



Repositioning leptin as a therapy for Alzheimer's disease

The data from the initial clinical trials utilizing recombinant human leptin as an obesity therapy were published in 1998. Since then, numerous studies have been described which address dosage, safety and efficacy of leptin replacement for a variety of disorders with diverse patient groups, including pediatric and adult subjects. We review the current clinical trial data, demonstrate that leptin administration is safe for long term use in humans, and summarize reported cognitive benefits. The functions of leptin in neuroprotection and cognition have been largely overlooked. Accumulating data suggest a very significant application of leptin may be a therapy for Alzheimer's disease.

KEYWORDS: Alzheimer's disease • cognition • leptin • neurodevelopment • neurons

Leptin is a 16 kDa hormone primarily produced by adipocytes whose name derives from leptos, the Greek word for thin. This hormone is best known for its effects on fat mobilization and energy homeostasis. Numerous studies of human leptin have been reported to date, and leptin deficiencies or resistance have been reported in a variety of disorders ranging from congenital obesity to Alzheimer's disease (AD). More than 60 studies, encompassing over a thousand subjects, have involved the administration of leptin to human subjects (PubMed database search using the search terms: 'recombinant leptin' and 'human clinical trial'). These studies, which utilized either recombinant methionyl human leptin (r-metHu-Leptin; Amylin Pharmaceuticals) or pegylated recombinant native human leptin (PEG-OB; Hoffman-La Roche), were designed to address dosage, safety and efficacy for the treatment of a number of human conditions, particularly obesity and leptin deficiency, and are discussed below. A major focus of this article is the consideration of leptin replacement for AD patients as an interventional therapeutic as well as a preventative agent for those at risk.

Overview of leptin biology

Leptin is an adipocyte-derived hormone, originally identified in 1994 [1], with important roles in fat storage and metabolism, immune and reproductive function, bone homeostasis, insulin sensitivity and neuronal protection. Endogenous leptin is secreted in a pulsatile rhythm with the highest levels secreted between midnight and early morning. Circulating leptin

levels can vary throughout the day, and are primarily dependent on adipose mass and secondarily on feeding status [2]. Leptin levels are higher in premenopausal women than in men, and physiological plasma leptin levels vary from 0 ng/ml in congenital leptin deficiency subjects, to more than 100 ng/ml in some morbidly obese subjects.

Leptin exerts activity through signal transduction at the leptin (obesity) receptor (ObR). Six isoforms of the ObR have been identified to date, with signaling pathways associated with the long isoform of the leptin receptor (ObRb) being the best studied [3]. Leptin receptors are widely distributed throughout the CNS as well as in peripheral tissues. Within the brain, the leptin receptor is highly expressed in the hypothalamus, hippocampus, midbrain and hindbrain [4]. Leptin from the hypothalamus is linked to a role in feeding behavior [5] as well as in neuroendocrine function [6]. Rodents with mutations in the leptin receptor (db/db, fa/fa) and those with two faulty copies of leptin (ob/ob) exhibit an obese phenotype, and only leptin-deficient mice (ob/ob) can attain normal weight following leptin infusion [7]. Of particular interest is the high expression of the ObRb in the hippocampus, a region of the brain intricately involved in memory and cognition, and which is highly affected by AD pathology.

The leptin receptor is a member of the class 1 cytokine receptor superfamily, which can activate a number of signal transduction components, including JAK2, which subsequently phosphorylates STAT3 to mediate transcription of a number of genes. Leptin has also been

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shown to activate PI3K in a number of tissue types (hypothalamic, adipose, liver and muscle) and MAPKs, particularly ERK1/2 [8].

