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Review Article

Leptin signaling and Alzheimer's disease

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Abstract: Leptin, an adipocytokine produced in the peripheral system as well as in the brain, is implicated in obesity, food intake, glucose homeostasis, and energy expenditure. Leptin expression levels and signaling pathways may also be linked to the pathophysiology of neurodegenerative diseases including Alzheimer's disease. Epidemiological studies have demonstrated that higher circulating leptin levels are associated with lower risk of dementia including Alzheimer's disease, and lower circulating levels of leptin have been reported in patients with Alzheimer's disease. Leptin receptors are highly expressed in the hippocampus, a brain area involved in learning and memory and severely affected during the course of Alzheimer's disease. In laboratory studies, several in vivo and in vitro studies have shown that leptin supplementation decreases amyloid-β (Aβ) production and tau phosphorylation, two major biochemical events that play a key role in the pathogenesis of Alzheimer's disease. In this review, we will review the structure of leptin, the type of receptors of leptin in the brain, the various biological functions attributed to this adipocytokine, the signaling pathways that govern leptin actions, and the potential role of leptin in the pathophysiology of Alzheimer's disease. Leptin exerts its functions by binding to the leptin receptor (ObR). This binding can involve several signaling pathways including JAK/STAT pathway, ERK pathway and the PI3K/Akt/mTOR Pathway. Modulation of these pathways leads to the regulation of a multitude of functions that define the intricate involvement of leptin in various physiological tasks. In this review, we will specifically relate the potential involvement of leptin signaling in Alzheimer's disease based on work published by several laboratories including ours. All this work points to leptin as a possible target for developing supplementation therapies for reducing the progression of Alzheimer's disease.

Keywords: Alzheimer's disease, BACE1, Abeta, leptin, leptin receptors, JAK/STAT pathway, hippocampus, hypothalamus, PI3K/AKT/mTOR pathway, ERK, SIRT

Introduction

Leptin is a 146 amino acid protein with a molecular weight of 16 kDa encoded by the *ob* gene and primarily, but not exclusively, expressed by the white adipose tissue (WAT) and is implicated in obesity, food intake, and energy homeostasis. Leptin protein was discovered by the molecular geneticist Jeffrey Friedman in 1994 at Rockefeller University and the work was published in a landmark *Nature* paper in December 1994 [1]. The human *ob* gene has been mapped to chromosome 7q31.3 [2] and encodes a 4.5 kb mRNA transcript that is translated into a 167 amino acid peptide and subsequently processed in the ER into the 146 amino acid mature leptin protein [1]. Antecedent to the discovery of the leptin protein and positional cloning of the *ob* gene in 1994, the *ob/ob* mouse characterized by hyperphagia and a marked obese phenotype was serendipitously discovered by animal caretakers in 1950 at Jackson Laboratories [3]. It was the general consensus that the *ob/ob* mouse possessed a mutation in the *ob* gene, but this was not elucidated and unequivocally established until the discovery of the leptin protein and mapping of the *ob* gene by Friedman and colleagues in 1994 who showed that the mutation resulted in the loss of leptin production. In 1966, the *db/db* mouse was discovered, again at Jackson Laboratories, which not only exhibited a similar hyperphagic, obese phenotype, but also hyperglycemia [4]. Tartaglia and colleagues in 1995 showed that the *db/db* mouse phenotype can be attributed to the mutation in the *db* gene that codes for the long-form of the leptin receptor ObRb [5]. However, it was the seminal work of Doug Coleman and colleagues who demonstrated by a series of parabiosis experiments

using *ob/ob* mice and *db/db* mice pairs and established that the *ob/ob* mice lacked a circulating factor whereas the *db/db* mice produced the circulating factor but were not able to respond to it [6, 7]. The validity of these breakthroughs was affirmed by subsequent discovery of the leptin protein and cloning of the *ob* gene [1] as well as the cloning of the *db* gene which coded for the long-form leptin receptor ObRb [5]. Further corroboration emanated from the finding that the *db* mice produced the truncated form of ObRb that was incapable of transducing leptin-mediated intracellular signal transduction [8-12] and administration of exogenous leptin obviated the obese, hyperphagic, hypothermic, and hypometabolic phenotype in *ob/ob* mice [13-15].

Leptin – structure, expression, and secretion

The crystal structure of leptin has revealed the secondary and tertiary structure of the leptin molecule. The three dimensional crystal structure of leptin depicts the presence of four antiparallel α-helices (A, B, C, and D) [16]. Two long crossover loops connect the A-B and C-D α-helices, while a short loop connects the B-C α-helices [16]. The entire leptin molecule is oblong shaped with the dimensions of 20x25x45 A^0 [16]. The entire molecule comprising of the bundle of four α-helical loops adopts a bilayered stratified structure with α-helices A-D in one layer contiguous with α-helices B-C in the other layer [16]. The conformation adopted by the leptin molecule results in the surface emergence of a few key hydrophobic residues like Phe^{41}, Phe^{92}, Trp^{100}, Trp^{138}, and Leu^{142} which not only play an indispensable role in the regulation of solubility and aggregation kinetics of the leptin protein, but are also critically requisite for as well as modulate the binding of leptin to the leptin receptor and determine the binding kinetics of the leptin-leptin receptor interaction [16]. The three dimensional four-helical bundle crystal structure of leptin exhibits an overt, conspicuous congruence with other cytokines such as growth hormone (GH) [17], leukemia inhibitory factor (LIF) [18], and G-CSF (G-colony stimulating factor) [19], despite lack of primary sequence homology with these proteins or other proteins [1].

