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REVIEW PAPER

Leptin Dysfunction and Alzheimer's Disease: Evidence from Cellular, Animal, and Human Studies

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Abstract There is accumulating evidence from epidemiological studies that changes in body weight are associated with Alzheimer's disease (AD) from mid-life obesity increasing the risk of developing AD to weight loss occurring at the earliest stages of AD. Therefore, factors that regulate body weight are likely to influence the development and progression of AD. The adipocyte-derived hormone leptin has emerged as a major regulator of body weight mainly by activating hypothalamic neural circuits. Leptin also has several pleotropic effects including regulating cognitive function and having neuroprotective effects, suggesting a potential link between leptin and AD. Here, we will examine the relationship between leptin and AD by reviewing the recent evidence from cellular and animal models to human studies. We present a model where leptin has a bidirectional role in AD. Not only can alterations in leptin levels and function worsen cognitive decline and progression of AD pathology, but AD pathology, in of itself, can disrupt leptin signaling, which together would lead to a downward spiral of progressive neurodegeneration and worsening body weight and systemic metabolic deficits. Collectively, these studies serve as a framework to highlight the importance of understanding the molecular mechanisms underlying the body weight and systemic metabolic deficits in AD, which has the potential to open new avenues that may ultimately lead to novel therapeutic targets and diagnostic tools.

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Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly with an estimated global prevalence of 24 million that is predicted to quadruple by 2050 if no effective therapy to prevent, slow down, or cure the disease is found (Reitz and Mayeux 2014). Despite extensive efforts, recent AD clinical trials have been largely disappointing with no new AD drug approved by the US Food and Drug Administrations (FDA) since memantine in 2003 (Cummings et al. 2014). Therefore, in order to develop effective new therapies for AD, it is critical to assess all possible factors that may contribute to the pathobiology of AD. While the cardinal clinical features of Alzheimer's disease (AD) remain the cognitive and memory decline associated with the neurodegeneration, there is rapidly accumulating evidence suggesting that alterations in body weight and systemic metabolism have a significant role in AD (Emmerzaal et al. 2015; Kim and Feldman 2015). Therefore, elucidating the exact nature behind this relationship between body weight/systemic metabolic alterations and AD has the potential to identify new pathways involved in AD.

An intriguing link between body weight/systemic metabolism and brain function is the adipocyte hormone leptin. Leptin is an adipocyte-derived hormone that was originally identified as an essential regulator of body weight and fat stores by modulating food intake and metabolism (Friedman 2014); however, leptin has been demonstrated to have other diverse physiological roles from regulating reproductive function, immune function,

bone metabolism, and neuronal function including cognition as well as having neuroprotective effects (Dalamaga et al. 2013). In addition, leptin receptors are found not only in the hypothalamus, which is the major site of action of leptin on body weight regulation, but leptin receptors are also expressed in the cortex and hippocampus, two major areas affected in AD (Schwartz et al. 1996b; Hâkansson et al. 1998). Furthermore, there is significant evidence to suggest that leptin dysfunction may have a role in the pathobiology of AD (Lieb et al. 2009; Bonda et al. 2014; Khemka et al. 2014). In this review, we will examine the role of leptin in AD by first briefly discussing the neuropathology of AD, then examining the association between AD and body weight/systemic metabolism, and finally summarizing selected findings from recent studies on the role of leptin in AD from cellular and animal models to clinically relevant human studies. By providing an integrated perspective on the role of leptin in AD, we hope to provide new insights into an important pathobiological feature of AD that remains relatively understudied and has the potential to lead to novel therapeutic targets and diagnostic tools.

Neuropathology of Alzheimer's Disease

While the exact etiology of AD remains unknown, AD is pathologically characterized by the accumulation of extracellular plaques, composed primarily of amyloid beta peptides (Aβ), and intracellular neurofibrillary tangles, composed primarily of hyperphosphorylated tau proteins (Huang and Mucke 2012; Musiek and Holtzman 2015). Aβ peptides are derived from the proteolytic cleavage of the amyloid precursor protein (APP) by the β- and γ-secretase complexes, leading to various peptide fragments of different lengths and composition including the neurotoxic Aβ1-42 (Huang and Mucke 2012; Musiek and Holtzman 2015). The buildup of Aβ peptides from increased proteolytic processing of APP and/or impaired clearance from the extracellular space are associated with synaptic dysfunction, cell toxicity, and neuronal death that culminates in the formation of extracellular plaques and the dementia in AD (Huang and Mucke 2012). The identification of rare genetic mutations in autosomal dominant familial forms of AD in APP or genes involved in APP processing leading to increased Aβ production further supports the importance of Aβ in the development of AD (Huang and Mucke 2012; Karch et al. 2014).

The microtubular associated protein tau also plays a prominent role in the pathophysiology of AD. Hyperphosphorylation and other abnormal post-translational modification of tau can cause the protein to adopt pathogenic conformations leading to aggregation and formation of intracellular neurofibrillary tangles, another pathological hallmark of AD, which leads to neuronal dysfunction and degeneration (Huang and Mucke 2012). Furthermore, tau pathology correlates with the severity of dementia in AD both temporally and spatially better than amyloid plaques (Arriagada et al. 1992; Musiek and Holtzman 2015). However, despite the fact that genetic mutations of tau have been linked to other neurodegenerative diseases such as frontotemporal lobar degeneration, unlike Aβ, no tau mutations, thus far, have been conclusively linked to AD (Huang and Mucke 2012; Karch et al. 2014). While the exact contributions of Aβ and tau to AD pathophysiology remain controversial, they likely play a significant factor in AD pathogenesis and serve as important AD biomarkers.

It is now recognized that the neuropathological abnormalities associated with AD such as the accumulation of Aβ and tau begin decades before the initial presentation of cognitive symptoms during the preclinical stage of AD (Sperling et al. 2011). The accumulation of Aβ and tau eventually lead to neuronal dysfunction and cognitive decline as seen in the mild cognitive impairment (MCI) or the symptomatic predementia phase of AD (Albert et al. 2011). As the accumulation of Aβ and tau progressively worsen over time leading to the formation of amyloid plaques and neurofibrillary tangles, the cognitive and mental decline continues and eventually manifests as clinical AD (McKhann et al. 2011). Death typically occurs within 4–8 years after diagnosis of AD but some may live as long as 20 years with AD (Alzheimer's Association 2015).

