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Role and involvement of leptin: Disease and disorders

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ABSTRACT

Leptin, a peptide molecule first identified through its role in the hypothalamus regulating food intake and body weight. In addition to the adipose tissue, leptin is expressed in lymphoid tissues, placenta, ovaries, mammary epithelium and bone marrow. Leptin binds to leptin receptor (ObR), which was first isolated from the choroid plexus by expression cloning strategies. ObRs (6 isoforms) are located in the central nervous system and peripheral tissues and show structural similarity with cytokines. Most of the physiological actions of leptin including feeding and energy balance. The other roles of leptin are in reproduction, thermogenesis, synaptic plasticity and neuroprotective effects. In conclusion, this review discusses leptin signaling in different brain areas and sheds light on the involvement of leptin in neurodegenerative disorders. Leptin has neuroplastic and neurotrophic effects and can be definitely useful for treating such diseases. Leptin may have an additional benefit as an insulin sensitizer but, further research is required to elucidate whether leptin sensitizers will be useful and if leptin has a major role in treating brain disorders. Better understanding of the mechanisms mediating leptin's neurodevelopmental actions and increased knowledge about the vulnerability of the brain to leptin level changes is needed.

KEYWORDS

Leptin;
Neurodegenerative disorders;
Cytokines;
Signaling;
Receptors.

INTRODUCTION

Leptin is a 167 amino acid peptide, encoded by *obese (ob)* gene and was first identified in 1994 through its role in the hypothalamus regulating food intake and body weight[1-3]. The name leptin comes from Greek word *'leptos'* that means 'thin' as ob/ob mice lost body weight when were given this protein[3]. In addition to the adipose tissue, leptin is expressed in lymphoid tissues, placenta, ovaries, mammary epithelium and bone marrow[4]. Leptin binds to leptin receptor (ObR), which was first isolated from the choroid plexus by expression cloning strategies[5]. ObRs are located in the central nervous system and peripheral tissues and show structural similarity with cytokines[6]. There are 6 ObR isoforms: ObRa, ObRb, ObRc, ObRd, ObRe, ObRf (TABLE 1), having identical extracellular ligand binding domains at the amino-terminus.

All the isoforms (except ObRe) are membrane-

TABLE 1 : Leptin receptor isoforms in the brain

Leptin receptor Isoform	Size (aa)	Location	JAK/STAT Activation	Signaling Cascades	Function
ObRa Short	894	Most abundant short form; high in blood brain barrier, choroid plexus, piriformcortex, thalamus, hypothalamus, hippocampus, insular cortex, and cerebellar granule cells; lower levels seen in the cerebral cortex	Low	STAT3 MEK/ERK	Leptin transport into endothelial cells; removal and degradation of leptin
ObRb Long	1162	Less abundant than short forms, in many tissues of nervous system; greatest concentration in piriform cortex, thalamus, hypothalamus, hippocampus, substantia nigra compacta, and cerebellar granule cells; lower levels seen throughout the cerebral cortex	High	STAT3 MEK/ERK CREB PI3-K	Primary signaling isoform
ObRc Short	892	Low expression; BBB, choroidplexus, cerebellar granule cells	Low	None	Leptin transport into endothelial cells, other?
ObRd Short	901	Low expression; BBB, Choroidplexus	Low	None	Leptin transport into endothelial cells, other?
ObRe Soluble	805	Secreted, blood	None	None	Binds circulating leptin; modulation of leptin bioavailability to BBB
ObRf Short	896	Low expression; BBB, choroids plexus, cerebellar granule cells	Low	None	Leptin transport into endothelial cells, other?