Leptin is expressed primarily by the white adipose tissue [1, 20] and circulating leptin levels are proportional to the white adipose tissue mass [21, 22]. In humans, leptin expression in the subcutaneous adipose tissue is significantly more in magnitude than omental adipose tissue [23-26]. Other studies have demonstrated no difference in leptin expression between the subcutaneous and omental adipose tissue [27]. Leptin expression in humans also exhibits sexual dimorphism with circulating leptin levels about 3-fold greater in females than males [25, 28, 29]. It is now certain that other tissues also produce leptin, including stomach [30, 31], mammary gland [32], human placenta [33], ovaries [34], heart [35], skeletal muscle [36], pituitary gland [37], and the brain [37-39]. In the brain leptin mRNA expression and immunoreactivity has been seen in the hypothalamus, cortex, dentate gyrus and the hippocampus of the rat [38, 39]. Leptin immunoreactivity has also been reported in the mouse and hamster brain [40].

Leptin expression and circulating leptin levels are primarily contingent on the white adipose tissue mass [21, 22] and are significantly elevated in obesity [21, 22, 41, 42]. Consistent with this observation, weight loss is associated with a decrease in leptin levels in the plasma [22]. Leptin levels in the plasma also fluctuate in an ultradian manner and exhibit diurnal rhythm [43, 44]. Leptin secretion occurs in a pulsatile rhythm with ~30 pulses of leptin secretion in a 24-hour cycle [43, 45]. Acute caloric restriction reduces leptin levels by ~30% within 24 hours [46-48] whereas caloric excess elevates leptin levels in the plasma by ~35% within 5-8 hours [47]. Therefore, nutritional intake regulates leptin expression in an acute as well as chronic fashion.

The physiological and hormonal parameters that increase leptin expression include obesity [21, 22, 41], overfeeding or excess caloric intake [49, 50], insulin [51-55], glucocorticoids [51, 52, 56, 57], glucose [58], tumor necrosis factor α (TNFα) [54, 59], estradiol [60-62], and IL1 [63, 64] among others. The physiological and hormonal factors that decrease leptin expression include androgens [61, 65], acute caloric restriction [49, 50], growth hormone [66-69], somatostatin [68, 70], exposure to cold temperatures [50, 71, 72], β_3 adrenergic agonists [70, 73-76], long-term exercise [77, 78], cAMP (51, 57), PPARγ agonists such as thizolidinediones Pioglitazone, Troglitazone, and Rosiglitazone [79], and free fatty acids [80]

among others.

Leptin receptors

Leptin receptors (ObR) are encoded by the *db* gene [5]. The ObR are transmembrane spanning proteins that transduce and mediate leptin signaling. The ObR exhibit structural and functional homology to the class I cytokine receptors [81, 82]. The ObR along with other class I cytokine receptors are typified by the characteristic presence of four cysteine residues and a "WSXWS" motif [81, 83] which are a part of multiple fibronectin Type III subdomains in their extracellular domains [84]. The ObR transcript undergoes alternate splicing to generate six different receptor isoforms (ObRa - Ob-Rf) [11]. The six isoforms of ObR are distinguished by and exhibit very little homology in their intracellular domain [85]. However, all the six isoforms have the same extracellular domain of over 800 amino acids and a transmembrane domain that spans 34 amino acid residues [85]. The six isoforms of ObR are pigeonholed into three different groups, namely – short form, long form, and secreted ObR [85]. The short-form of ObR subsuming ObRa (894 amino acids), ObRc (892 amino acids), ObRd (901 amino acids), and ObRf (896 amino acids) possess a short 30-40 amino acid residue intracellular domain [85]. ObRb (1162 amino acids) is the only functionally active leptin receptor isoform capable of transducing leptin signaling as it contains an intracellular domain that spans ~280 amino acid residues [5]. The ObRe isoform (805 amino acids) lacks the intracellular domain and is therefore classified as a secreted soluble receptor and functions as a buffering system involved in the transport of leptin and bioavailibility of free circulating leptin [86, 87]. The short isoforms ObRa, ObRc, ObRd, and ObRf are abundantly expressed in the choroid plexus and endothelial cells of the brain microvasculature that form the BBB and may therefore regulate the flux of leptin across the BBB [88, 89].

ObRb is pervasively expressed in the human and rodent brain with the highest density in the ventromedial, arcuate, and dorsomedial hypothalamic nuclei [90-93]. ObRb is termed the long-form leptin receptor and is solely responsible for propagating signal transduction mechanisms initiated by leptin [5, 94]. The short forms of the leptin receptor Ob-Ra, Ob-Rc, ObRd, and ObRf are devoid of intracellular signaling motifs that are obligatory for signal transduction [5]. However the short form receptors ObRa and ObRc are highly expressed in the choroid plexus and it is speculated that they mediate the uptake of leptin across the BBB (88, 89). ObRb expression has been reported in several regions of the rodent and human brain including the hypothalamus [90, 92, 93], hippocampus, brain stem (nucleus of the solitary tract and the dorsal motor nucleus of the vagus), amygdala and the substantia nigra [92, 93, 95, 96]. In the hippocampus leptin receptor immunoreactivity is observed in the CA1/ CA3 region and the dentate gyrus [95, 97]. Furthermore, axonal and somato-dendritic regions and hippocampal synapses exhibit leptin receptor immunolabeling in primary hippocampal cultures [97].