Body Weight and Systemic Metabolic Alterations in Alzheimer's Disease

Several epidemiological studies have demonstrated a strong association between changes in body weight and AD (Emmerzaal et al. 2015). Weight loss has been appreciated as a clinical manifestation of AD as early as 1927, where a case report described a 70 year-old woman with dementia and rapid weight loss from 34.5 kg on presentation to 28 kg at the time of death (Stief 1927). In fact, weight loss was originally listed in the 1984 report by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) work group as one of the clinical features that was consistent with a diagnosis of probable AD (McKhann et al. 1984). Furthermore, the weight loss in AD correlates with disease morbidity and mortality (White et al. 1996, 1998). Interestingly, the weight loss in AD can present prior to the initial cognitive symptoms, suggesting that the weight loss cannot simply be explained by changes in cognitive and mental functions associated with AD (Stewart et al. 2005;

Johnson et al. 2006). In addition, several different populations studies have consistently demonstrated that low body weight in late-life is associated with an increased risk of developing cognitive decline and AD (Barrett-Connor et al. 1996; Stewart et al. 2005; Buchman et al. 2005; Johnson et al. 2006; Hughes et al. 2009; Gao et al. 2011; Power et al. 2013). Further confirming the strong association between low body weight and AD, several studies have found that low body mass index (BMI) is associated with both worsening AD pathology in postmortem brains (Buchman et al. 2006; Vidoni et al. 2011) and worsening CSF biomarkers (tau and Aβ1-42) (Ewers et al. 2012). As it is now recognized that AD can begin years to decades before the initial cognitive symptoms (Sperling et al. 2011), the late-life changes in body weight likely reflect the initial symptoms of AD or a consequence of AD. These studies collectively suggest that weight loss in AD is an intrinsic aspect of the disease.

In addition to the weight loss seen in AD, weight changes in mid-life have also been associated with AD. Several epidemiological studies have consistently shown that mid-life obesity is a risk factor for developing AD independent of other known metabolic factors such as hypertension and diabetes (Whitmer et al. 2008; Hassing et al. 2009; Xu et al. 2011; Emmerzaal et al. 2015). However, in late-life, high BMI/body weight has been found to be protective against AD and cognitive decline (Hughes et al. 2009; Emmerzaal et al. 2015). While many epidemiological studies have demonstrated this relationship between body weight and AD risk (Emmerzaal et al. 2015), a recent epidemiological study from the UK found that mid-life obesity had a decreased risk, while being underweight in mid- and late-life had an increased risk of developing AD (Qizilbash et al. 2015). Additional studies are clearly needed to clarify the discrepancies among these studies. Regardless of the exact correlation between body weight and AD, mid-life body weight changes likely influence or contribute to the risk of developing AD, while the late-life changes in body weight can potentially be a contributor and/or an early consequence of AD.

Recent epidemiological studies have also found that diabetes and insulin resistance are associated with increased risk of cognitive impairment and the development of AD (Kim and Feldman 2015). One of the earliest studies showing this connection between diabetes and AD was the Rotterdam study, which reported that type 2 diabetes doubles the risk of AD (Ott et al. 1999). Similar results have been consistently found in several other epidemiological studies (Leibson et al. 1997; Peila et al. 2002; Biessels et al. 2006). In addition to the epidemiological studies, animal studies have also consistently found that diabetes worsens AD pathology, as inducing type 1 diabetes by streptozotocin treatment or insulin resistance by feeding a high-fat diet or sucrose-sweetened water in AD mouse models exacerbates both the amyloid and tau pathology (Cao et al. 2007; Ke et al. 2009; Julien et al. 2010; Kim and Feldman 2015). As evidence accumulates for impairment of brain glucose metabolism and insulin signaling in AD, some investigators have suggested that AD be considered as "type 3 diabetes" (La Monte de 2014).

Due to this strong association between body weight/systemic metabolism and AD, understanding how factors that regulate body weight and systemic metabolism are affected in AD could provide important insights into the pathobiology of AD. The regulation of body weight and systemic metabolism is a complex physiological process requiring tight homeostatic modulation by numerous factors including changes in inflammation, metabolites, and various adipocyte-derived hormones or adipokine levels. While we will focus exclusively on the adipokine leptin, other circulating factors relevant in regulating body weight and systemic metabolism such as insulin, adiponectin, and ghrelin may also play a significant role in AD (Kiliaan et al. 2014; Stoyanova 2014; Kim and Feldman 2015).

Regulation of Body Weight and Systemic Metabolism by Leptin

Leptin is a 16-kDa adipokine that was originally discovered as the causative gene behind the *ob/ob* mouse, a spontaneously occurring autosomal recessive genetic mouse model characterized by hyperphagia, morbid obesity, hyperglycemia, insulin resistance, and severe neuroendocrine abnormalities (Zhang et al. 1994; Friedman 2014). Leptin is synthesized and secreted by adipocytes into the blood in amounts proportional to the amount of fat or energy storage in the body with fasting plasma concentrations ranging anywhere from approximately 1–100 ng/mL (Maffei et al. 1995; Considine et al. 1996; Boden et al. 1996; Ostlund et al. 1996). As leptin is secreted in a pulsatile and circadian manner, the amount of circulating leptin is dynamic and changes throughout the day with the lowest levels at mid-afternoon and the highest levels at midnight (Licinio et al. 1997; Park and Ahima 2015). Furthermore, plasma leptin levels exhibit sexual dimorphisms with women having higher plasma leptin levels even after controlling for body adiposity (Saad et al. 1997; Park and Ahima 2015). As body weight and fat stores fall, circulating leptin levels decrease, and this decrease in leptin levels signals to the brain to restore body weight by increasing food intake and reducing energy expenditure (Fig. 1). Conversely, as body weight and fat stores increase, leptin levels increase and signal to the brain to decrease food intake and increase energy expenditure. In this broad role of regulating energy homeostasis, leptin

functions as the afferent signal in a negative feedback loop to maintain body weight homeostasis by modulating key pathways in the brain to change behavior (e.g., appetite) and physiology (e.g., energy expenditure, thermogenesis, glucose and lipid metabolism, sympathetic and parasympathetic tone, etc.) (Friedman 2014). Rare recessive mutations leading to leptin deficiency cause morbid obesity and severe metabolic derangements such as diabetes and insulin resistance in both rodents and humans (Zhang et al. 1994; Montague et al. 1997) with reversal of the body weight and metabolic deficits by exogenous leptin treatment (Halaas et al. 1995; Farooqi et al. 1999). However, most common forms of obesity are not due to leptin deficiency but are likely due to central leptin resistance that could be from lack of effective leptin transport across the blood–brain barrier, leptin receptor desensitization, and/or inhibition of downstream intracellular pathways (Myers et al. 2012).

