

The role of leptin in central nervous system diseases

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Leptin is a peptide hormone produced by adipose tissue and acts in brain centers to control critical physiological functions. Leptin receptors are especially abundant in the hypothalamus and trigger specific neuronal subpopulations, and activate several intracellular signaling events, including the JAK/STAT, MAPK, PI3K, and mTOR pathway. Although most studies focus on its role in energy intake and expenditure, leptin also plays a critical role in many central nervous system diseases. *NeuroReport* 27:350–355
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Leptin

The endocrine hormone leptin is an adipose-derived protein, consisting of 167 amino acid residues, and is encoded by the *ob* gene on chromosome 6, the murine homolog of the human leptin gene *Lep*. Leptin enters the brain through saturable, passive transport across the blood–brain barrier [1–3] and then influences a multitude of biological processes, including controlling food intake [4], glucose homeostasis [5], and energy expenditure [6].

Although the adipose tissue is the main source of leptin, it is also produced by other peripheral tissues, such as the stomach [7], mammary gland [8], placenta [9], skeletal muscle, heart [10,11], kidney [12], and the brain [4,13]. Therefore, this hormone has a wide range of pleiotropic effects, affecting the cardiovascular, nervous, immune, and reproductive systems [14,15], all of which are dysregulated when the leptin signaling pathways are compromised. In the brain, leptin mRNA expression and immunoreactivity have been observed in the hypothalamus, cortex, dentate gyrus (DG), and the hippocampus of the rat [16].

Indeed, a lack of leptin in mice and humans leads to neuroendocrine dysfunction, including neurodegenerative disease, stroke, and cognitive impairment [17]. Recent studies have reported that higher circulating leptin levels are associated with a lower risk of Alzheimer's disease (AD), and lower circulating levels of leptin have been reported in patients with AD [18–20]. Several studies have suggested that Parkinson's disease (PD) patients have lower BMI and serum leptin levels than controls among the elderly [21,22]. It is also known

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that patients with depression experience weight loss and a decrease in circulating leptin levels [23]. Other works have suggested that higher circulating leptin levels increase the risk of vascular disease, such as stroke [24,25].

Leptin receptor

Leptin receptors (ObRs) belong to the class of the I cytokine receptor superfamily. Alternative splicings of the ObRs gene are classified as six leptin receptor forms (ObRa–ObRf), which have an identical N-terminal [26, 27]. In mice and humans, only five (ObRa–ObRe) and four (ObRa–ObRd) alternative spliced isoforms have been described, respectively [28,29]. They all share the same complex extracellular domain, consisting of two cytokine receptor homology (CRH) domains separated by an immunoglobulin-like domain, followed by two membrane proximal fibronectin type III (FN III) domains. The membrane proximal CRH2 domain is necessary and sufficient for leptin binding with an affinity in the nanomolar range [30]. The two FN III domains have no affinity for the ligand, but are nevertheless essential for receptor activation as mutation of two conserved cysteines on positions 672 and 751 completely blocks leptin signaling [31]. The long isoform ObRb is essential for mediating leptin's intracellular signal transduction [32]. The ObRb is present in several neural tissues, but is mainly expressed in multiple hypothalamic regions including the arcuate nucleus (ARC), the ventromedial hypothalamus, the paraventricular nucleus, the dorsomedial hypothalamus, the lateral hypothalamic area, and the ventral premammillary nucleus [33,34]. Leptin's action on two distinct populations of ARC neurons is well described, one of which is the orexigenic neuropeptides neuropeptide Y (NPY) and agouti-related peptide (AgRP) [35], whereas the other is anorexigenic

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neuropeptides cocaine and amphetamine-related transcript and pro-opiomelanocortin [36,37]. In contrast to ObRb, the short-form leptin receptor ObRa have short C-terminal domains and are considered to be mainly involved in endocytosis and transport of leptin across the blood–brain barrier [38]. Whereas ObRe is the only soluble isoform, accumulated evidence showed that it is probably binding circulating leptin and affecting its stability and availability [39].

Leptin signaling pathways

ObRb, which is lacking in db/db mice [40], is expressed in several brain nuclei, with higher expression in the hypothalamic ARC [5]. On binding to the ObRb, leptin leads to the activation of several intracellular signaling pathways [41,42], including signal transducer and activator of transcription 3 (STAT3) [43], and activates mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) [29]. In addition, the mammalian target of rapamycin (mTOR) has emerged as a key downstream pathway in ObRb signaling and in mediating leptin's effects [29,44]. Whether these short isoforms are still able to bind Janus kinase 2 (JAK2) and signal *in vivo* is still doubtful as none of the short isoforms mediates activation of JAK2 at physiologic levels of JAK2 [45,46].