Biological and physiological functions

Leptin was discovered as the endogenous hormone that precludes obesity and regulates energy homeostasis [1]. Antecedent to the discovery of leptin in 1994, about two decades ago, Doug Coleman had posited the role of a circulating hormone that thwarted obesity via its action in the brain to regulate food intake and energy homeostasis and in the peripheral tissues to regulate energy catabolism, thermogenesis as well as basal metabolism [7]. This was corroborated in the mid 1990s after the discovery of leptin by studies that demonstrated in rodents that administration of exogenous leptin decreased food intake and augmented energy expenditure [13-15, 98, 99]. Leptin administration augments energy expenditure by actuating the β-oxidation of fatty acids in the mitochondria and also inducing the expression of enzymes involved in β-oxidation [100]. However, the notion that high levels of leptin augment weight loss and circumvent obesity must be tempered with the fact that high endogenous leptin levels have been effete in thwarting obesity in humans and other mammals [21, 22, 41]. This can be ascribed to a phenomenon termed "leptin resistance" [101-103].

Leptin plays a pivotal role in the induction of puberty and fertility. Leptin reinstates puberty, restores fertility in *ob/ob* mice, escalates puberty and fosters reproductive behavior in wild-type rodents [104-107]. Leptin directly regulates the hypothalamic-pituitary-gonadal (HPG) axis by inducing gonadotropin release and modulating estradiol production in the ovarian follicles [108, 109]. Leptin also regulates the hypothalamic-pituitary-adrenal (HPA) axis by

attenuating corticotrophin releasing hormone (CRH) production and release [110, 111] as well as directly inhibiting ACTH (adrenocorticotropic hormone)-induced glucocorticoid release from the adrenal cortex [111-113].

Leptin is also integrally involved in the physiological homeostasis of the circulatory system. Emerging evidence implicates leptin in hematopoeisis as leptin is involved in proliferation and differentiation hematopoietic precursors [114-116]. Higher plasma levels of leptin (~100ng/mL), such as those observed in obese individuals, foster and promote platelet aggregation [117]. Leptin is also one of the most potent inducers of vascular epithelial cell growth and angiogenesis and the short forms and the long-form of the leptin receptor is abundantly expressed in the vasculature [117-119].

Leptin function in the brain

Hypothalamus

Leptin signaling in the hypothalamus regulates food intake and energy homeostasis in mammals. The arcuate nucleus (ARC), dorsomedial nucleus (DMH), and the ventromedial nucleus (VMH) of the hypothalamus express the ObRb in the greatest density. In the ARC, the ObRb is abundantly expressed in two disparate neuronal cell types, ones that express neuropeptide Y (NPY) and agouti-related peptide (AgRP) and the others that express pro-opiomelanocortin (POMC) [92, 120-122]. Leptin induced activation of the ObRb in the POMC neurons results in depolarization and increased biosynthesis of α-melanocyte-stimulating hormone (α-MSH) which signals downstream by actuating the melanocortin system comprising of melanocortin-3-receptors (MC3R) and melanocortin-4-receptors (MC4R) expressed by the second order neurons downstream to evoke an anorexiogenic (decreased appetite) response [122-127]. Activation of the melanocortin pathway not only suppresses appetite but also increases energy expenditure by increasing sympathetic tone resulting in β-oxidation of fatty acids in skeletal and adipose tissue. While leptin activates the POMC-expressing neurons, the actuation of ObRb by leptin in the NPY/AgRP neurons results in the decreased genesis of NPY and AgRP peptides which are orexiogenic (increase appetite) in nature [122, 128]. Therefore, in conspectus, leptin signaling in the hypothalamus results in the decreased expression of orexiogenic peptides (NPY, AgRP) and increased expression of anorexiogenic peptides (α-MSH) as well as increased energy expenditure in the adipose tissue and skeletal muscle tissue.

Hippocampus

Leptin receptors are abundantly expressed in the CA1 and CA3 regions of the hippocampus as well as the dentate gyrus [95, 97]. Leptin regulates the excitability and firing of hippocampal neurons via the modulation of BK potassium channels [97]. Leptin also improves memory processing and retention when administered directly into the CA1 region in mice [129] and rodents that are deficient in the leptin receptor (*db/db* mice and *fa/fa* rats) exhibit profound deficits in spatial learning and memory [129-131]. Treatment of acute hippocampal slices with leptin results in the conversion of short-term potentiation (STP) to long term potentiation (LTP) by enhancing Ca^{2+} influx through NMDA receptors [132]. Leptin increases synaptogenesis and aids in memory formation in the hippocampus and is purported to be a cognitive enhancer [133]. Leptin also increases neurogenesis in the dentate gyrus of adult mice [134]. Leptin also plays a critical role in hippocampal neuronal survival by activating the PI3K-Akt and JAK2/STAT3 signal transduction pathways [135]. Leptin upregulates the expression of potent endogenous antioxidant enzyme Mn-SOD (manganese superoxide dismutase) and the anti-apoptotic protein Bcl-xL (B-cell lymphoma xL) in a STAT3-dependent manner in the hippocampus [135]. Leptin stabilizes mitochondrial membrane potential and attenuates the glutamate-induced mitigation in mitochondrial membrane potential and also extenuates the free iron-induced augmentation in mitochondrial ROS [135].

Leptin signaling

Leptin binding to its long-form receptor ObRb actuates four major signal transduction pathways that are coupled to ObRb – JAK/STAT pathway, ERK pathway, PI3K/Akt/mTOR pathway, as well as the AMPK/SIRT1 signal transduction pathways.