Independent of its effects on body weight, leptin also acts by central and peripheral mechanisms to regulate systemic metabolism including glucose utilization and insulin sensitivity (Coppari and Bjørbæk 2012; Knights et al. 2014). Several studies over the years have demonstrated in different rodent models that exogenous leptin administration can improve glucose metabolism by increasing insulin sensitivity (Kamohara et al. 1997; Coppari and Bjørbæk 2012; Knights et al. 2014). Importantly, leptin can also improve glucose metabolism by insulin-independent effects as seen when exogenous leptin effectively treated the severe metabolic deficits in insulin-deficient mice (Yu et al. 2008; Wang et al. 2010). Additionally, chronic peripheral leptin treatment can reverse the severe metabolic derangements such as insulin resistance, hyperglycemia, and hepatic steatosis in both rodent models and humans with severe lipodystrophy (Shimomura et al. 1999; Petersen et al. 2002). Finally, leptin deficient *ob*/*ob* mice have severe glucose abnormalities such as hyperglycemia and insulin resistance that is reversed by leptin replacement but only partially rescued when body weight is simply reduced by pair-feeding or restricting the amount of food eaten to leptin-treated levels, strongly suggesting that leptin and not weight loss is the key factor in restoring the metabolic derangements due to leptin deficiency (Schwartz et al. 1996a). These studies demonstrate the importance of proper leptin function in maintaining both body weight and systemic metabolism.

The leptin receptors are part of the class I cytokine receptor family and have multiple isoforms with the long form of the receptor (Lep-Rb) believed to be the primary isoform responsible for ligand binding and downstream activation of intracellular pathways (Allison and Myers 2014). Once leptin binds to Lep-Rb, JAK2, which is bound to the box1 and box2 motif of LepRb, is autophosphorylated and activated leading to the phosphorylation of key cytoplasmic tyrosine residues on Lep-Rb and subsequent activation of several important downstream signaling pathways. In particular, the phosphorylation of Tyr^{1138} on LepRb recruits STAT3 to LepRb, where JAK2 can phosphorylate and activate STAT3, while the phosphorylation of Tyr^{1077} on LepRb leads to the phosphorylation and activation of STAT5. The phosphorylation of STAT3 and STAT5 leads to the dimerization of STAT proteins and translocation to the nucleus, where it can mediate the expression of key target genes (Allison and Myers 2014). Similarly, the phosphorylation of Tyr^{985} on LepRb allows it to bind to the SH2 domain of protein tyrosine phosphatase (SHP2) leading to the activation of the ERK pathway (Allison and Myers 2014). Finally, leptin receptor signaling can also activate the PI3 kinase/Akt/mTor pathway through insulin receptor substrate (IRS) phosphorylation (Allison and Myers 2014).

The hypothalamus has been identified as the major site of action of leptin in the brain (Fig. 1) (Friedman 2014). Lep-Rb is strongly expressed in the arcuate nucleus (ARC) of the hypothalamus in the brain, regions known to tightly regulate body weight and systemic metabolism (van Swieten et al. 2014). Leptin is secreted from adipocytes and enters the brain through saturable, passive transport across the blood–brain barrier (Banks et al. 1996). While the exact molecular mechanism for leptin transport into the brain remains to be elucidated and could involve one of the isoforms of the leptin receptor (Hileman et al. 2002), there is also evidence to suggest that leptin may bind to megalin (or LRP2, low-density lipoprotein receptor-related protein-2) at the choroid plexus epithelium to help facilitate transport of leptin into the brain (Dietrich et al. 2008). The first-order neurons that are responsive to leptin react according to the concentration of leptin binding to the Lep-Rb, which then activates the corresponding neural circuit (van Swieten et al. 2014). There are two major subpopulations of arcuate neurons that are responsive to leptin, an orexigenic population of neurons that co-expresses agouti-related peptide (AgRP) and neuropeptide Y (NPY) and an anorexigenic population of neurons that co-expresses cocaine-amphetamine-related transcript (CART) and proopiomelanocortin (POMC). Leptin inhibits the orexigenic AgRP/NPY-expressing neurons and activates the POMC/CART-expressing neurons. These arcuate neurons have projections to other hypothalamic nuclei including the paraventricular nucleus (PVN), ventromedial nucleus (VMH), dorsomedial hypothalamus (DMH), and lateral hypothalamic area (LH). The coordinated response to leptin leads to the modulation of food intake, energy expenditure, and parasympathetic/sympathetic tone to maintain body weight homeostasis. Of note, leptin can modulate hypothalamic neurons to not only affect body

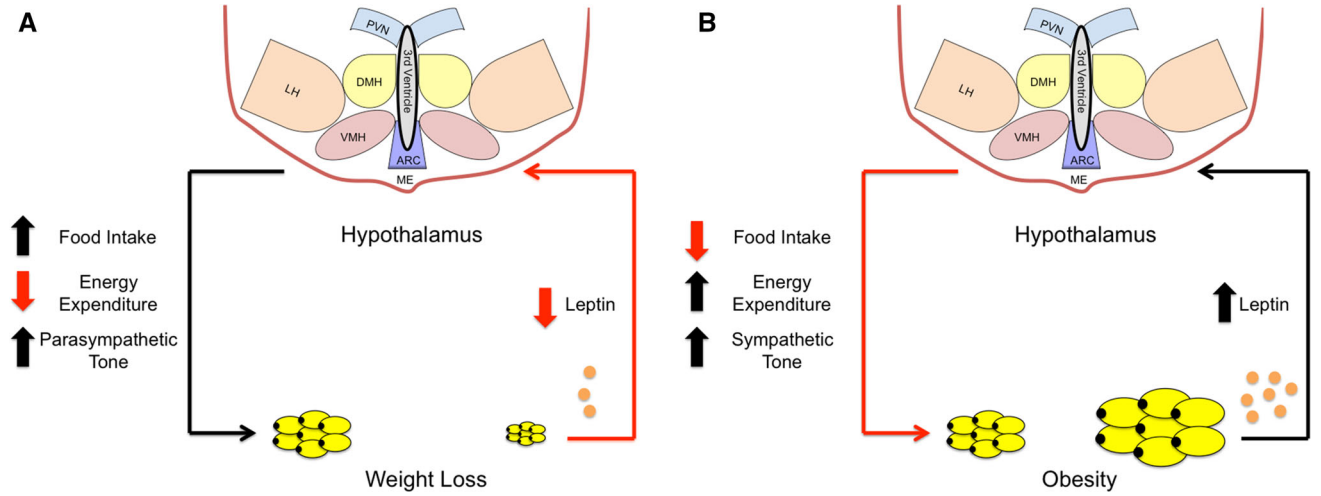

Fig. 1 The regulation of body weight and systemic metabolism by leptin. Leptin acts as the afferent signal in a negative feedback loop to maintain constant body weight and fat stores. **a** Loss of body fat as in weight loss leads to a decrease in circulating leptin levels, which in turn signals to the hypothalamus to start a complex cascade resulting in increased food intake, decreased energy expenditure, increased parasympathetic tone, and restoration of fat mass and body weight. **b** Conversely, an increase in body fat as in obesity leads to an increase in circulating leptin levels, which in turn results in decreased food intake, increased energy expenditure, increased sympathetic tone, and restoration of fat mass and body weight. *ARC* arcuate nucleus, *DMH* dorsomedial nucleus, *LH* lateral hypothalamic area, *ME* median eminence, *VMH* ventromedial nucleus

