal muscle, therefore may represent one of the most direct pharmacological targets for metabolic intervention. (Figure 6A) For instance, BDNF in hypothalamic and skeletal muscle compartments improves lipid metabolism by activating TrkB. In the obesity model with a high-fat diet, injecting BDNF in the hypothalamus can also reduce body weight, indicating that the central BDNF-TrkB axis has intrinsic pharmacological potential as an anti-obesity target.[48] Notably, multiple strategies for exogenous TrkB activation have been validated in animal studies, including recombinant BDNF protein, BDNF-derived peptides and small molecule TrkB agonists. The BDNF mimetic 7,8-dihydroxyflavone, administered in the drinking water, activates skeletal muscle TrkB, increases energy expenditure and protects mice from high-fat diet induced obesity and insulin resistance.[17] This effect is abolished in skeletal muscle-specific *TrkB* knockout mice,[85] suggesting that its anti-obesity action is TrkB dependent.

In contrast, the NT-3-TrkC axis appears to exert particularly strong regulatory effects within adipose tissue.[16] Hence, TrkC targeted drugs are especially attractive candidates for development as adipose targeted peripheral agonists. By mimicking the endogenous pathway whereby adipose-derived NT-3 activates TrkC to promote thermogenesis, such agents could bypass the blood brain barrier and avoid many neuropsychiatric safety concerns associated with central administration. Notably, recent studies on obesity-associated adipose denervation and adipose-targeted adipocyte-tropic adeno-associated virus (AAV)-NTs/Trk gene therapy indicate that earlier correction of adipose nerve axis dysfunction yields more pronounced therapeutic effects.[169] These findings provide both a key time window and a tissue-specific conceptual framework for the future development of adipose specific TrkC activation strategies or gene therapies.