JAK/STAT pathway

Leptin signaling via the ObRb is integrally coupled to the JAK2/STAT3, JAK2/STAT5 and

JAK2/STAT6 pathways [10]. The long-form of the leptin receptor ObRb is constitutively coupled to Janus kinase 2 (JAK2) via the evolutionary conserved domains proximal to the membrane [136]. The binding of leptin to ObRb evokes a conformational change in the receptor that actuates JAK2 by phosphorylation at $Tyr^{1007/1008}$ residues [136]. Activated phosphorylated JAK2 subsequently phosphorylates evolutionary conserved tyrosine residues of ObRb [94] at Tyr^{985}, Tyr^{1077} and Tyr^{1138} [137, 138]. The ObRb phosphorylated at Tyr^{1077} and Tyr^{1138} serves as a docking site and recruits Src-homology 2 (SH2)- and Src-homology 3 (SH3)-domain comprising proteins that subsume proteins such as Signal Transducer and Activator of Transcription 3 (STAT3), Signal Transducer and Activator of Transcription 5 (STAT5), and Src homology region 2 domain-containing phosphatase 2 (SHP2) [139]. The phosphorylated Tyr^{1138} residue of ObRb recruits STAT3 and STAT5 which are subsequently phosphorylated by JAK2 at Tyr^{705} and Tyr^{694} respectively. The phosphorylation STAT3 and STAT5 causes their disengagement from the leptin receptor, results in the dimerization of STAT proteins via their phosphotyrosine residues in the SH2 domains [140-142], and culminates in their nuclear translocation [142]. In the nucleus, STAT dimers bind to distinct motifs or elements in the DNA called γ-IFN-activated site (GAS) in the enhancer regions of target genes and thereby modulate and regulate gene expression of target genes [142-146]. In the nucleus, the STAT signaling is abrogated by dephosphorylation and subsequent export of STAT proteins from the nucleus to the cytosol [142, 144, 147] or by targeted degradation of the STAT proteins via the Ubiquitin Proteasomal System (UPS) [148].

The JAK/STAT pathway is negatively regulated by three classes of proteins, namely – suppressors of cytokine signaling (SOCS), protein inhibitors of activated STATs (PIAS), and protein tyrosine phosphatases (PTP) [149]. There are eight members of the SOCS family and their expression is induced by JAK/STAT signaling (STAT3 in particular) thereby suggesting the existence of a negative feedback loop that abrogates JAK/STAT signaling [150]. The SOCS proteins negatively regulate the JAK/STAT pathway by competitively engaging and occupying the phosphotyrosine residues in ObRb via their SH2 domains and obviating the recruitment of STAT proteins to ObRb, thereby precluding STAT activation [150, 151]. SOCS proteins via their SH2 domains also directly bind to JAK2 and extenuate the kinase activity of JAK2 [150, 151]. The PIAS proteins negatively regulate the JAK/STAT signaling pathway by impeding the binding of STAT proteins to the response elements in the DNA by physically interacting and binding with STAT proteins via their zinc-binding RING-finger domains [151]. SHP1 and SHP2 are most well characterized protein tyrosine phosphatases implicated in the negative regulation of the JAK/STAT pathway [149]. SHP1 and SHP2 possess two SH2 domains and therefore bind to phosphotyrosines of JAK2 and ObRb and effectuate the dephosphorylation of JAK2 and ObRb thereby terminating the JAK/STAT signaling [149].

ERK pathway

The extracellular regulated kinase (ERK) pathway is an integral part of a larger signaling network called mitogen activated protein kinase (MAPK) pathway that is activated by leptin signaling via the leptin receptor (ObRb). While phosphorylation of Tyr^{1138} and Tyr^{1077} are both requisite and mediate the activation of STAT3 and STAT5 respectively, the phosphorylation of Tyr^{985} of ObRb mediates the activation of ERK pathway [138]. Leptin signaling via the ObRb evokes the actuation of ERK pathway, both centrally and peripherally, as well as in *in vivo* and *in vitro* experimental paradigms [85]. Leptin evokes the activation of ERK pathway by both JAK2-mediated and JAK2-independent signaling effects [94, 152]. Contemporary evidence has implicated the protein tyrosine phosphatase SHP2 and the adaptor protein Grb2 (growth receptor bound 2) as the requisite mediators in the leptin-induced activation of ERK signaling pathway [153]. Leptin signaling also activates other members and signaling cascades subsumed under the MAPK signaling pathway, namely p38 [154-157] and JNK pathways [156].

PI3K/Akt/mTOR pathway

Leptin signaling also induces the activation of the ubiquitous, pervasive, nutrient-sensitive anabolic, and the broad spectrum PI3K/Akt/mTOR pathway [152, 158-161]. Empirical evidence has demonstrated that the adaptor proteins IRS1 (insulin receptor substrate 1) and IRS2 (insulin receptor substrate 2) mediate the

leptin-ObRb induced activation of PI3K-Akt pathway [94, 158, 162]. A multitude of studies have demonstrated that leptin induces the activation of Akt via phosphorylation of Akt at Ser^{473} [163, 164]. As a consequence, Akt activation is ensued upon leptin signaling which results in inhibition of GSK3β through phosphorylation at Ser^{9} residue [165-167]. Evidently leptin also activates the serine/threonine kinase mammalian target of Rapamycin (mTOR) in the hypothalamus and macrophages [168, 169] through the PI3K-Akt pathway [170]. mTOR is an evolutionary conserved kinase that modulates translation of several mRNA transcripts involved in cell growth and proliferation. mTOR regulates translation by phosphorylation and attenuation of the inhibitor of mRNA translation, eukaryotic initiation factor 4E-binding protein (4E-BP) [171-175], as well as through the phosphorylation and activation of S6 kinase (p70S6K1) [176, 177]. mTOR is autophosphorylated at Ser^{2481} and exhibits spontaneous intrinsic kinase activity under the activation of Akt [178, 179]. mTOR phosphorylation and activation is negatively regulated by the TSC1/TSC2 protein complex [170]. Akt phosphorylates TSC2 causing disintegration of the TSC1/TSC2 complex which consequently results in mTOR activation [180]. Furthermore, Akt has been shown to directly phosphorylate mTOR at Ser^{2448} residues and consequently activate mTOR [181, 182]. Therefore, Akt positively regulates mTOR activation by direct phosphorylation at Ser^{2448} as well as by indirect means which involves relieving the repressive effects of the upstream inhibitor TSC1/2 complex. Thus leptin, by virtue of its inherent ability to activate Akt, is expected to increase mTOR phosphorylation and activity.