weight and systemic metabolism but also a wide variety of neuroendocrine functions from reproduction to bone metabolism (Dalamaga et al. 2013).

Neurotrophic and Neuroprotective Effects of Leptin

Leptin has also been demonstrated to have strong neurobiological effects outside of its role in regulating body weight and systemic metabolism. Leptin receptors are found in neuronal and non-neuronal cells such as astrocytes in not only the hypothalamus but also in the cerebral cortex as well as the dentate gyrus, CA1 and CA3 areas of the hippocampus, areas known to be highly involved with cognition and memory (Schwartz et al. 1996b; Hâkansson et al. 1998; Pan et al. 2012; Kim et al. 2014). In normal elderly population studies, plasma leptin levels have been correlated with grey matter volume in various brain regions including the hippocampus (Narita et al. 2009) and inversely correlated with age-related cognitive decline (Holden et al. 2009). Furthermore, leptin is critical for normal neuronal and glial maturation and development (Ahima et al. 1999; Matochik et al. 2005; Paz-Filho et al. 2008). Compared to wild-type mice, the brains of leptin-deficient *ob*/*ob* mice are significantly smaller with decreased levels of synaptic proteins that are at least partially reversed by exogenous leptin administration (Ahima et al. 1999). Similarly, humans with congenital leptin deficiency have neurocognitive deficits and structural brain abnormalities that are rescued by exogenous leptin (Matochik et al. 2005; Paz-Filho et al. 2008).

There is accumulating evidence that leptin can regulate the morphology and synaptic function of hippocampal neurons (Irving and Harvey 2014). Leptin appears to be critical for hippocampal spine formation as *db*/*db* mice lacking LepR have reduced spine density on CA1 and CA3 neurons, while leptin treatment in cell lines can induce hippocampal spine formation through multiple pathways including CREB-regulated microRNA-132 suppression of p250GAP and activation of TrpC channels and the calcium/CaM-dependent kinase cascade (Dhar et al. 2014a, b). Leptin can modify excitatory synaptic transmission at hippocampal CA1 synapses and enhances not only long-term potentiation (LTP) but also improves hippocampal-dependent learning and memory tasks (Shanley et al. 2001; Oomura et al. 2006; Irving and Harvey 2014). The leptin-mediated LTP effect, while still present, was markedly attenuated in hippocampal slices from aged 12–14-month-old rats compared to slices from younger 3–4 month old rats, suggesting that the leptin-mediated effects on the hippocampus are age-dependent and worsen with aging (Moult and Harvey 2011). Under conditions of enhanced excitability, leptin can also induce a novel form of NMDA receptor-dependent long-term depression (LTD) (Durakoglugil et al. 2005). Finally, leptin receptor deficient Zucker *fa*/*fa* rats have impaired hippocampal LTP and LTD that was associated with impaired spatial memory as seen in the Morris water-maze test (Li et al. 2002). These studies demonstrate the important role that leptin has on maintaining hippocampal structure and function.

Leptin has also been demonstrated to have neuroprotective effects under a variety of in vitro and in vivo conditions. Excitotoxic lesions caused by the administration of the glutamate analog ibotenate to mouse brains were significantly reduced when co-administered with leptin (Dicou et al. 2001). Leptin also exerts a cytoprotective effect against the mitochondrial neurotoxin 1-methyl-4-pyridinium (MPP+) as well as 6-hydroxydopamine, both experimental models of Parkinson disease (Lu et al. 2006; Weng et al. 2007). Leptin treatment also protected neurons from ischemic damage in both cell models of oxygen-glucose deprivation and animal models of transient cerebral ischemia (Zhang et al. 2007; Zhang and Chen 2008). Conversely, compared to wild-type mice, leptin-deficient *ob*/*ob* mice have larger infarct volume size after cerebral ischemia (Terao et al. 2008) and increased morbidity and worse outcomes after methamphetamine and kainic acid neurotoxicity (Sriram et al. 2002). The exact mechanisms underlying the neuroprotective effects of leptin remain to be elucidated but could involve production of anti-apoptotic protein Bcl-xL, stabilization of mitochondrial membrane permeability, and reduction of mitochondrial generated oxidative stress (Guo et al. 2008; Davis et al. 2014).

Collectively, these studies strongly suggest that leptin is an important regulator of hippocampal structure and function and exerts neuroprotective effects under a variety of neurotoxic conditions. Therefore, leptin signaling deficits from either decreased absolute levels (e.g., leptin deficiency or low plasma leptin levels) or decreased function (e.g., central leptin resistance) could potentially lead to worsening cognitive and memory function as well as susceptibility to neurotoxic conditions such as from neurodegenerative diseases.