Leptin and the JAK/STAT3 pathway

The JAK/STATS pathway is one of the best illustrated pathways in leptin signaling [4,47]. The binding of leptin to ObRb results in the activation of JAK2. Activated phosphorylated-JAK2 subsequently phosphorylates conserved tyrosine residues of ObRb [48] at Tyr⁹⁸⁵, Tyr¹⁰⁷⁷, and Tyr¹¹³⁸ [49]. The ObRb phosphorylated at Tyr¹⁰⁷⁷ and Tyr¹¹³⁸ serves as a docking site and recruits Src homology 2 (SH2) and Src homology 3 (SH3) domain comprising proteins such as STAT3 [50]. The activation of STAT3 induces its dimerization and translocation into the nucleus, where it mediates changes in the expression of several genes, including suppressor of cytokine signaling 3 (SOCS3), an inhibitor of ObRb signaling [51], and coordinates the regulation of food intake and energy homeostasis by altering the expression of NPY, AgRP, and pro-opiomelanocortin [52].

In addition to STAT3, leptin also induces phosphorylation of STAT1, STAT5, and STAT6 in cultured cells [53,54], but only leptin-induced STAT5 phosphorylation in the hypothalamic ARC of mice [55] and STAT5 nuclear translocation in rat hypothalamic nuclei [56] were detected.

Leptin and the MAPK pathway

Leptin modulates the phosphorylation of ObRb tyrosine residues that activate MAPK. Then, MAPK activates cAMP response element-binding (CREB) protein, which has an antiapoptotic effect on the cell. Recent studies suggest that leptin could mediate neuroprotective effects on dopaminergic cells through the MAPK/CREB

pathway in the central nervous system (CNS) [28]. Leptin induces phosphorylation of Tyr⁹⁸⁵ in the ObRb, thereby creating a binding site for the carboxyterminal SH2 domain of SH2-containing protein tyrosine phosphatase 2 (SHP2) [57]. Phosphorylated SHP2 then recruits the adaptor protein to induce extracellular signal-regulated kinase (ERK), a member of the MAPK family [58]. Stimulation of ERK by leptin can also be achieved by direct interaction with JAK2 [4]. ERK-dependent upregulation of the immediate early genes *egr-1* and *c-fos* has been shown in cell culture and *in vivo* in the hypothalamus [57,59]. The physiological importance of the MAPK pathway is underscored by the observations that pharmacological inhibition of ERK1/2 in the hypothalamus reverses the anorectic and weight-reducing effects of leptin [60].

Other members of the MAPK family such as p38 and JNK have also been reported to be activated by leptin in several cell types [61], but the associated pathways have not been well characterized.

Leptin and the PI3K/Akt pathway

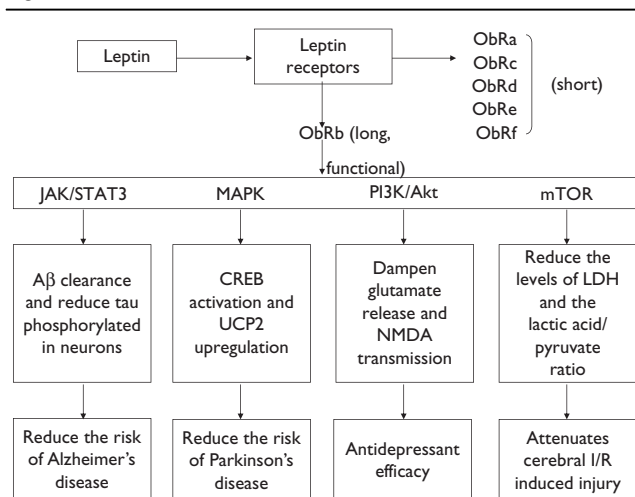
The PI3K/Akt pathway was found to be the critical pathway for the mediation of leptin-induced neuroprotection [62]. ObRb activation induces phosphorylation of several members of the insulin receptor substrate (IRS) family and then IRS in turn recruits the regulatory p85 subunit and activates PI3K, and leads to sequential activation of Akt. The hypothalamic PI3K pathway of leptin signaling is impaired during the development of diet-induced obesity [63,64] and pharmacological inhibition of PI3K activity blocks the anorectic effect of leptin [5]. Leptin and insulin may act in coordination to control energy homeostasis [65] as their intracellular signalings converge at the PI3K pathway. Although the relative contributions of leptin in functional hypothalamic signaling are difficult to assess, the importance of the PI3K pathway is clear.