AMPK-SIRT1 pathway

The 5'AMP activated protein kinase (AMPK) is the master regulatory kinase termed the "fuel gauge" that integrates signals from upstream mediators and effectors of hormones and cytokines to maintain metabolic homeostasis [183]. AMPK activation leads to increase β-oxidation of fatty acids in the mitochondria and inhibition of lipogenesis [184, 185]. Multiple lines of evidence have cogently demonstrated that leptin activates AMPK and consequently increases fatty acid oxidation [186-188]. One exception to this is the hypothalamic neurons, where leptin inhibits AMPK activation to evoke satiety and other hypothalamic effects of leptin [189-191]. In general, AMPK plays a catabolic role and engenders energy production via effects on glucose and lipid metabolism. AMPK activation also effectuates the induction of the NAD^{+} - dependent deacetylase SIRT1 (silent mating type information regulation 2 homolog) [192, 193], a metabolic master regulator unequivocally implicated in ageing and the regulation of lifespan [194-198] as well as regulating metabolism [199, 200]. The anorexic effect of leptin mediated by the activation of POMC neurons in the hypothalamus is contingent on SIRT1 expression and activation in the neurons of the arcuate nucleus of the hypothalamus [201].

Role of leptin in Alzheimer disease

Alzheimer Disease (AD) is a progressive, debilitating and the most prevalent neurodegenerative disorder typified by memory impairment and cognitive dysfunction eventually leading to fatality. The gross pathologic hallmarks of autopsied brains of patients with AD include atrophy with widened sulci and narrowed gyri in the temporal, parietal, and frontal lobes as well as the neocortex and cingulated gyrus areas of the cerebral cortex. The entorhinal cortex, amygdala, hippocampus and the para-hippocampal gyrus also exhibit pronounced atrophy due to neuronal loss [202, 203]. There is a decrease in gross weight of brain by 10-15% in AD patients [202]. The thickness of the six cortical layers (cortical ribbon) is usually reduced by 10-20% in AD [202] and ventricular dilation is apparent prominently in the temporal horn as a consequence of the atrophy of the amygdala and the hippocampus. Furthermore, there is a propensity for the loss of larger neurons than the loss of smaller neurons or glial cells in AD [202]. Microscopically, AD is characterized by two most common and distinct "hallmark" microscopic lesions namely senile plaques and neurofibrillary tangles (NFT). Senile plaques are extraneuronal deposits of accumulated and aggregated amyloid-β (Aβ) protein in the brain parenchyma, while the NFT are intraneuronal aggregates of protein tau in the hyperphosphorylated state. Other pathological features of the AD brain include synaptic loss, neuronal and dendritic loss, neuropil threads, granulovacuolar degeneration, dystrophic neurites, Hirano bodies, and cerebrovascular amyloid deposition.

There is substantial evidence that leptin modulates Aβ production and metabolism. Chronic

peripheral leptin administration in Tg2576 mice has been reported to reduce the brain Aβ levels [204]. Moreover leptin also decreases the BACE1 activity in SH-SY5Y cell line [204]. Leptin decreases tau phosphorylation explicitly at residues Ser^{202}, Ser^{396}, and Ser^{404} in retinoic acid-induced differentiated SH-SY5Y cells, differentiated human NT2 cells (NT2N), and rat primary cortical neurons [205-207]. Leptin also increases synaptogenesis and aids in memory formation in the hippocampus and is purported to be a cognitive enhancer [133]. Leptin has been shown to convert STP into LTP in hippocampal cultures and hippocampal slices [132]. Recent evidence suggests that leptin facilitates spatial learning and memory [130] and also increases neurogenesis in the dentate gyrus of adult mice [134]. Recent epidemiological studies have also unequivocally implicated decreased leptin levels in the pathogenesis of AD. In the Framingham prospective study, 785 subjects were followed between 1990 and 1994 from the original Framingham cohort [208]. The study concluded that leptin levels were inversely related to the risk of developing dementia of the Alzheimer type [208]. A year preceding the findings of Lieb and colleagues, a morphometric study in Japan conducted by Narita and group found higher leptin levels were positively correlated with higher hippocampal volumes [209].