Leptin and Alzheimer's Disease: Cellular and Animal Models

As there have been accumulating evidence that leptin can have neuroprotective effects against a wide variety of neurotoxic conditions, it is perhaps not surprising that leptin has also been demonstrated to have neuroprotective effects against AD pathology. Several reports have consistently shown that leptin treatment can decrease Aβ levels by targeting all aspects of Aβ metabolism including Aβ production, clearance, degradation, and aggregation (Fig. 2) (Fewlass et al. 2004; Marwarha et al. 2010b; Greco et al. 2011; Niedowicz et al. 2013; Marwarha et al. 2014; Yamamoto et al. 2014). Using neural cell lines, leptin treatment was found to decrease Aβ levels by reducing β-secretase activity that was associated with alterations in the lipid composition of lipid rafts (Fewlass et al. 2004). The reduction of β-secretase activity by leptin appears to be mediated at least in part by AMPK/SIRT1 pathways (Greco et al. 2011; Marwarha et al. 2014). In cell culture models, leptin treatment also decreased Aβ levels by down-regulating the transcription of presenilin 1, one of the components of the γ-secretase complex; however, β-secretase mRNA levels remained either unchanged (BACE1) or increased (BACE2) in this study (Niedowicz et al. 2013). The clearance and degradation of Aβ appears to be enhanced by leptin as well. Exogenous leptin treatment has been demonstrated in vitro to increase the LRP1 mediated uptake of ApoE bound Aβ in a dose-dependent manner (Fewlass et al. 2004). Furthermore, in organotypic rat slices treated by 27-hydroxycholesterol to elevate Aβ and phosphorylated tau levels, leptin treatment can increase the protein levels of LRP1 and the insulin degrading enzyme, a key enzyme involved in the degradation of Aβ (Marwarha et al. 2010b). Aggregation of Aβ to insoluble fibrillar structures can also be inhibited with leptin treatment by decreasing GM1 gangliosides on the neuronal cell surface through PI3 kinase/Akt/mTor pathways (Yamamoto et al. 2014). Exogenous leptin can also protect hippocampal and hypothalamic cell lines from the neurotoxic effects of oligomeric soluble Aβ by preventing superoxide production, rise in calcium, and mitochondrial dysfunction (Martins et al. 2013; Gomes et al. 2014). Additionally, in organotypic slices from rabbit hippocampus, exogenous leptin treatment reversed the Aβ-mediated decrease of insulin-like growth factor-1 (IGF-1), a neuroprotective and neurotrophic factor, suggesting that leptin can potentially exert neuroprotective effects by restoring IGF-1 levels in the hippocampus (Marwarha et al. 2011). Finally, leptin has been demonstrated in vitro to ameliorate the Aβ1-42-mediated inhibition of hippocampal LTP, enhancement of LTD, and synaptic dysfunction (Doherty et al. 2013).

Leptin can also reduce phosphorylated tau levels through established intracellular leptin signaling pathways (Greco et al. 2008, 2009b; Doherty et al. 2013). In a cellular model where retinoic acid induced the phosphorylation of tau at the key amino acid residues Ser^{202}, Ser^{396}, and Ser^{404}, exogenous leptin treatment led to a decrease in hyperphosphorylation of tau that was approximately 300-fold more potent than insulin, another metabolic hormone that has been suggested as a neuroprotective agent against AD pathology (Greco et al. 2008). The reduction of tau phosphorylation by leptin appears to be mediated through AMPK, Akt, and p38 pathways (Greco et al. 2008, 2009b). Importantly, these leptin-induced signaling pathways converge to phosphorylate glycogen synthase kinase-3β (GSK3β), a key tau kinase, at Ser^{9} resulting in inhibition of GSK3β and decrease in hyperphosphorylation of tau (Greco et al. 2009a).

In vivo studies using animal models have supported many of the findings from the in vitro studies. Chronic

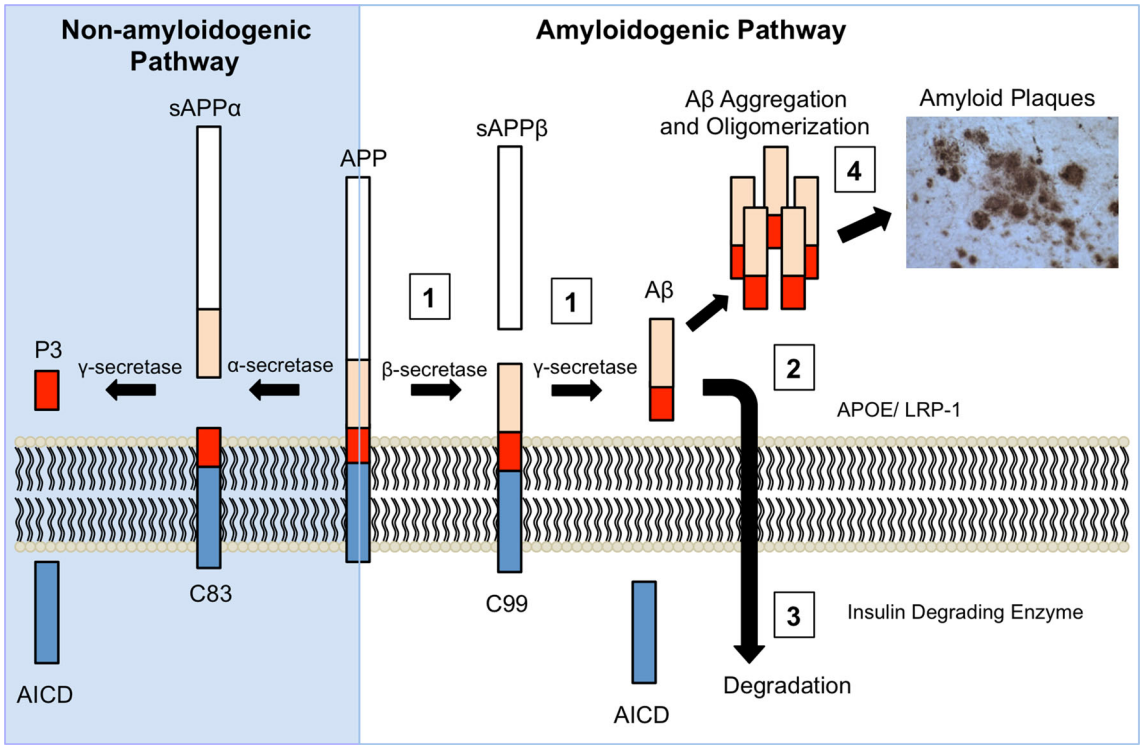

Fig. 2 The neuroprotective effects of leptin against amyloid-beta. Amyloid-precursor protein (APP) can be proteolytically processed to form both amyloid and non-amyloidogenic peptides. The cleavage of APP by α-secretase forms non-amyloidogenic peptides. When APP is proteolytically processed by β-secretase, the amyloidogenic pathway is initiated. The subsequent cleavage by γ-secretase produces Aβ and amyloid precursor protein intracellular domain (AICD) fragments. The various Aβ fragments can then aggregate to form insoluble extracellular plaques. Leptin can affect Aβ metabolism by targeting the (*1*) production, (*2*) clearance, (*3*) degradation, and (*4*) aggregation of Aβ. (*1*) Leptin can reduce Aβ production by decreasing β-secretase activity as well as by down-regulating the transcription of presenilin 1, one of the components of the γ-secretase complex. (*2*) Leptin can promote Aβ clearance by increasing LRP-1 mediated uptake of ApoE bound Aβ. (*3*) Leptin can help degrade Aβ by increasing insulin degrading enzyme, a key enzyme involved in the degradation of Aβ. (*4*) Leptin can decrease the formation of insoluble fibrillar Aβ structures by decreasing GM1 gangliosides