Leptin and the mTOR pathway

The mTOR protein is a highly conserved serine–threonine kinase that regulates cell-cycle progression and growth by sensing changes in energy status. The mTOR signaling is critically involved in the regulation of several cellular functions and plays a key role in the CNS regulation of energy balance and peripheral metabolism [66]. Leptin increases hypothalamic mTOR activity and inhibition of mTOR signaling by rapamycin blunts leptin's anorectic effect [67]. Systemic deletion of the ribosomal p^{70S6} kinase, a major physiological downstream effector of mTOR, alleviates leptin's acute anorexigenic action [68].

Leptin in central nervous system disease

All the above evidence suggests that leptin-binding ObRb initiates the main intracellular signaling pathways

Fig. 1

Summary of intracellular molecular signaling pathways of leptin and their possible effects for central nervous system diseases. See text for more information. CREB, cAMP response element-binding; I/R, ischemia–reperfusion; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NMDA, *N*-methyl-D-aspartate; ObR, leptin receptor, UCP2, uncoupling protein-2.

to play a protective role in CNS (Fig. 1). To what extent can leptin salvage neurons affected by the pathophysiological processes of diseases involving not only neurodegeneration but also acute cerebral ischemia–reperfusion (I/R) injury? If it can be shown to be leptin-induced neuroprotection, what is the functional outcome of leptin treatment on diseases such as AD, PD, depression, and acute cerebral I/R injury?

Leptin in Alzheimer's disease

AD is a progressive neurodegenerative disorder resulting in neurological deficits including memory loss and diminished cognitive function, making it the most common neurological condition in the USA [69]. The brains of patients with AD, in addition to showing nerve and synapse loss, are histopathologically characterized by two hallmark lesions, amyloid- β (A β) [70] and neurofibrillary tangles, which are composed of hyperphosphorylated forms of the tau protein [71,72]. Normally an abundant soluble protein in axons, the tau is a microtubule-associated protein that promotes assembly and stability of microtubules and vesicle transport [73]. In light of the common belief that the abnormal deposition of both A β and neurofibrillary tangles is critical for the pathobiology of AD, it has been shown that leptin plays a role in reversing both pathological hallmarks of AD and results in better neurological outcomes for the disease state [74].

Leptin receptors are particularly vulnerable in AD [22]. Leptin treatment of neuronal cells reduces the amount of A β secreted into the medium in a time-dependent and dose-dependent manner [75,76]. Furthermore, leptin

promotes ApoE-driven uptake of A β into neurons [77]. Modulation of the tau protein phosphorylation by leptin represents a significant pathway for protection against AD pathology. Moreover, growing evidence indicates that leptin prevents the toxic accumulation of A β and phosphorylated tau in neurons and it has the ability to improve performance in various memory tasks in murine AD models [78].

Recent clinical research has shown that individuals with higher serum leptin levels have a much lower risk of developing AD in line with rodent models and cellular studies [20,79]. Moreover, leptin levels are also significantly reduced in rodent models of AD [70]. Direct injection of leptin into the hippocampus of rodents can improve memory processing and modulate long-term potentiation and synaptic plasticity [80]. Recent studies have shown the potential beneficial effects of leptin as an AD therapeutic [81]. Taken together, our preclinical data, showing that leptin ameliorates both A β -related and tau-related pathologies, along with its pharmacological profile, support its use as a novel therapeutic for AD [49].

Leptin in Parkinson's disease

PD, following AD, is the second most common neurodegenerative disease. Epidemiological studies using 2010 US census estimates have estimated that ~630 000 PD were diagnosed in the USA in 2010 [82]. PD is characterized clinically by a classic tetrad of motor symptoms: low-frequency resting tremor, rigidity of the skeletal muscles of the face and hands, reduced motor activity (bradykinesia), and in later stages of the disorder, postural instability [83]. As reported earlier, leptin has been found to promote the survival of neuroblastoma and neural dopaminergic cells against 1-methyl-4-pyridinium (MPP⁺) toxicity (dopamine cell-specific neurotoxins commonly used in experimental Parkinsonian models) by maintaining ATP levels and mitochondrial membrane potential [84]. Leptin was shown to protect the neuroblastoma cells through a PI3K/Akt-dependent pathway [85], altered Akt, and its downstream target glycogen synthase kinase-3 β (GSK-3 β) in depression. Meanwhile, a MEK/ERK1/2-induced increase in CREB activation preserved dopaminergic cell survival in proapoptotic conditions [85,86]. In-vivo experimentation showed that up to 2 months after neurotoxin exposure, motor behavior is salvaged in leptin-treated animals compared with controls in degeneration of dopaminergic neurons' environments in part through preservation of nigrostriatal functionality. Furthermore, leptin treatment increased the expression in neuroblastoma cells of mitochondrial uncoupling protein-2 (UCP2) and uncoupling protein-4 (UCP4), both vital to the reduction of oxidative stress in the mitochondria [84]. UCP2 knockdown cells were shown to lose the protective effects of leptin when challenged with MPP⁺. The present study showed that leptin rescued dopaminergic neurons, reversed behavioral asymmetry, and restored striatal catecholamine

levels in the unilateral 6-hydroxydopamine (6-OHDA) mouse model of dopaminergic cell death [85,87].