Leptin decreases Amyloid-β (Aβ) levels by attenuating the genesis and augmenting the clearance of the peptide

The Aβ peptide is derived from a two-step successive proteolytic cleavage of Amyloid-β precursor protein (AβPP) [210]. In the first step, AβPP is cleaved by the membrane-bound protease BACE1 (β-site APP cleaving enzyme 1) (also called β-secretase) to generate CTFβ (carboxy terminal fragment β) (also known as C99 fragment) [211-215] which in the second step is subsequently cleaved by the γ-secretase complex to generate Aβ peptide [216-218]. According to the "amyloid cascade hypothesis", Aβ is considered as the culpable factor in the instigation and progression of all the neurodegenerative events that characterize AD [219]. A plethora of studies have demonstrated that leptin decreases Aβ levels in several *in vivo* and *in vitro* paradigms [204, 220-223]. Leptin has been shown to mitigate Aβ production by extenuating BACE1 activity in neural cultures [204]. Recent studies have implicated the AMPK/SIRT1 pathway in the leptin-induced modulation of Aβ levels [222]. Emerging data from our unpublished work has not only corroborated the finding that leptin regulates Aβ metabolism via SIRT1, but also implicated the ubiquitous transcription factor NF-κB as a SIRT1 target downstream in the modulation of Aβ genesis (unpublished). Leptin decreases Aβ levels by targeting all facets of Aβ metabolism, namely – production, clearance, and degradation. We have shown that leptin increases the expression levels of insulin degrading enzyme (IDE) putatively by activating the Akt pathway [223], thus augmenting the degradation of Aβ. Furthermore, leptin also increases the expression levels of LRP1 [223], suggesting that leptin may foster the uptake of Aβ by astrocytes and microglia or reuptake of Aβ by neurons and therefore target Aβ for intracellular degradation or for clearance across the blood-brain-barrier (BBB). Leptin also effectuates the ApoE-mediated clearance of Aβ [204]. Specifically, leptin dose-dependently increased the LRP1-mediated uptake of ApoE-bound Aβ, therefore committing Aβ toward the endosomal/lysosomal degradation pathway [204].

Leptin attenuates BACE1 expression and activity

The first line of evidence linking leptin signaling dyshomeostasis in the pathogenesis of Alzheimer disease emanated from the work of Tezapsidis and colleagues [204], who demonstrated in neural cultures from transgenic mice that leptin mitigates BACE1 activity by evoking changes in lipid composition of lipid rafts of cell membranes. Furthermore, the study also demonstrated that the lipolytic ability of leptin as a consequence of increased β-oxidation of fatty acids and decrease *de novo* synthesis of fatty acids and triglycerides underlies the mechanistic link between the effects of leptin on lipid composition of membranes and BACE1 activity. Recent data from our studies [223] and other laboratories [221] cogently demonstrate that leptin negatively regulates BACE1 expression, both *in vitro* and *in vitro* paradigms. Moreover, Greco and colleagues have attributed this effect of reduced BACE1 expression on the ability of leptin to induce PPARγ expression and activation [221]. Indeed, leptin is a well characterized inducer of PPARγ expression and activity [220, 224]. In light of this, it is important to reiterate that multiple lines of evidence exist in current

literature demonstrating the role of PPARγ as a negative regulator of BACE1 expression [225]. Another mediator of leptin induced modulation of BACE1 expression may be the transcription factor STAT3. The BACE1 promoter contains a multitude of STAT3 binding sites [226]. Multiple lines of evidence have implicated STAT3 in the regulation of BACE1 expression [226-228]. Leptin may also modulate BACE1 activity via the activation of the PI3K/Akt and ERK signaling pathways [229]. BACE1 expression is also modulated by the master transcription factor NF-κB [230]. We have found that leptin represses NF-κB transcriptional activity via induction of SIRT1 expression and activity and thereby attenuates BACE1 expression (unpublished). Furthermore, inhibition of SIRT1 activity significantly compromised the mitigating effect of leptin on BACE1 expression (unpublished). Therefore, the entire range of discrete signal transduction pathways activated by leptin may be implicated in the modulation of BACE1 expression.

Leptin mitigates tau phosphorylation

It is now the consensus that tau hyperphosphorylation precedes and leads to PHF formation in NFT [231] and aberrant tau hyperphosphorylation is implicated in neurodegeneration in AD [232-236]. Recent studies by Tezapsidis and colleagues as well as our work has cogently demonstrated that leptin decreases hyperphosphorylation of tau, primarily by the activation of known canonical signal transduction pathway coupled to leptin receptors. Firstly, Greco *et al.* demonstrated *in vitro*, in SH-SY5Y and NTera-2 human neuronal cell lines, that leptin reduces the phosphorylation of tau at Ser^{202}, Ser^{396}, and Ser^{404} residues [205]. In the same study, it was shown that leptin was ~300-fold more potent than insulin at mitigating tau phosphorylation and the activation of AMPK pathway was implicated in mediating this effect [205]. The following year, the same group systematically investigated the involvement of other signal transduction pathways activated by leptin that may contribute to the attenuation of tau phosphorylation and concluded that leptin-induced activation of Akt, p38 MAPK, as well as AMPK were all intricately involved [206]. Notably, of great mechanistic importance, was the revelation that all the three aforementioned pathways activated by leptin, culminated in the phosphorylation of the tau kinase GSK3β at Ser^{9} residue leading to the inhibition of its kinase activity. Therefore, leptin-induced activation of Akt, p38 MAPK, and AMPK signal transduction pathways converged at the focal point – GSK3β, a bona fide tau kinase [206, 207]. Data from our studies carried out in organotypic slices from the hippocampi of adult rabbits has also cogently demonstrated that leptin inhibits GSK3β-induced tau phosphorylation at AT8 (Ser^{202}, Thr^{205}) and PHF1 (Ser^{396}, Ser^{404}) epitopes via the activation of Akt [223, 237]. Of greater importance and relevance, was the finding that 8-weeks of leptin treatment in CRND8 transgenic mice resulted in a ~2-fold decrease in tau phosphorylation at AT8 and PHF1 epitopes [221].