exogenous leptin administration to transgenic mice overexpressing APP decreased the brain levels of Aβ and phosphorylated tau (Greco et al. 2010). Similarly, lentiviral gene transfer of leptin to transgenic APP/PS1 mice decreased brain Aβ accumulation that was associated with a decrease in BACE1 levels and activation of microglial cells in the cortex and hippocampus (Pérez-González et al. 2014). Additionally, lentiviral gene transfer of leptin in APP/PS1 mice increased the proliferation of neuronal progenitors in the subgranular zone of the dentate gyrus and partially rescued the synaptic deficits seen in APP/PS1 mice (Pérez-González et al. 2011, 2014). Both exogenous leptin administration and leptin viral gene transfer led to improvements in behavior and memory tasks in transgenic mouse models of AD (Greco et al. 2010; Pérez-González et al. 2014). Furthermore, chronic intracerebroventricular leptin administration can also alleviate the Aβ1-42-mediated spatial memory impairments and suppression of in vivo hippocampal late-phase LTP in rats (Tong et al. 2015). In contrast, leptin deficiency can worsen brain amyloid burden and cognitive function as demonstrated when transgenic mice overexpressing APP were crossed to leptin-deficient *ob*/*ob* mice (Takeda et al. 2010). Additionally, leptin receptor-deficient Zucker *fa*/*fa* rats have increased phosphorylated tau levels compared to leptin sensitive Zucker lean rats (Doherty et al. 2013). Therefore, consistent with a role for leptin as a neurotrophic and neuroprotective agent, pathologically low leptin levels or leptin insensitivity can contribute to the worsening cognitive decline and AD pathology in animal models.

There is also evidence to suggest that Aβ can directly inhibit endogenous leptin expression and leptin receptor activation. Incubation of organotypic slices from rabbit hippocampus with either soluble or fibrillary forms of Aβ led to a decrease in leptin expression by inhibiting the PI3k/Akt/mTORC1 signaling pathway (Marwarha et al. 2010a). However, based on these studies, it is unclear if Aβ can directly decrease leptin expression in vivo particularly in the adipose tissues, where the vast majority, if not all, the leptin necessary for the central regulation of body weight is produced (Odle et al. 2014). Additionally, in the organotypic slices, both soluble and fibrillary forms of Aβ

were found to decrease the phosphorylation and therefore activation of leptin receptor (Marwarha et al. 2010a). The inhibitory effects of Aβ on leptin receptor activation could be due to the overall decrease in endogenous leptin expression mediated by Aβ and/or from the increase in expression levels of the negative regulator SOCS-3 seen after Aβ treatment (Marwarha et al. 2010a).

We recently demonstrated that Aβ could directly inhibit leptin signaling in the hypothalamus (Ishii et al. 2014). Similar to the early weight loss seen in human patients with AD, Tg2576 mice, a transgenic mouse model overexpressing APP, had significantly lower body weight and plasma leptin levels prior to amyloid plaque formation or cognitive dysfunction that were associated with inhibition of hypothalamic NPY neurons by Aβ (Ishii et al. 2014). Based on these results, we hypothesized that Aβ could early in the disease process inhibit hypothalamic pathways involved in the regulation of body weight resulting in a catabolic state with low body weight and pathologically low plasma leptin levels. The low circulating leptin levels, in turn, could potentially contribute to cognitive decline and worsening AD pathology leading to a downward spiral of further weight loss and progression of AD. The presence of amyloid plaques, neurofibrillary tangles, and neurodegeneration in the hypothalamus of human AD brains suggest that Aβ-mediated inhibition of leptin responsive cells in the hypothalamus is a distinct possibility (McDuff and Sumi 1985; Saper and German 1987; Callen et al. 2001; Ishii and Iadecola 2015). Therefore, leptin may have a bidirectional role, where leptin signaling dysfunction can exacerbate AD pathology, while AD pathology, in of itself, can cause leptin signaling dysfunction.

Leptin and Alzheimer's Disease: Human Studies

Recent epidemiological and human studies suggest that leptin can play an important role in AD. Similar to the association of low body weight to an increased risk of developing AD late in life, low plasma leptin levels in late-life have been consistently associated with increased risk for cognitive decline and the development of AD (Holden et al. 2009; Lieb et al. 2009; Zeki Al Hazzouri et al. 2013; Littlejohns et al. 2015). Furthermore, in several studies, plasma leptin levels have been found to be lower in MCI or AD subjects compared to control subjects (Bigalke et al. 2011; Johnston et al. 2013; Khemka et al. 2014; Baranowska-Bik et al. 2015) with the plasma leptin levels negatively correlating with the degree of dementia (Bigalke et al. 2011; Khemka et al. 2014). However, not all studies have found an association between plasma leptin levels and AD or cognitive decline (Oania and McEvoy 2015; Teunissen et al. 2015). Additionally, in the Prospective Population Study of Women in Gothenburg, Sweden, a longitudinal cohort study, mid-life serum leptin levels were not related to late-life dementia (Gustafson et al. 2012), suggesting that the changes in circulating leptin levels associated with AD may occur in late-life but not in mid-life. Any discrepancies among these studies could be due to several factors including relatively small sample sizes in some of the studies, confounding factors such as exercise or diet that were not taken into account, and possible misclassification of AD as the diagnosis often relied exclusively on clinical criteria without the use of neuropathological confirmation or newer AD neuroimaging or CSF biomarkers. Appropriately powered studies using AD neuroimaging or CSF biomarkers taking into account the possible confounding factors could help address these problems.

While peripherally circulating leptin levels presumably correlate with the amount of leptin acting on the brain, this may not be accurate in AD as megalin (or LRP2) mediated transport of leptin across the blood–brain barrier could be downregulated in AD (Dietrich et al. 2008). In order to address this issue, some investigators have examined leptin levels in the CSF as a marker of brain leptin levels. However, the results from these studies are somewhat conflicting with reports of both increased or unchanged CSF leptin levels in AD subjects compared to controls (Bonda et al. 2014; Maioli et al. 2015). One possible explanation for the unchanged or increased CSF leptin levels in AD is the development of neuronal leptin resistance in AD. In a study of postmortem human AD brains, leptin receptor (LepRb) mRNA was found to be significantly decreased in the hippocampus (Bonda et al. 2014). Additionally, a significant number of leptin receptor positive cells were co-localized with neurofibrillary tangles, which was associated with an overall decrease in the number of phosphorylated active leptin receptors (Bonda et al. 2014). Based on these results, the authors of the study hypothesized that the neurofibrillary tangles blocked the accessibility of leptin receptor to the circulating leptin in the brain to effectively cause leptin resistance in those neurons leading to an increase in CSF leptin levels (Bonda et al. 2014). Another postmortem human AD brain study found overall similar results with a decrease in the number of hippocampal neurons positive for leptin receptor, phosphorylated active leptin receptor, and phosphorylated STAT3, a marker of leptin activity (Maioli et al. 2015). Together, these studies support the possibility that neuronal leptin resistance may develop as a consequence of AD pathology; however, additional studies are clearly needed to verify these findings in not only the hippocampus but in other brain regions that are known to be responsive to leptin such as the hypothalamus.