spanning receptors. Short forms of the receptor (ObRa, c, d and f) consist of 30-40 cytoplasmic residues while, long form (ObRb) consist of 302 cytoplasmic residues[7]. Most of the physiological actions of leptin including feeding and energy balance are due to ObRb as it can activate downstream signaling cascades more efficiently[8]. While, short forms are involved in mediating the leptin transfer from periphery into the brain through blood brain barrier (BBB), especially ObRa and ObRc isoforms that are capable of binding and internalizing leptin and are expressed on BBB microvessels and choroid plexus[9-11]. Leptin is transported into the brain *via* two mechanisms: saturable transport system that involves ObRa, receptor mediated transcytosis, epinephrine, triglycerides regulated leptin transport or CSF mediated transport mechanism[12-15]. The other roles of leptin are in reproduction, thermogenesis, synaptic plasticity and neuroprotective effects[16-24] (Figure 1).

A wide range of signaling pathways that are regulated by leptin (TABLE 2) includes: a. JAK/STAT pathway, b. Src-like homology 2 (SH2) domain containing protein tyrosine phosphatase (SHP-2), c.Mitogen-activated protein kinases (MAPK), d. Suppressors of cytokine signaling (SOCS), e. Phosphatidylinositol (PI) 3-kinase and insulin receptor substrate (IRS) proteins, f. Protein kinase B (PKB, also called Akt), g. Protein kinase C (PKC), h. Cyclic AMP PDE, i. Nitric oxide (NO) and j. Rho family proteins and the actin cytoskeleton[25] (Figure 2).

Leptin signaling in hypothalamus, hippocampus and neuronal

In the hypothalamus, leptin regulates food intake and energy homeostasis. ObRb is expressed in the arcuate nucleus (ARC), dorsomedial nucleus (DMH) and the ventromedial nucleus (VMH) of the hypothalamus. In the ARC, the ObRb is found in the neuropeptide Y (NPY), agouti-related peptide (AgRP) and pro-opiomelanocortin (POMC) expressing neuronal cell types. When leptin binds to ObRb in the POMC neurons, depolarization and increased bio-

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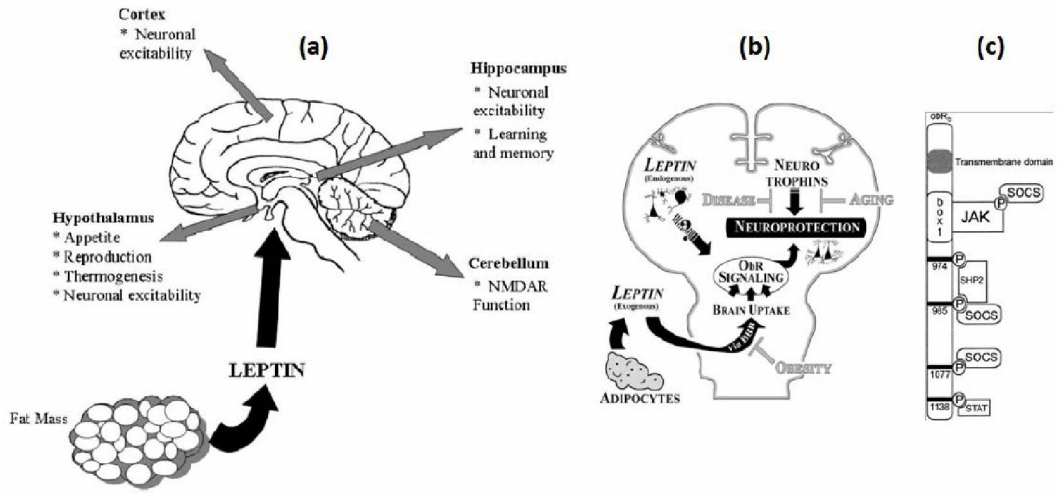