A number of significant extrahypothalamic activities have been described for leptin including an influence on neuronal plasticity that could be important for cortical development, cognition and repair [9]. More specifically, the cellular events mediated by leptin include synaptogenesis, neurogenesis, axon growth and neuroprotection [10]. Leptin's role in neurodevelopment is clearly evident in the brains of the ob/ob, genetically obese and diabetic mice, who have been shown to have striking structural differences compared with those of normal control mice [11]. The brain abnormalities in ob/ob mice include an overall reduced density of neurons, reduced levels of synaptic protein expression and elevated levels of growth-associated protein in the hippocampus and neocortex [12,13]. These abnormalities are reversed by an injection of leptin during early life. Leptin has been shown to alter the morphology of dendrites [14] and influence the density of synapses as well as plasticity of cortical circuits in the developing brain [9,10,13], and these changes occur rapidly in response to ongoing synaptic activity [14].

A strong association between leptin and cognition and memory formation has been demonstrated by many studies ranging from human trials (clinical and observational/epidemiological) to *in vitro* studies. Specifically, our studies showed, for the first time, that leptin can reduce levels of amyloid- β (A β) burden and of phosphorylated tau protein in neuronal cells within hours in culture [15,16]. Furthermore, administration of leptin to transgenic mouse models of AD reduces pathology and improves cognitive performance [17]. Others have shown that leptin increases cell proliferation in the dentate gyrus and hippocampus [18]. Accumulating evidence from numerous sources strongly supports that leptin therapies for a number of CNS disorders are likely to be developed in the near future. To date, the major clinical focus has been metabolic disorders including obesity, lipoatrophy, lipodystrophy and amenorrhea. These studies were carried out in a large number of cases, as described below, and met with limited success, only in rare genetic conditions of leptin deficiency. These studies suggest that leptin may have a minimal effect on feeding in our environment of excess. Clearly, leptin has numerous actions and possible therapeutic targets and therefore should not be classified solely as an antiobesity agent. A much larger group of patients, afflicted with cognitive

CNS diseases, including eating disorders, depression, memory impairment in HIV-infected individuals and AD, are more likely to benefit from leptin intervention, given the additional role of leptin in neuronal physiology.

Leptin in clinical studies

■ Obesity

Leptin studies to date have utilized one of two leptin sources, r-metHu-Leptin, or PEG-OB, both administered by subcutaneous injection. The majority of clinical studies have utilized r-metHu-Leptin initially as a therapy for obesity following the discovery of the leptin–obesity connection. However, these studies were largely unsuccessful likely due to the fact that obese human individuals already have high circulating leptin levels and are in a leptin-resistant state [19]. The mechanism behind leptin resistance is not fully understood, although it has been suggested that leptin resistance might result from the saturation of the endogenous leptin transporter, however, additional mechanisms such as blockade of the leptin transporter by C-reactive protein and/or circulating fatty acids such as palmitate [20], as well as triglycerides [21,22] known to be elevated in obesity, have been implicated in leptin resistance. Clinical studies have since shown that up to 0.3 mg/kg/day of recombinant leptin, administered peripherally to obese patients, is able to cross the blood–brain barrier, and increase leptin levels measured in the cerebrospinal fluid, possibly through an independent mechanism [23]. These observations support the hypotheses that the leptin resistance evident in obesity may result from impaired signal transduction at the leptin receptor or mechanisms other than leptin itself saturating the transporter.

Congenital leptin deficiency, a rare homozygous mutation of the leptin gene, results in extreme obesity, voracious appetite, hyperinsulinemia, hyperlipidemia and neuroendocrine abnormalities. Leptin replacement in children and adults afflicted with this disorder has been shown to restore serum insulin and cholesterol levels as well as having beneficial effects on appetite and weight loss, and menstrual abnormalities in females [24–30]. Such studies have demonstrated that low-dose leptin (0.01–0.04 mg/kg/day) is efficacious in ameliorating the metabolic disturbances associated with congenital leptin deficiency and can be used safely, even in children, for years with no adverse effects [31].