The Bidirectional Role of Leptin in Alzheimer's Disease: A Model and Considerations for Future Studies

The past few years have seen significant advances in elucidating the complex interactions between AD and body weight/systemic metabolism and in particular the role of leptin in AD. One seeming paradox that should be addressed is how to reconcile that mid-life obesity is generally associated with an increased risk of developing AD, but late-life weight loss is associated with an increased risk for developing AD and is also a common early clinical manifestation of AD (Emmerzaal et al. 2015). This could potentially be explained by considering that being either obese or underweight effectively results in a low leptin or leptin deficient state. Obesity would lead to pathologically high levels of circulating leptin and the subsequent development of central leptin resistance, while pathologically low body weight would lead to low production of circulating leptin (Fig. 3). Thus, the net effect from being either significantly obese or underweight would therefore be the same from a brain leptin signaling perspective.

Based on our current understanding, we propose the following model for how leptin can have a bidirectional role in AD that ultimately results in a progressive downward spiral of worsening AD pathology and leptin dysfunction (Fig. 3). On the one hand, pathologically low leptin levels and leptin signaling deficits would be directly detrimental to overall brain health and in particular AD in two significant ways. As leptin is important in maintaining proper hippocampal structure and function, low brain leptin signaling could lead to impairment in hippocampal function resulting in decline in cognition and memory (Irving and Harvey 2014). In addition, low brain leptin signaling would also decrease the neuroprotective effects of leptin from Aβ and tau leading to worsening AD pathology (Fewlass et al. 2004; Greco et al. 2009a, 2011; Yamamoto et al. 2014). On the other hand, AD pathology, in of itself, may also contribute to leptin signaling dysfunction and its associated body weight and systemic metabolic deficits. Accumulation of Aβ and tau in the choroid plexus could lead to inhibition of transport of leptin across the blood–brain barrier (Dietrich et al. 2008), while accumulation of Aβ and tau in the hypothalamus could lead to insensitivity to circulating leptin levels in pathways that are critical for maintaining body weight and metabolic homeostasis (McDuff and Sumi 1985; Saper and German 1987; Ishii et al. 2014; Ishii and Iadecola 2015). Therefore, the worsening AD pathology would lead to further dysfunction in leptin signaling and worsening deficits in body weight and systemic metabolism. The bidirectional nature would mean that detrimentally affecting either leptin signaling or AD pathology would directly affect the other and lead to a progressively worsening downward spiral.

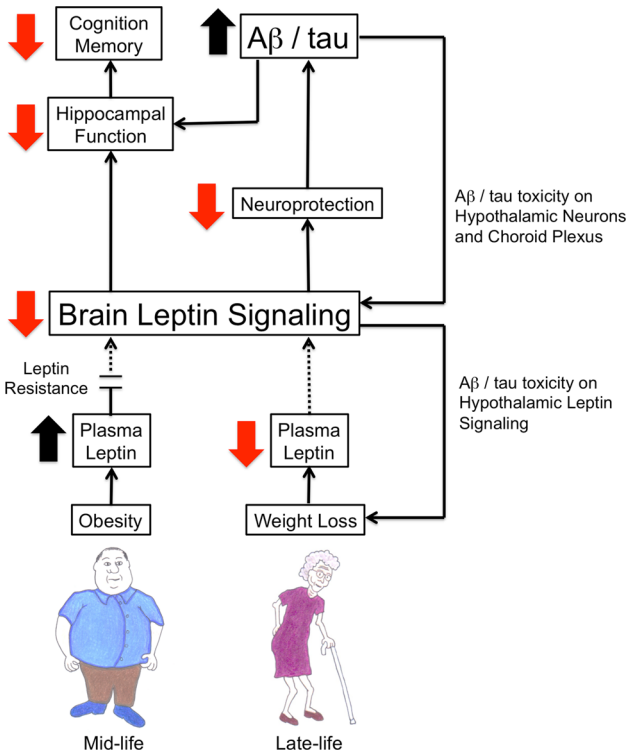

Fig. 3 Model: the bidirectional role of leptin in Alzheimer's disease. Both mid-life obesity and late-life weight loss are associated with worsening cognitive decline and increased risk of developing Alzheimer's disease (AD). This seemingly paradoxical relationship between body weight and AD could be explained as both mid-life obesity and late-life weight loss constitute a low brain leptin signaling state. Mid-life obesity leads to high circulating leptin levels and subsequent central leptin resistance to the pathologically high leptin levels, while late-life weight loss leads to low circulating leptin levels. The low brain leptin signaling would lead to worsening hippocampal function and decreased neuroprotective effects against AD pathology such as Aβ and tau. Increased accumulation of Aβ and tau could further disrupt hippocampal neurons and inhibit cognition and memory. In addition, Aβ and tau could affect hypothalamic neurons or the choroid plexus to inhibit hypothalamic leptin signaling or block the transport of leptin across the blood–brain barrier, respectively. This would lead to further inhibition of brain leptin signaling and progressively worsening body weight and systemic metabolic deficits. Therefore, this proposed model demonstrates how leptin can be both a contributor and a consequence of AD pathology that ultimately results in a progressive downward spiral of worsening AD pathology and leptin dysfunction