Figure 1 : (a) Diverse neuronal actions of leptin. Leptin regulates key brain functions in brain cortex, hippocampus, hypothalamus and cerebellum (b) Leptin neuroprotection in the brain showing two sources of brain leptin exogenous *via* ObRe (adipcytes in the periphery) and endogenous (leptin synthesized by brain neuronal elements) (c) Role of phosphotyrosines on ObRb in leptin signaling. ObRb contains a JAK (Janus-family tyrosine kinase)-binding Box 1 motif, as well as four tyrosine residues. On phosphorylation, these interact with SH2 domain containing proteins such as SOCS (suppressor of cytokine signalling), SHP-2 (Src-like homology 2 (SH2) domain containing protein tyrosine phosphatase) and STAT (signal transducers and activators of transcription)

TABLE 2 : Leptin signaling regulated by leptin

Signaling Pathway	Primary Site of Action	Known Mechanism of Action	Clinical Results
JAK-STAT3	Hypothalamus	Stimulates transcription of POMC and suppresses transcription of NPY	Regulates appetite and thus, body weight. May also contribute to neuroendocrine function as neuralspecific STAT3 deletion results in decreased linear growth and infertility.
P13K	Hypothalamus	Stimulates POMC neurons Inhibits FOXO1, an inhibitor of POMC transcription, to increase POMC expression	Regulates appetite and body weight. May contribute to leptin resistance in obesity, given the overlapping pathway with insulin. May mediate the stimulation of sympathetic outflow.
MAPK	Hypothalamus, liver, pancreas, adipose tissue, and myocytes	Stimulates POMC neurons and inhibits AgRP/NPY neurons	Regulates appetite and body weight. Increases sympathetic activity to brown adipose tissue. Increases fatty acid oxidation in peripheral tissues. Promotes cardiomyocyte hypertrophy.
AMPK	Hypothalamus, muscle	Stimulates ACC activity in the hypothalamus to regulate food intake and weight. Inhibits ACC activity in muscle.	Regulates appetite and weight. Stimulates fatty-acid oxidation in muscle and may sensitize muscle to insulin.
mTOR	Hypothalamus	Induces phosphorylation of S6K1 to regulate protein synthesis.	Regulates appetite and weight.

Abbre*via*tions: ACC, acetyl coenzyme A carboxylase; AMPK, 5'adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; FOXO1, forkhead box O1; JAK-STAT3, janus kinase-signal transducers and activator of transcription 3; K+, potassium; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; P13K, phosphatidylinositol 3-kinase; S6K1, S6 Kinase.

synthesis of α-melanocytestimulating hormone (α-MSH) occurs that in turn activates downstream melanocortin system, which not only suppresses appetite but also increases energy expenditure. Leptin acts on its receptors on the NPY and POMC neurons and decreases release of the inhibitory neurotrans-

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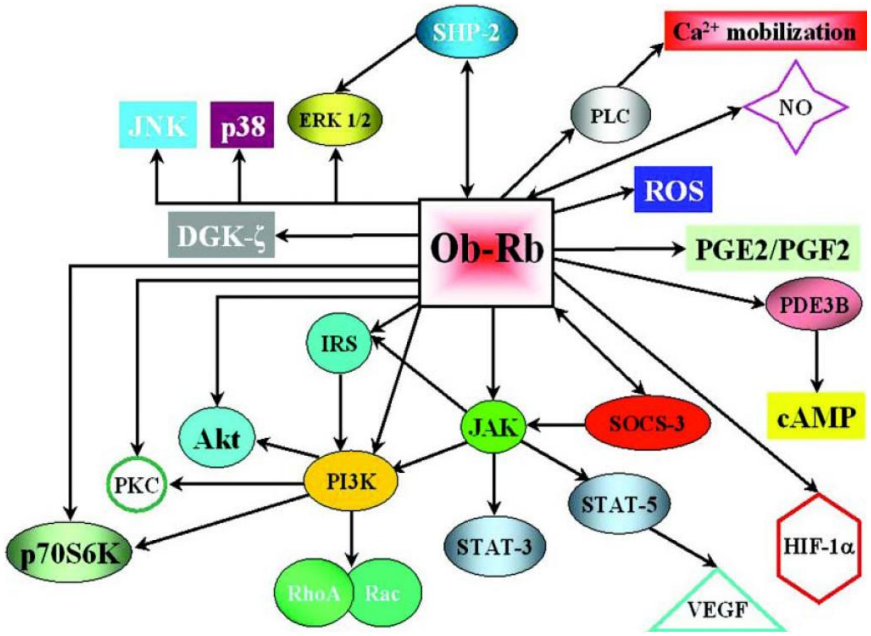