A larger group of obese individuals without the leptin-related genetic mutations were tested in clinical trials with supraphysiologic doses of

leptin, up to 0.3 mg/kg/day, in an attempt to overcome leptin resistance in these patients [19,32]. However, increasing leptin levels in subjects with already high circulating leptin levels was ineffective at inducing weight loss [19,32]. Even at these high leptin doses, no adverse effects of therapy were found, with the major reported event being a mild-to-moderate reaction at the injection site. Weekly injections of PEG-OB (at higher doses of 20–60 mg), which has a longer half-life than r-metHu-Lep, was also found to be safe and well-tolerated, although the subjects did not lose weight or body fat when compared with obese subjects receiving placebo [33,34]. In combination with a low energy diet, a higher PEG-OB dose (80 mg) was found to induce moderate weight loss when compared with placebo-injected obese control subjects [35,36]. More recently, r-metHu-Leptin used in combination with pramlintide, an amylin analog, was found to produce significantly more weight loss in individuals than either therapy alone [37–40]. These findings suggest that a leptin monotherapy for obesity is ineffective, and while additional pharmaceutical intervention may have some benefit, the benefit is small. Currently, leptin combinational trials for obesity have been suspended and leptin is no longer under development as either a mono- or combination therapy.

■ Lipodystrophy

Lipodystrophy is a disorder of adipose tissue that is characterized by degeneration of body fat. Lipodystrophy may result from a rare congenital disorder or be acquired as a result of an underlying autoimmune or infectious disease. The loss of body fat, or lipoatrophy, leads to the loss of circulating leptin in afflicted individuals, which in turn leads to hyperglycemia, dyslipidemia, fatty liver and hypertriglyceridemia. In the case of patients with congenital lipodystrophy, leptin levels are <4 ng/ml, and replacement therapy at physiological doses (0.03–0.04 mg/kg/day) decreases triglycerides and liver volume, and improves glycemic control enough to reduce the patient's dependence on antidiabetic medications [41–43]. Leptin replacement also had beneficial effects on menstrual abnormalities in females with congenital or severe lipodystrophy. More specifically, leptin improved their menstrual profile, raised estrogen E2 levels and restored the luteinizing hormone response to luteinizing hormone releasing hormone [41–44].

The benefits of leptin therapy remain less clear in other forms of partial lipodystrophy. Plasma leptin levels are low in patients with

partial lipodystrophy, although higher than those of patients with congenital lipodystrophy. Partial lipodystrophy afflicts a greater number of patients than congenital lipodystrophy and the leptin deficiency is secondary to a primary disorder such as anorexia or HIV infection. Clinical studies of leptin administration to HIV-positive patients have shown that replacement of leptin (0.04–0.08 mg/kg/day) improves fasting insulin, insulin resistance, high-density lipoprotein and truncal fat mass, and has no adverse effects on HIV control [45–47]. These studies suggest that leptin replacement may be beneficial to some patients with partial lipodystrophy, including HIV-positive patients, and can be used in combination with existing antiviral medication programs [48].

Leptin, the hippocampus & the cortex

Accumulating evidence suggests that leptin has pleiotropic effects on the brain [10], although the most studied mechanisms of leptin's actions are those related to the neuroendocrine functions of the hypothalamus.

Altered neuroanatomical organization in the CNS of genetically obese (ob/ob) mice [11] was first reported in 1979, and these mice have significantly reduced brain weights and cortical volumes compared with lean, control mice. Neurons from almost all brain regions studied have a reduced density and although the hypothalamus is spared from this, hypothalamic neurons have an altered dendritic orientation. Human studies using volumetric MRI of the brain have since shown that both genetically and nongenetically obese individuals have reduced gray matter in several brain regions including the anterior cingulate gyrus, the inferior parietal lobule and the cerebellum, when compared with normal individuals [49,50]. Additional studies of the brains from (ob/ob) mice have shown that leptin deficiency alters glial and synaptic proteins in a number of regions including the neocortex and hippocampus [12]. The administration of exogenous leptin corrects these deficits and restores cell densities [13].