In PD patients who experience unintentional weight loss, circulating leptin levels have been found to be lower than in weight-stable PD patients, with lowered leptin levels consistent with reduced body fat [73]. The weight-loss associated with PD would then result in less stored adipose, and thus lowered serum leptin levels [83]. This scenario is an example of the association between low leptin levels in the brain and pathogenesis of neurodegenerative disease. Basic science findings suggest that leptin can reduce or prevent neuronal apoptosis induced by a variety of pathological conditions and could result in better functional outcomes for neurodegenerative disease states, especially those associated with obesity and metabolic disorders [22].

Leptin in depression disease

Depression is a chronic and debilitating mental illness with a 17% lifetime prevalence and is a major cause of morbidity, disability, and mortality [88]. Currently available pharmacologic treatments for depression primarily target monoamine systems [72]. Systemic administration of leptin exerts antidepressant-like behavioral effects in male rats and mice. Several lines of evidence suggest that leptin exerts its antidepressant-like effects by activating ObRb in the hippocampus. First, direct infusion of leptin into the DG of the hippocampus induces an antidepressant-like effect [89]. Second, deletion of ObRb from the hippocampus causes depression-like behaviors and attenuates leptin's antidepressant-like effects [89,90]. Third, blockade of leptin signaling in the DG reverses the antidepressant-like effects of leptin. These findings support an important role of leptin actions on mood-related behavior.

Compelling evidence supports the important role of the glutamatergic system in the pathophysiology of major depression and also as a target for rapid-acting antidepressants [91]. Blockade of *N*-methyl-D-aspartate (NMDA) receptors by intra-CA3 infusion of MK-801 (a noncompetitive NMDA receptor antagonist) reversed behavioral despair [78]. A subpopulation of granule neurons that innervated the CA3 region expressed leptin receptors and these cells were not activated by stress. Leptin treatment dampened tail suspension-evoked glutamate release in CA3 [92]. However, intra-CA3 of the hippocampus infusion of NMDA blocked the antidepressant-like effect of leptin in reversing behavioral despair in both the tail-suspension tests and forced-swim tests, which involved activation of Akt signaling in DG [89]. Results suggest that the DG-CA3 glutamatergic pathway is critical for mediating behavioral despair and antidepressant-like responses to leptin in the hippocampus [92]. Elevating leptin signaling in brain represents a novel approach for the treatment of depressive disorders.

Leptin in stroke

A stroke occurs when blood flow to the brain is interrupted, either by a blockage or by a burst vessel. Stroke is responsible for roughly one-tenth of deaths, making it the second most common cause after heart disease worldwide [93]. Acute ischemic stroke injuries to brain tissue are among the leading causes of death and long-term disability in humans. The pathophysiologic mechanisms of cerebral I/R injury are primarily related to the energy deficiency of neurons, cell excitatory responses, inflammation, and the start of the apoptosis cascade [62]. Recent research suggested that leptin decreases tissue lactate dehydrogenase levels and thereby decreases the lactic acid/pyruvate ratio, resulting in a mitigation of acidosis because of anaerobic metabolism within the brain. This effect is reversed by LY294002, indicating that the PI3K/Akt signaling pathway plays a critical role in leptin-mediated neuroprotection [94]. Research shows that the neuroprotection exerted by leptin in a rat model of permanent focal cerebral ischemia is associated with modulation of STAT3 phosphorylation in different cellular populations of the injured brain [95]. The impressive positive effects of leptin administration in rodent models of ischemic stroke are promising and of potential therapeutic value to humans [94]. More robust clinical and scientific studies are necessary before leptin can be used in clinical practice.

Conclusion

The discovery of leptin 16 years ago was a major breakthrough. Beyond its role in glucose homeostasis and energy balance, leptin has been found to be an important protective factor contributing toward reproductive function, bone metabolism, and neuroplasticity. A large and growing basic research supports the hypothesis that leptin plays a critical role in neuroprotection. Although recent literature describes the mode of action of leptin, it remains to be seen as to how the disease-modifying effects of the hormone in preclinical trials will translate into a potential therapeutic for patients with neuroendocrine dysfunction.

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Conflicts of interest

There are no conflicts of interest.

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