Figure 2 : Signalling pathways regulated by leptin. Involvement of ieptin has been shown in various cascades including, JNK (NH2-terminal c-Jun kinase), p38 (p38 MAPkinase), ERK (extracellular regulated kinase), SHP-2 (Src-like homology 2(SH2) domain containing protein tyrosine phosphatase), PLC (phospholipase C), NO (nitric oxide), DGK-z (diacylglycerol kinase zeta), PGE2/PGF2 (prostaglandins E2/F2), PDE (phosphodiesterase), cAMP (cyclic AMP), SOCS-3 (suppressor of cytokine signaling 3), JAK (Janus-family tyrosine kinase), STAT (signal transducers and activators of transcription), PI3K (phosphatidylinositol 3-kinase), IRS (insulin receptor substrates), PKB (protein kinase B, also known as Akt), PKC (protein kinase C), p70S6K (ribosomal p70 S6 kinase) and ROS (reactive oxygen species) by the leptin receptor (ObRb). Arrows mentioned in the figure depict regulation

mitter gamma amino butyric acid (GABA). Thus, POMC neurons become free of inhibition and increase their firing rate leading to the production of α-MSH that is an inhibitor of appetite. Overall, in the hypothalamus, leptin signaling decreases expression of orexiogenic peptides (NPY, AgRP) and increases expression of anorexiogenic peptides (α-MSH) in addition to the increased energy expenditure in the adipose tissue and skeletal muscle tissue[26-27](Figure 3a).

In hippocampal neurons, leptin receptors are located at both presynaptic and postsynaptic sites. Leptin regulates hippocampal excitability *via* synaptic and non-synaptic mechanisms[28]. Firing of hippocampal neurons is regulated by leptin *via* modulation of BK potassium channels. Leptin receptors are expressed in the CA1, CA3 and dentate gyrus in the hippocampus[29]. Leptin treatment of hippocampal slices results in the conversion of short-term potentiation (STP) to long-term potentiation (LTP) by enhancing Ca^{2+} influx through NMDA receptors[20]. Leptin increases synaptogenesis and neurogenesis in the dentate gyrus of adult mice. Leptin activates PI3KAkt and JAK2/STAT3 signaling cascades thus, playing important role in hippocampal neuronal survival[30](Figure 3b).

Leptin binding to ObRb increases the activity of intracellular JAK2 kinases and ERK signaling. JAK2 activation leads to phosphorylation of Y985 and Y1138 of ObRb and Y705 of STAT3, after binding to pY1138. STAT3, PI3-K and ERK activation leads to regulation of gene transcription. STAT3 pathway negatively regulates ObRb signaling in addition to regulating the expression of (SOCS)-3 (cytokine signaling). There may be involvement of PI3-K in the regulation of rapid nongenomic events that may affect neuropeptide release and neuronal activity[6](Figure 3c).

Role of leptin in CNS development

It has been proved by previous studies that leptin has important role in CNS development. High levels of leptin in the placenta and synthesis of leptin and leptin receptors in foetal tissues is an indication