Despite our increased understanding of leptin dysfunction in AD, there are several issues that need to be addressed. As evidence accumulates that mid-life obesity and systemic metabolic changes such as diabetes are strongly associated with an increased risk of dementia (Emmerzaal et al. 2015), the role of leptin in mid-life and how it influences the development of AD needs to be further explored. While several epidemiological studies have consistently reported

that low plasma leptin levels later in life are associated with worsening cognitive decline and increased risk of developing AD (Holden et al. 2009; Lieb et al. 2009), a study that investigated mid-life plasma leptin levels found no significant changes (Gustafson et al. 2012). The results from this study need to be verified in other populations. Furthermore, additional studies investigating how leptin affects AD pathobiology including identifying the underlying cellular and molecular mechanisms are needed. Here, carefully designed animal models would be particularly useful. For example, pair-feeding studies with and without exogenous leptin treatment in animal models would be extremely informative in delineating the effects specifically due to leptin from those that are due to changes in body weight and its associated metabolic and hormonal derangements (Schwartz et al. 1996a). Nutrition and exercise also clearly influence the risk of developing AD (Barnard et al. 2014). Both Mediterranean diet and regular aerobic exercise have been demonstrated to reduce the risk of developing AD; however, the cellular and molecular mechanisms underlying the beneficial effects of specific diets and exercise need to be investigated (Barnard et al. 2014). Since diet and exercise can potentially influence the circulating leptin levels and central leptin sensitivity (Bouassida et al. 2010; Greco et al. 2014; Balaskó et al. 2014), leptin may serve as one of the intermediary signals linking diet and/or exercise to AD. However, studies are needed to clarify whether any effects of diet and/or exercise are due to changes in leptin levels or from alterations in body weight and other factors. Also, adipokines and other metabolic factors such as insulin, adiponectin, resistin, and RBP4 may affect AD pathobiology either in isolation or more than likely in concert with leptin (Kiliaan et al. 2014).

Additionally, it is unclear once Aβ and tau begin to accumulate in the brain how these pathogenic factors affect brain circuits involved in the leptin pathway. There is some evidence from our work in mouse models that Aβ can affect the normal responses to leptin in hypothalamic NPY neurons (Ishii et al. 2014); however, the exact cellular and molecular mechanisms underlying the Aβ-mediated inhibition of these neurons are unknown. Furthermore, as AD affects numerous physiological and behavioral functions that are associated with the hypothalamus such as sleep and circadian rhythm (Musiek et al. 2015; Ishii and Iadecola 2015), other hypothalamic cell populations are likely to be affected by Aβ and tau. Therefore, studies that seek to identify the specific cell populations affected by Aβ and tau are needed.

Leptin and Alzheimer's Disease: Moving from the Bench to the Bedside

The evidence summarized in the previous sections demonstrates the significant role that leptin has on the pathobiology of AD. Furthermore, there are several appealing aspects of leptin as a novel therapy and a potential new diagnostic tool for AD. First and foremost, chronic leptin administration has been found to be safe and well tolerated in several human clinical trials (Paz-Filho et al. 2015). Importantly, leptin treatment has been found to be effective for lipodystrophy and congenital leptin deficiency syndromes, and a form of leptin, metreleptin (recombinant methionyl human leptin), was recently approved by the US FDA as a medical therapy for congenital or acquired (non-HIV-related) generalized lipodystrophy (Paz-Filho et al. 2015). However, it remains unclear without a clinical trial whether leptin would be an effective treatment for AD. When considering any potential clinical trial using leptin as a therapy for AD, it is important to determine which patients would potentially benefit the most from leptin therapy. As treating AD once the dementia begins may be too late to reverse the neurodegeneration, starting treatments as early as possible is likely to yield the highest success. Insights obtained from clinical trials with leptin as an anti-obesity agent also suggest that leptin treatment may have the highest benefits in those who have low levels of circulating leptin as a replacement therapy as opposed to those with possible central leptin resistance due to high circulating leptin levels, where exogenous leptin administration may have little effect. Therefore, leptin may be a beneficial therapy for those individuals at high risk for developing AD or in the preclinical AD stages that have low plasma leptin levels. Since leptin treatment with an adjunct such as amylin has been shown to restore the responsiveness of leptin (Roth et al. 2008), a combination therapy approach can be considered in those individuals who have evidence of both central leptin resistance and AD. Finally, targeting pathways down-stream of leptin such as the first order NPY and POMC-expressing arcuate neurons should also be considered (Ishii et al. 2014).

Leptin could also have a role in the diagnosis of AD. Even in the hands of the most skilled clinician, accurately diagnosing AD based solely on clinical criteria can be challenging. In one study investigating the accuracy of the clinical diagnosis of AD at National Institute on Aging Alzheimer Disease Centers, the sensitivity in diagnosing AD ranged from 70.9 to 87.3 % while the specificity ranged from 44.3 to 70.8 % (Beach et al. 2012). Therefore, neuropathological confirmation is still needed in many cases. The introduction of new AD neuroimaging and CSF biomarkers based on Aβ and tau can increase the sensitivity and specificity of the diagnosis and may eventually be integrated into the routine diagnosis of AD; however, they are currently most useful in the research setting for AD risk stratification or identifying and classifying individuals who are at the earliest stages of AD including

asymptomatic or preclinical AD (Sperling et al. 2011; Fagan 2014). As studies directly investigating leptin as a diagnostic tool for AD are lacking, it is unclear at this point if measuring leptin levels either from plasma or CSF would add any additional diagnostic benefit. However, if epidemiological studies demonstrating that low plasma leptin levels especially in late-life correlate with increased risk of AD are confirmed (Lieb et al. 2009), then plasma leptin levels or changes in plasma leptin levels over time may play an important role in identifying those who are either at high risk of developing AD or in the asymptomatic or preclinical stages of AD. Therefore, leptin by itself or more likely as an adjunct diagnostic tool could be useful in identifying those at the earliest stages of AD. In addition, longitudinal studies would be helpful in identifying whether changes in leptin levels correlate and track with disease progression and worsening AD pathology. While there is potential for leptin to serve as both a novel therapeutic and diagnostic target, particularly early in AD, additional studies are clearly needed to test the clinical utility of leptin in AD.

Conclusions

The past few years have seen an increased recognition for the role that body weight and systemic metabolism have on the pathobiology of AD. This association highlights the importance that hormones regulating body weight and metabolism such as leptin may have on AD. In this review, we briefly summarized the role of leptin in AD from cellular and animal models to recent human studies. The accumulating evidence from these studies collectively suggests that leptin has a pro-cognitive and neuroprotective role against AD. Furthermore, we propose that leptin has a bidirectional role in AD, where dysfunctional leptin signaling can worsen cognition and increase AD pathology, while worsening AD pathology can in turn cause dysfunctional leptin signaling, which together results in a downward spiral of progressive neurodegeneration and worsening weight loss and metabolic deficits. Therefore, leptin is well positioned to serve as a vital link between body weight/systemic metabolism and AD. While there are many unanswered questions that need to be addressed, future studies will help determine whether leptin and leptin signaling pathways will fulfill its potential as a novel drug target and diagnostic tool in AD.

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Compliance with Ethical Standards

Conflict of Interest All authors declare no conflicts of interest.

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