More recent experiments have shown that the neuronal circuits of the hypothalamus, cortex and hippocampus develop during early development and abundantly express leptin receptors. A leptin deficiency during this period results in a reduced number of cortical neurons during embryonic life, as demonstrated by 5-bromodeoxyuridine labeling [7,9]. In adulthood, reduced neurogenesis is a feature of aging as

well as Alzheimer's degeneration [51], impairing recovery from disease and injury. Injection of leptin in adult mice has been shown to increase neurogenesis in the dentate gyrus, leading to integration of neurons in the hippocampus [52] as well as enhanced memory and learning [15,53]. In addition, leptin has neuroprotective effects against cell death induced by excitotoxic and oxidative insults and death induced by neurotrophic factor withdrawal in both the developing and adult hippocampus [15,16,54]. Culture of hippocampal neurons has localized leptin receptors to axonal processes, somatodendritic regions and synapses, and the density of dendritic filopodia and synaptic morphology can be modulated by leptin [14]. The effects of leptin on hippocampal plasticity are mediated through the MAPK/ERK pathway and the synaptic activation of NR2A-containing *N*-methyl-D-aspartate receptors. These studies support a role for leptin in learning and memory processing, which are functions that are impaired in aging and AD. Leptin may additionally affect neuronal survival through action on non-neuronal cells, such as astrocytes [55] and oligodendrocytes [56], known to provide trophic support for neurons.

The effects of leptin on neuronal function in humans have been illustrated by clinical studies of leptin in the human brain. In one such study, Matochik *et al.* reported that three adults with congenital leptin deficiency showed sustained increases in gray matter volume in the anterior cingulate gyrus, the inferior parietal lobule and the cerebellum, but not the hypothalamus, after 18 months of leptin replacement at physiological doses [49]. These changes persisted over 3 years of leptin replacement and could be reversed following a period of leptin withdrawal [57]. A second study by the same group, evaluated the effect of leptin on the neurocognitive development of a 5-year-old boy with congenital leptin deficiency [30]. In addition to the typical features of obesity, dyslipidemia and poor glycemic control, this subject had neurocognitive baseline tests lower than developmentally expected. After 2 years of physiological leptin replacement, the authors noted significantly improved neurocognitive skills.

Leptin replacement may also benefit HIV-infected subjects, who have been shown to exhibit poor learning and memory performance correlating with low leptin levels [58]. In addition, leptin levels have been linked to mood and eating disorders [59–62], autism [63], Parkinson's disease [64,65], aging [66] and AD [67–70]. In the majority of these disorders, circulating leptin

levels are low, although in the case of autism, high leptin levels in the absence of obesity may lead to dysfunctional neural pathways [63].

Leptin & AD

The animal and human studies to date demonstrate that leptin can affect brain structure and function and strongly implicate a role for leptin in cognitive disorders (TABLE 1). Indeed, accumulating evidence from independent studies link altered circulating leptin levels to AD. The first small study, reported in 2001 [68], showed that AD patients have significantly lowered serum leptin levels. A much larger prospective study of 2871 subjects demonstrated that elderly individuals, followed over 4 years, with high leptin levels were less likely to develop AD than those with low leptin levels [69]. One recent study of 41 patients correlated low circulating leptin levels with early AD and vascular risk factors [67]. A fourth study followed 785 healthy individuals from the Framingham cohort for 8.3 years and showed that higher leptin levels were associated with a lower risk of dementia [70]. In addition, participants within the lowest quartile for leptin levels were at a fourfold higher risk for developing AD than those in the highest quartile leptin group. When leptin levels were correlated with total brain volumes, body mass index and percentage body fat, it was noted that high leptin levels were protective among lean individuals but not the obese, whose high leptin levels may contribute to leptin resistance (see above).

These data underscore the significance of leptin in cognition and AD pathology. Plasma leptin deficiency and other metabolic disturbances may be disease risk factors more than a decade before symptoms of AD present [71,72]. The disease unfolds with increasing impaired cognitive function and accumulating extracellular deposition of A β , in the form of proteinaceous plaques, along with neurofibrillary changes, which result from hyperphosphorylation of tau that forms threads, which disrupt microtubule function and lead to dendritic breakage [73], synapse loss and somal deposits of neurofibrillary tangles. While the risk of disease increases with advancing age, the underlying cause is unknown, except for a few rare genetic familial AD cases. However, the strongest genetic risk factor for late-onset AD is expression of the apolipoprotein E4 allele (APOE) [74,75], suggesting that aberrant lipoprotein function can increase AD pathogenesis. Studies in cell culture and animal models have shown that lipids, such as ceramide and cholesterol, can influence amyloidogenic pathways [76].