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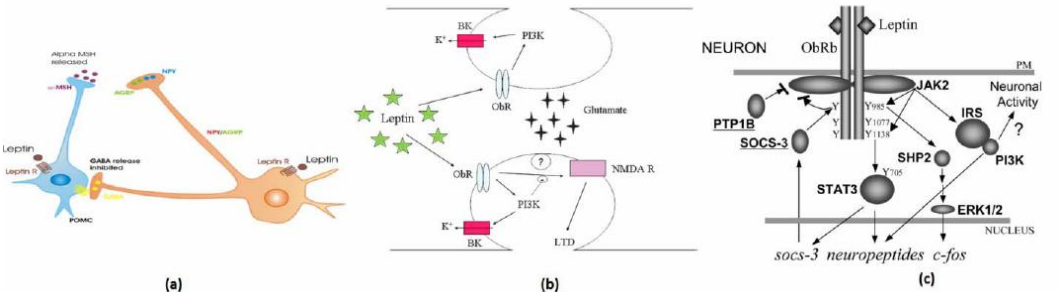

Figure 3 : (a) Leptin activation of neurons in the arcuate nucleus. Leptin inhibits appetite by acting on its receptors on the NPY and POMC neurons resulting in a decrease in the release of the GABA. Thus, POMC neurons become free of inhibition and increase their firing rate leading to the production of α-MSH that is an inhibitor of appetite. Leptin also acts directly on the POMC neurons. (b) Leptin signaling in hippocampus showing CA1 glutamatergic excitatory synapse illustrating the possible mechanisms underlying the effects of leptin on neuronal excitability. Leptin receptor activation results in PI 3-kinase-dependent actin depolymerization followed by stimulation of large conductance Ca2+activated K+ (BK) channels. During enhanced excitability, leptin reduces the strength of excitatory synaptic transmission and induces NMDA receptor-dependent long-term depression (LTD). (c) Neuronal leptin receptor signaling. SH-2-domain phosphotyrosine phosphatase (SHP-2) is important for activation of the ERK pathway. PM, plasma membrane; IRS, insulin receptor substrate

of leptin involvement in development[31-32]. In compared study of ob/ob and db/db mice it was found that leptin deficiency or insensitivity leads to decreased brain weight and protein content[33]. Postnatal administration of leptin showed a normalizing effect on the levels of several synaptic proteins, growth-associated protein in the neocortex, striatum and hippocampus as well as brain weight in ob/ob mice[33]. Deficiencies in brain myelin, reduced neuronal soma size and altered dendritic orientation has been reported in ob/ob mice compared to control mice. This further supports the view that leptin deficiency affects CNS development[34]. During embryonic and early postnatal stages, mRNA expression of leptin receptor stays restricted to the ependymal cells of the third ventricle. The increased expression of SOCS3 mRNA in the cells lining the third ventricle of mice when they were injected with leptin suggesting that functional leptin receptors are present during early life. A significant activation of STAT3 has been observed in the hypothalamus of mice on peripheral leptin injection[35]. However, postnatal brain structures do not show pSTAT3-immunoreactivity (IR) following leptin administration, suggesting, peripheral leptin insensitivity, activation of alternate signaling pathways such as MAPK or PI3K/Akt in brain sites lacking pSTAT3-IR or mRNA transcripts of leptin receptors do not get translated into protein in these brain regions[36].

Neurogenesis, neuronal migration, cell death, axon growth and synapse formation are the major cellular mechanisms involved in hypothalamic circuits during developmental period[37]. Leptin is a neurotrophic agent that promotes formation of ARH neural projections and increases the density and length of axons from the ARH *in vitro*. Leptin treatment restores normal pattern of ARH connectivity in neonates but not in the adults. Overall, leptin has an influence on brain neurocircuitry and leptin may program hypothalamic organization during early life[36,38].

ROLE OF LEPTIN IN NEURODEGENERATIVE DISEASES

Alzheimer's disease (AD)

AD is a multifactorial neurodegenerative disorder characterized by accumulation of β-amyloid plaques and neurofibrillary tangles (hyperphosphorylated tau)[39-40]. Leptin helps in elimination of free fatty acids, cholesterol, lipoprotein and APOE thus, slows amyloidogenesis. Leptin may interfere with the AD pathogenesis in different ways by reducing the amyloidogenic process by decreasing the activity of β site APP cleaving enzyme (BACE) and thus, decreasing the amount of protein β-amyloid formed, decreasing the activity of glycogen synthase kinase-3β (GSK3β) resulting in reduced

levels of tau hyperphosphorylation and improving the cognitive function[30,39-42]. In addition, leptin may enhance elimination of the β-amyloid protein *via* APOE-dependent uptake.