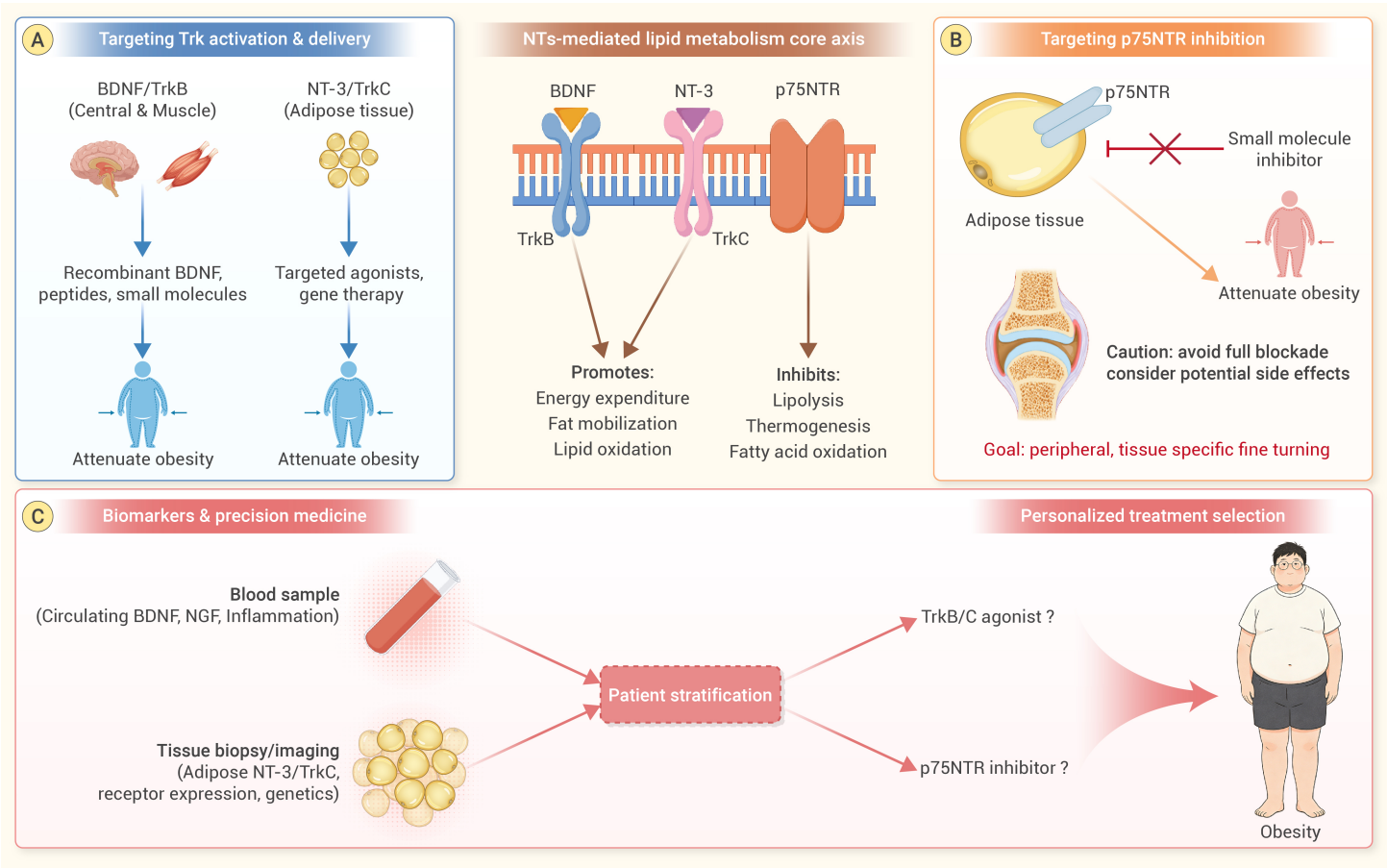

Figure 6. Clinical application strategies targeting neurotrophins and their receptors for the treatment of obesity. (A) Activation and delivery targeting Trk receptors. (B) Inhibition targeting p75NTR (C) Biomarkers and patient stratification.

Inhibition targeting p75NTR

Unlike TrkB/C receptors, which primarily convey signals that enhance energy expenditure, p75NTR functions as an inhibitory gatekeeper within neurotrophic signaling networks. (Figure 6B) For instance, upregulation of p75NTR in adipocytes suppresses lipolysis, fatty acid oxidation and thermogenesis, whereas adipocyte-specific deletion of *p75NTR* prevents weight gain and insulin resistance.[91] Thus, p75NTR represents a highly druggable target. Notably, the small-molecule p75NTR modulator LM11A-31, administered orally in the context of neurodegenerative disease, attenuates degenerative signaling, preserves synaptic integrity and neuronal survival in multiple Alzheimer's disease models and has progressed to clinical trials.[170] Although these trials primarily focused on neurodegenerative diseases, from a metabolic perspective they at least demonstrate that long term oral administration of p75NTR targeting small molecule drugs is feasible and associated with a favorable safety profile in the general population. These findings provide an important reference for the future development of p75NTR modulators aimed at metabolic regulation. Moreover, blockade of p75NTR does not depend on elevating BDNF or NT-3 levels, making it theoretically particularly amenable to small molecule drug development.

However, the clinical translation of p75NTR targeted therapies must fully take into account the adverse effects observed with anti-NGF antibodies. Specifically, anti-NGF monoclonal antibodies such as tanezumab and fulranumab, although exhibiting robust analgesic efficacy in osteoarthritis pain, have been associated in multiple clinical trials with rapid osteoarthritis progression and increased risk of adverse joint outcomes.[171] Therefore, future p75NTR-targeting strategies should preferentially employ peripheral biased, tissue specific small molecule modulators that finetune receptor activity rather than completely block it, so as to avoid irreversible disruption of the physiological functions of NGF/p75NTR in bone and sensory nerves.

Biomarkers and patient stratification

Notably, integrating NTs into precision medicine for obesity and lipid metabolism disorders will likely require biomarker and patient stratification strategies centered on NTs levels and receptor status. (Figure 6C) Although current clinical data on circulating BDNF in metabolic diseases remain somewhat inconsistent, several overarching patterns have emerged. On the one hand, meta-analyses indicate that serum and plasma BDNF concentrations are significantly lower in patients with type 2 diabetes or impaired glucose metabolism than in healthy controls and that this reduction is strongly correlated with poor glycemic control.[28,64,172] On the other hand, cohort analyses in populations with obesity or metabolic syndrome have reported decreased[23] or unchanged[24,173] serum BDNF levels, as well as elevated levels.[174] These observations suggest that circulating BDNF levels need to be interpreted in the context of disease stage, comorbid complications and genetic background in order to clarify their relationship with obesity-related metabolic disorders.

Furthermore, the roles of NGF and other NTs in metabolic syndrome and obesity are similarly complex.[29,175-176] In the early stages of metabolic syndrome, circulating NGF levels are often elevated, in parallel with low grade inflammation and immune activation and may contribute to adipose tissue remodeling, vascular responses and neuroimmune interactions.[175] As the disease progresses, some patients exhibit relative depletion of NGF and other NTs, suggesting that NTs deficiency may contribute to vascular, neural and metabolic complications.[175] Nevertheless, these observations offer an important implication for clinical application: peripheral blood BDNF and NGF concentrations could serve as dynamic indicators of NTs load and compensatory status. When integrated with inflammatory markers and metabolic phenotypes, they may enable a coarse stratification of patients into subgroups characterized primarily by compensatory neurotrophic upregulation versus NTs deficiency.