Leptin fosters synaptogenesis and synaptic plasticity

Several studies have shown that synaptic dysfunction and synaptic loss are the cardinal hallmarks of incipient AD [238-244]. Electron microscopy [238, 241, 245-248], immunohistochemical and biochemical studies [240, 249-251] have demonstrated that synaptic loss in the neocortex and the hippocampus is an early episode in Alzheimer's disease [252, 253]. Synaptic loss is also the most important structural correlate of cognitive impairment in AD [250, 254-260]. Synaptic dysfunction can be detected in patients diagnosed with mild cognitive impairment (MCI), a condition which may or may not progress to AD and characterized by many as a prodromal state of AD [247, 261]. Leptin plays an indispensable role in learning, memory, and maintenance of synaptic plasticity [262]. Leptin receptor mutant *db/db* mice and *fa/fa* rats have deficits in spatial memory and inadequate short term memory processing as assessed by the Morris water maze [130] and T-maze foot-shock avoidance test paradigms [129]. In the CA1 region of the hippocampus, leptin exclusively enhances the NMDA receptor-mediated synaptic transmission [132]. Leptin facilitates the trafficking of NMDA receptors to the plasma membrane and this may contribute to the effect of leptin on enhancing the NMDA receptor-mediated current [133]. This was also corroborated in a *Xenopus* oocyte model system expressing recombinant NMDA receptors [132]. Leptin evokes the conversion of STP to LTP in acute hippocampal slices. Further delving into the molecular mechanism underlying this effect has implicated the PI3K/Akt and ERK signaling cascades at the nexus as the inhibitors of these

signaling pathways mitigated this effect of leptin [132]. Furthermore, in the CA1 region of the hippocampus, leptin also fosters the induction of a novel form of LTD and this effect was attributed to NMDA receptor activation [263]. The study by Durakoglugil also examined the signal transduction cascades involved in the induction of this novel LTD by leptin and concluded that this effect was contingent on the PI3K signaling cascade, but independent of the ERK signaling pathway [263]. In addition to regulating synaptic strength by modulation of LTP and LTD, leptin also fosters synaptogenesis. The leptin deficient *ob/ob* mice have decreased synapse density and exogenous leptin corrects this deficit in these mice [264, 265]. Leptin also induces the expression of a multitude of pre- and post-synaptic proteins such as synapsin2A and synaptophysin in the hippocampus [266]. Leptin also has a profound effect on dendritic morphology. Leptin augments filopodial stabilization, fosters mobility and boosts their density, thus promoting synapse formation [267]. Interestingly, this effect of leptin on filopodial stability and density is contingent on ERK signaling pathway and not on the PI3K signaling pathway [267].

Leptin increases neuronal survival and mitigates cell death

There is growing consensus that leptin is a growth and survival factor in the CNS. Leptin increases the viability of SH-SY5Y cells and suppresses apoptosis by down-regulation of caspase-10 and TRAIL and this effect is contingent on the ability of leptin to activate the JAK-STAT, PI3K-Akt, as well as ERK signaling pathways [268]. Leptin has been shown to exert neuroprotective properties in cultured MN9D rat dopaminergic cells against 6-OHDA. Leptin also averted the 6-OHDA-induced dopaminergic cell loss in the substantia nigra of mice when administered intracranially [269]. This pro-survival effect of leptin on dopaminergic neurons was attributed to the JAK2-dependent activation of the ERK signaling pathway resulting in increased levels of survival factors p-CREB and BDNF [269]. Our recent work has unequivocally demonstrated that leptin upregulates the expression of Insulin-like Growth Factor – 1 (IGF-1), a known neurotrophic and survival factor in the brain [270]. Leptin has also been shown to attenuate apoptotic cell death of cultured cortical neurons in an *in vitro* oxygen-glucose deprivation model of global ischemia [271]. Furthermore, the study by Zhang *et al.*, also cogently showed that intraperitoneal administration of leptin in mice reduced the infarct volume and significantly improved behavioral parameters in a middle cerebral artery occlusion (MCAO) model of global ischemia [271]. This effect of leptin was attributed to the activation of ERK signaling pathway as the general inhibitor of ERK signaling abolished this effect of leptin, both *in vitro* and *in vivo* [271]. Another study employing hippocampal cultures has demonstrated that leptin inhibits neuronal cell loss in response to growth factor withdrawal and oxidative insult by evoking JAK-STAT activation leading to enhanced expression Mn-SOD and Bcl-xL and stabilizing the mitochondrial membrane potential [135]. Leptin also mitigated neuronal loss in response to excitotoxic insult evoked by glutamate in hippocampal cultures by the aforementioned molecular mechanism [135]. Leptin also protected the hippocampal neurons from kainite-induced damage in response to excitotoxicity evoked seizures in a mice model of temporal lobe epilepsy [135]. A recent study found that leptin also attenuates MPP^+-induced cell death in neuronal cultures via the activation of STAT3 and inducing the expression of UCP-2 that culminates in the obviation of mitochondrial dysfunction by MPP^+ [272]. Of particular interest is the finding that cultured cortical neurons secrete prodigious amounts of leptin in response to oxygen-glucose-serum deprivation that results in enhanced expression of IL-1β and increased intransigence to apoptotic cell death [273]. Moreover, neutralization of this endogenous leptin with an antibody resulted in increased susceptibility of these cultured cortical neurons to oxygen-glucose-serum deprivation – induced cell death [273]. The salutary effects of leptin on neuronal viability and function have also been corroborated by electrophysiological studies. One such study has cogently demonstrated that leptin combats the hypoxia-induced inhibition of spontaneously firing hippocampal neurons by activating the BK channels (large conductance Ca^{2+} activated K^+ channels) [274].