Leptin signaling is related to changes in *Apoe* gene expression and helps in the removal of β- amyloid aggregates when administered chronically in a transgenic mice model for AD[30,43]. AMPK and SIRT1 are the potential targets associated with AD and form another mechanism that may be involved in the neuroprotective effects of leptin[44]. β-amyloid levels and phosphorylated tau increases during low levels of leptin as less leptin is insufficient to stimulate AMPK. On the other hand, activation of SIRT1 has beneficial effects in AD by upregulation of α-secretase production[45]. Leptin regulates tau phosphorylation through a pathway *via* AMPK and GSK3β and inactivates the form by the activation of serine-9 phosphorylation[39-41]. The leptin signaling reduces neuronal apoptosis through the activation of sirtuin 1 activity, which further destabilizes p53 by an acetylation process. Impaired mitochondrial metabolism and generation of reactive oxygen species promotes activation of p53[24]. Thus, leptin holds promise as a therapeutic for AD as it ameliorates both β- amyloid and tau related pathological pathways and has potential to reduce risk of AD (Figure 4). Leptin has role in neurogenesis, axon growth, synaptogenesis, dendritic morphology, development of oligodendroglial cells, neuron excitability, neuroprotection and regulation of beta amyloid levels. Possible effects of leptin in the brain that may protect against Alzheimer's disease are neuroprotection by Inhibition D attenuation of apoptotic cell death, improvement of cell survival, protection against glutamatergic cytotoxicity, protection against oxidative stress, promotion of the proliferation of hippocampal progenitor cells and *via* regulation of beta-amyloid levels by reduction of beta-amyloid extra-cellular levels, reduction of beta-secretase activity, increase of ApoE-dependent beta-amyloid uptake, increase of beta-amyloid clearance, decrease of amyloidogenic pathways and reduction of protein tauphosphorylation[46].

Parkinson's disease (PD)

PD is the second most common devastating neurodegenerative disease, caused by the loss of dopaminergic neurons in the substantia nigra leading to motor disturbances. Leptin may play an important role in the homeostatic regulation of the nigrostriatal pathway. Mice lacking leptin have re-