Compared with serum or plasma levels alone, tissue NTs concentrations and receptor expression patterns are likely to be more informative for selecting NTs targeted therapies for obesity. On the one hand, mice with enhanced NT-3 or TrkC signaling in adipose tissue exhibit denser sympathetic innerva-

tion and increased thermogenesis, whereas *TrkC* deletion or adipose neuropathy are associated with reduced thermogenic capacity and an increased risk of obesity.[16,169] In the future, such alterations in the adipose NT-3/TrkC axis may be assessable through adipose tissue biopsy and advanced imaging techniques. On the other hand, expression profiles of TrkB/TrkC and p75NTR in the central nervous system and adipose tissue, together with related gene polymorphisms, may serve as genetic and molecular markers for predicting sensitivity to TrkB/TrkC agonism or p75NTR blockade, thereby supporting individualized treatment decisions. In summary, biomarker panels centered on NTs levels and receptor status, combined with population stratification strategies, are expected to improve NTs targeted therapies for obesity and related lipid metabolism disorders and thereby accelerate the translation from mechanistic insight to clinical application.

CONCLUSIONS AND PERSPECTIVES

Collectively, NTs and their receptors constitute a regulatory network that links the central nervous system to multiple metabolic target organs. One end of this network engages nutrient sensing and sympathetic-integrating hypothalamic nuclei, including ARC, VMH, PVH and DMH, while the other extends to key lipid metabolizing organs such as the liver, adipose tissue, skeletal muscle, pancreatic islets and intestine. By regulating neuronal excitability, axonal integrity and synaptic plasticity, BDNF, NGF, NT-3 and their receptors not only participate in neural development and repair but also largely determine sympathetic output intensity, thresholds for fat mobilization and thermogenesis, hepatic lipid load and the homeostasis of the intestinal barrier and bile acid circulation. Thus, NTs mediated nutrient sensing regulates lipid metabolism according to a structural, network level logic, providing a new conceptual dimension for understanding obesity and lipid metabolic disorders. However, translating these mechanistic insights into broadly applicable clinical strategies still faces several major challenges. NTs pathways are highly pleiotropic, so any long-term intervention must carefully balance metabolic benefit against neuropsychiatric, sensory and musculoskeletal safety. Cross-species differences and etiological heterogeneity also constrain the explanatory power of a single pathway for human obesity and lipid metabolic disorders, suggesting that signaling via NTs and Trk/p75 receptors is more likely to function as a potentiating, phenotype-specific adjunct to existing options such as GLP-1 receptor agonists[177] and Sodium glucose cotransporter 2 (SGLT2) inhibitors[178] rather than as a replacement for first-line therapy. Moreover, central nervous system targeted delivery, peripheral tissue specificity and the feasibility and cost-effectiveness of chronic administration still need to be further validated and optimized in large-animal models and early phase clinical trials.

In this context, future research should delineate the relative contributions of NTs and their receptor-mediated pathways to feeding regulation, sympathetic output, adipose thermogenesis, hepatic lipid metabolism and gut-brain integration. Second, the mechanisms by which mature NTs and their precursors, distinct Trk receptor subtypes, and p75NTR jointly shape tissue-specific and context-dependent metabolic outcomes remain to be clarified. Furthermore, future studies should also determine whether peripherally restricted or tissue-specific targeting strategies can improve metabolic function while minimizing adverse effects involving the central and sensory nervous systems. Notably, clinical assessment should not rely solely on body weight and circulating lipid levels, but should also incorporate organ-specific fat deposition, adipose tissue innervation, brown/beige adipose activity, and sympathetic function to determine whether the intervention has truly remodeled the neuro-metabolic network. In parallel, robust patient stratification strategies and local biomarkers are needed, as circulating NTs levels are strongly influenced by sample type, analytical methodology, and diurnal variation, and therefore do not reliably reflect local neurotrophic signaling status. Ultimately, resolving these issues will be essential for advancing neurotrophic signaling from mechanistic association to therapeutic translation. With improved mechanistic resolution, biomarker frameworks, and patient stratification strategies, NTs and their receptors may emerge as verifiable and combinable therapeutic targets for obesity, while laying the foundation for a broader conceptual framework of metabolic neurotrophic medicine.

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AUTHOR CONTRIBUTIONS

M.Z.: Writing-original draft, Conceptualization, Visualization, Writing-review & editing. **J.Y.:** Conceptualization, Supervision, Writing-review & editing. **Q.H.:** Supervision, Visualization, Writing-review & editing. **Y.Y.:** Supervision, Visualization, Writing-review & editing.

DECLARATION OF INTERESTS

Yulong Yin is an Editorial Board member of The Innovation Nutrition and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.

DATA AND CODE AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.