Leptin induces proliferation of neuronal progenitors – evokes neurogenesis

As Alzheimer disease is typified with selective neuronal loss in the hippocampus and other regions of the brain, the debunking of the dogma that neurogenesis occurs exclusively

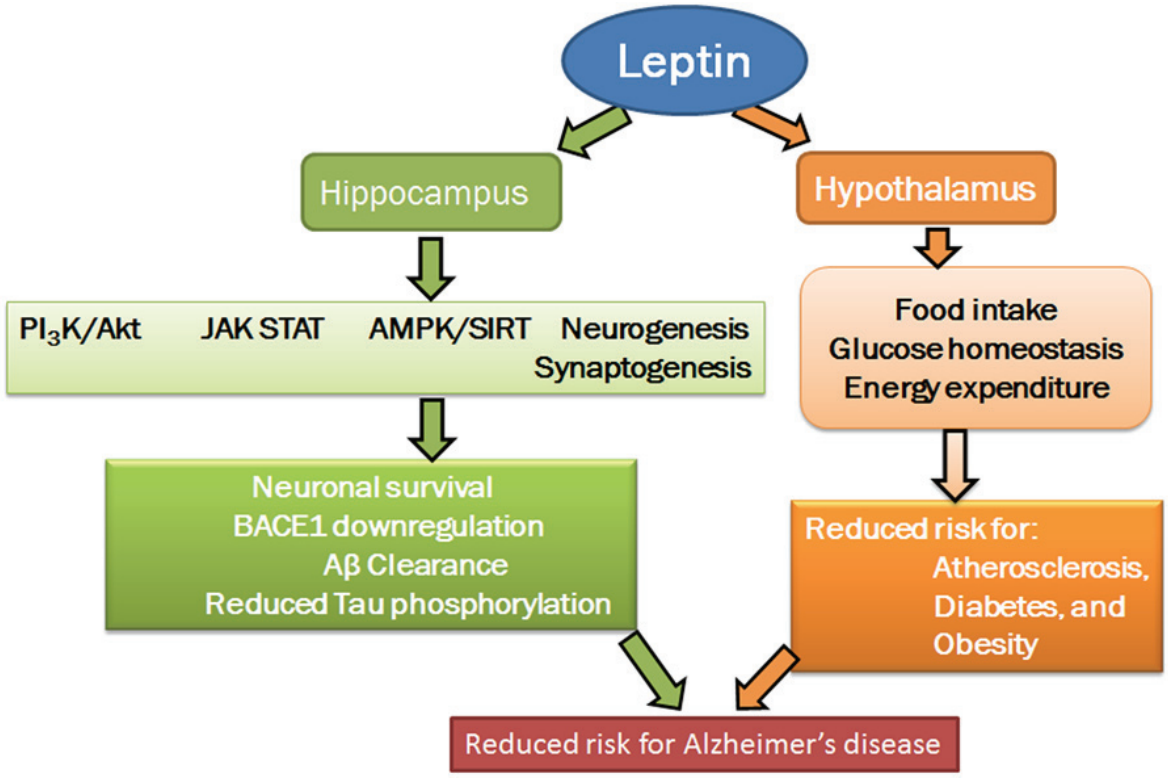

Figure 1. Leptin signaling via the leptin receptor ObRb in the hippocampus and hypothalamus. In the hypothalamus, leptin regulates food intake, glucose homeostasis, and energy expenditure. Loss of leptin signaling may thus increase the risk for atherosclerosis, obesity and type 2 diabetes, which are all risk factors for Alzheimer's disease. In the hippocampus, leptin promotes neurogenesis and synaptogenesis, thus facilitating learning and memory. Additionally, leptin activates the PI_3K/Akt, JAK STAT, and AMK/SIRT pathways, thus promoting neuronal surviaval, reducing Aβ production and increasing its clearance, and reducing tau phosphorylation. All these leptin effects in the hypothalamus and hippocampus confer protection against the risk of Alzheimer's disease.

prenatally and the revelation that neurogenesis persists in the adult mammalian brain has opened novel therapeutic avenues to combat the neuronal loss in AD. Chronic leptin treatment increases hippocampal neurogenesis in mice and induces proliferation of adult hippocampal progenitor cultures [134]. This effect of leptin on adult hippocampal neurogenesis is attributed to increased cell proliferation in the dentate gyrus and not enhanced cell differentiation or cell survival [134]. The study by Garza and colleagues unequivocally implicated the JAK2-STAT3 and PI3K-Akt signal transduction pathways in the leptin induced enhancement of hippocampal neurogenesis [134]. Furthermore, leptin rescues the attenuation in adult hippocampal neurogenesis in a mouse model of chronic unpredictable stress-evoked depression via the inhibition of GSK3β and subsequent stabilization of β-catenin [275]. Leptin has also been documented to evoke neurogenesis and angiogenesis in a mouse stroke model (Avraham *et al.*, 2011).

Conclusion

Here we have reviewed the contemporary knowledge on the protective role of the adipokine leptin and its signaling in Alzheimer's disease. In conspectus, leptin impinges on all facets of Alzheimer's disease pathophysiology (**Figure 1**). These attributes of leptin such as the decrease in Aβ production and increase of Aβ clearance, reduction in tau hyperphosphorylation as well as increased synaptogenesis, increased memory, increased spatial learning, and increased neurogenesis catapult leptin treatment as a unique therapeutic intervention and an indispensable tool in the elucidation of biochemical mechanisms involved in the etiol-

ogy of the sporadic form of Alzheimer's disease.

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