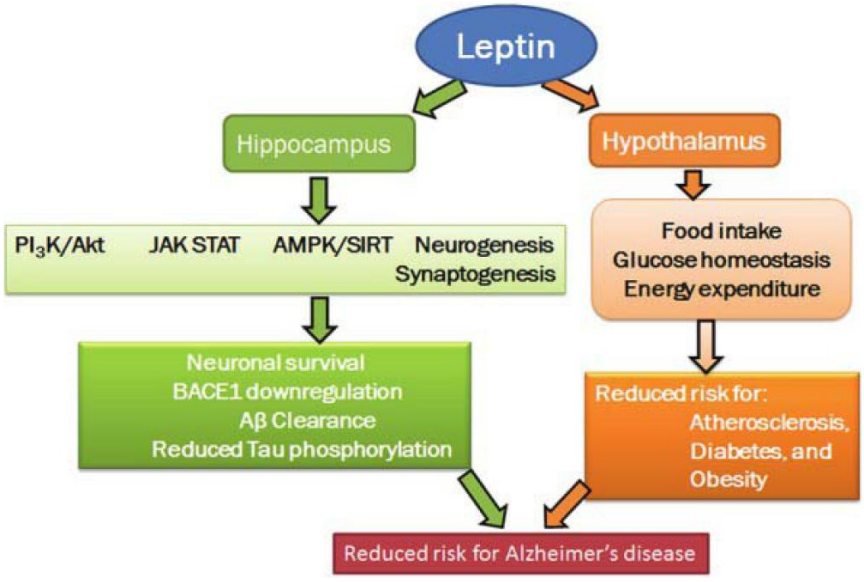

Figure 4 : Leptin signaling in the hippocampus and hypothalamus. Loss of leptin signaling in the hypothalamus may increase the risk for atherosclerosis, obesity and type 2 diabetes that are all risk factors for AD. In the hippocampus, leptin facilitates learning and memory. Leptin activates PI3K/Akt, JAK STAT and AMK/SIRT pathways, thus promoting neuronal sur*via*val, reducing Aβ production and increasing its clearance, and reducing tau phosphorylation

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duced dopamine levels that result in diminished neurotransmission[47]. Loss of dopaminergic neurons in 6-hydroxydopamine (6-OHDA) model of PD is reversed by leptin administration. Leptin mediated neuroprotection of dopaminergic cells involve key signaling mechanisms mediated by the activation/ phosphorylation of JAK-STAT, MEK/ERK and GRB2 which further activate downstream nuclear transcription factors including ERK1/2 and phospho-cAMP-response element binding protein. ObRb activation leads to leptin induced neuroprotective and anti-apoptotic effects[22]. Leptin can increase the levels of brain-derived neurotrophic factor (BDNF), a survival factor for dopaminergic neurons that gets diminished in PD[22,48-49]. BDNF binds to the TrkB receptor kinase and further activates PI3-K and MAPK/ERK similar to leptin mediated signaling, including SH2 and GRB2[50]. Activation of common signaling cascades by leptin and BDNF may induce a form of positive feedback by increasing BDNF expression thus in turn activating same signals. Leptin induced increase of BDNF levels may be one of the main mechanisms mediating neuroprotection[8,24].

Ischaemia

Studies in rodent models of cerebral ischaemia have demonstrated neuroprotective role of leptin *via* ERK1/2, AKT, NF-kb transcription and STAT3 signaling pathways[22,51,52]. Activation of the transcription factor NF-kB is associated with the induction of the anti-apoptotic Bcl-xL gene, a member of the BCL-2 family[53]. Thus, anti-apoptotic property of leptin in ischaemia can be explained by modification of the BclxL/ Bax ratio and the neuroprotective properties can be explained by the activation of ERK1/2 that phosphorylates Bad at Ser-112 and prevents its apoptotic activity[24].

Epilepsy

Epilepsy is a set of neurological disorders characterized by seizures and is associated with neuronal cell death. Research shows that leptin has both neuroprotective and anticonvulsant properties against seizures. Leptin receptors coupled to STAT3 activation has been found in the hippocampus, most susceptible brain area to seizure activity[52,54]. The leptin inhibits the firing of hippocampal neurons by activating large conductance calcium-activated potassium channels thus, may prevent aberrant firing that usually occurs during seizure activity[29]. High fat and low carbohydrate diet is antiepileptogenic as such diet can increase leptin plasma serum levels in rats[55,56]. Leptin helps in preventing seizures and neuronal toxicity. The leptin deficient ob/ob mice, which are more prone to seizures, that leptin protects hippocampal neurons against excitotoxicity[56]. The non-invasive delivery of leptin could also produce significant neuroprotection and other physiological responses in the brain. The serum and brain leptin levels were significantly increased[6].

Potential role of leptin as therapeutics in Alzheimer's disease

Leptin has an important role in cognitive pro-

TABLE 3 : Recombinant leptin administration and cognitive effects in humans. A summary of studies in which subjects received leptin therapy followed by functional MRI and/or cognitive assessment

Study	N	Main Findings
Effects of exogeneous leptin on satiety and satiation in patients with lipodystrophy and leptin insufficiency	8	Leptin treatment increased time between eating a meal after fasting to voluntary eating again
Effect of leptin replacement on brain structure in genetically leptin-deficient adults	3	Sustained gray matter increases in anterior cingulated gyrus, inferior parietal lobule and cerebellum
Leptin replacement alters brain response to food cues in genetically leptin-deficient Adults	3	During food viewing, leptin replacement reduced activation of regions linked to hunger (insula, parietal and temporal cortex) while enhancing activation of regions linked to satiety (prefrontal cortex)
Leptin replacement improves cognitive development	1	Neurocognitive tests were lower than expected but improved dramatically with leptin
Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli	6	Functional MRI in obese patients revealed that leptin could change neural activities in response to food cues in the brain stem, parahippocampal gyrus, frontal guri temporal gyrus and frontal gyrus

TABLE 4 : Summary of the effects of leptin replacement therapy

Endocrine effects	Reversal of type 2 diabetes, Increase in insulin sensitivity; decrease in insulin secretion and in hepatic extraction. Reversal of hypogonadotropic hypogonadism. Increase in 24-h cortisolemia, with changes in rhythmicity towards a more regular pattern. Increase in insulin-like growth factor binding protein (IGFBP1) and insulin-like growth factor binding protein (IGFBP2). Maintenance of adequate growth velocity. Regulation of the thyroid-stimulating hormone (TSH) rhythmicity.
Body composition	Weight loss, mostly fat – up to 54% of initial body weight
Brain and behaviour	Decrease in caloric intake, with changes in food preference. Increase in physical activity. Increase in grey matter concentration. Activation of brain areas involved with satiety and inhibition of areas involved with hunger. Increase in cognitive development. Changes from docile and infantile to assertive and adult-like behavior.
Metabolic effects	Lower decrease in energy expenditure after weight loss. Decrease in triglycerides and increase in high-density lipoprotein cholesterol (HDL-c) Inhibition of lipogenesis and stimulation of lipolysis.
Biomarkers of inflammation, coagulation, fibrinolysis and platelet aggregation	Leptin withdrawal: changes towards a decreased state of thrombogenesis and increased fibrinolysis
Immunity	Decrease in the absolute lymphocyte count (CD3, CD4, CD19 cells) Increased T-cell responsiveness

cesses as well as shows pleiotropic effects on the brain and is critical for brain development as it increases neurogenesis, axonal growth and hippocampal synaptogenesis. Low levels of leptin have been linked to AD in four independent studies with over 3000 patients. There have been reports on decrease of neuronal tau phosphorylation and beta amyloid accumulation/secretion, in cell cultures *in vitro* after leptin treatment[42,57]. Also, leptin injection improved cognitive performance and brain pathology in transgenic AD mouse models. Circulating leptin levels are inversely correlated with AD severity and disease modifying effects of leptin will benefit AD and improve cognition[57] (TABLE 3). The dysfunctioning are due to complete or partial lack of leptin (hypoleptinemia) can be reversed with leptin treatment and there are strong effects of leptin replacement therapy[57-59] (TABLE 4). Previous studies indicate that leptin is safe, even for use in children, at the proposed physiological doses and long-term use is indicated and no immunological reaction to leptin[60].

CONCLUSION

In conclusion, this review discusses leptin signaling in different brain areas and sheds light on the involvement of leptin in neurodegenerative disorders. Leptin has neuroplastic and neurotrophic effects and can be definitely useful for treating such diseases. In addition, leptin contributes to the regulation of energy homeostasis, reward processing, neuroendocrine function, metabolism and brain deveopment. Leptin may have an additional benefit as an insulin sensitizer but, further research is required to elucidate whether leptin sensitizers will be useful and if leptin has a major role in treating brain disorders. Better understanding of the mechanisms mediating leptin's neurodevelopmental actions and increased knowledge about the vulnerability of the brain to leptin level changes is needed. Hopefully, more clinical trials will establish leptin's efficacy and safety so that leptin may become part of our therapeutic arsenal for such conditions in future and this relatively new area of research will open new avenues for understanding neuronal development and neurodegeneration.

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