Table 1. Plasma leptin levels and human brain function: a summary of current literature strongly correlate leptin levels with many aspects of cognition and behavior.

Study	n	Main findings	Ref.
Leptin in anorexia nervosa	44	Serum leptin levels were found to be lower in anorexic subjects than in control subjects	[61]
Circulating leptin levels and weight loss in Alzheimer's disease patients	8	Low leptin levels correlate with Alzheimer's disease	[68]
Leptin in functional hypothalamic amenorrhea	88	Plasma leptin is significantly lower in women with hypothalamic amenorrhea	[90]
The role of leptin in the etiopathogenesis of anorexia nervosa and bulimia	58	Serum leptin was found to be reduced in anorexic patients compared with healthy controls. No differences were observed with bulimic subjects	[60]
Low CSF leptin in female suicide attempters with major depression	72	Women admitted to hospital following a suicide attempt were found to have a correlation between low leptin levels and major depression	[62]
Low CSF leptin levels are associated with worse learning and memory performance in HIV-infected men	59	Lower CSF leptin levels correlated with impaired learning and memory when patients were adjusted for viral RNA and treatments	[58]
Relationship between plasma leptin concentration and human brain structure: a voxel-based morphometric study	32	Plasma levels correlate with gray matter volume of the left cerebellum and left inferior temporal gyrus and negatively correlate with inferior frontal operculum, left postcentral gyrus and right putamen. Gray matter is reduced in these areas in obese individuals	[50]
Serum leptin levels are higher in females affected by frontotemporal lobar degeneration than Alzheimer's disease	84	Females, but not males, with frontotemporal lobar degeneration with eating disorders had higher plasma leptin than females with Alzheimer's disease	[59]
Serum leptin and cognition in the elderly: findings from the health ABC study	2871	Elders with high leptin had less cognitive decline than those in the low leptin group	[69]
Association of plasma leptin levels with incident Alzheimer's disease and MRI measures of brain aging	785	A prospective study comparing plasma leptin to brain volume that correlated low leptin with dementia and severity of dementia	[70]
Relationship between plasma leptin level and brain structure in elderly: a voxel-based morphometric study	34	Plasma leptin correlated with gray matter in the right hippocampus, left parahippocampus and right cerebellum	[66]
Adipocytokines and CD34 ⁺ progenitor cells in Alzheimer's disease	41	Low plasma leptin levels and common vascular risk factors correlate with Alzheimer's disease	[67]

CSF: Cerebrospinal fluid.

Further epidemiological and clinical studies have shown that there is an increased AD risk in patients with diabetes mellitus [77,78], insulin resistance or hyperinsulinemia [79]. In these patients, abnormal insulin signaling and aberrant glucose utilization in the CNS may metabolically disrupt brain cells with increasing severity over time. Accordingly, several related metabolic disruptions may trigger, and/or contribute to, the extracellular accumulation of A β and the formation of neurofibrillary tangles (FIGURE 1).

Leptin has been shown to directly regulate both *in vitro* and *in vivo* levels of A β [15,17]. In cell culture studies, leptin reduces extracellular

A β secretion and increases apoE-dependent A β uptake through the regulation of lipids and neuronal membrane fluidity. In addition, we have shown that leptin reduces the accumulation of phosphorylated tau in SH-SY5Y cells as well as in primary neurons [16]. The ability of leptin to reduce both A β accumulation and hyperphosphorylation of tau, independently and directly, implicates a leptin target upstream of both pathological cascades. Indeed, it was demonstrated that AMPK could serve as such a target [80]. AMPK activation switches cells from lipid biosynthesis to glucose oxidation to generate ATP and control energy availability [81]. AMPK is

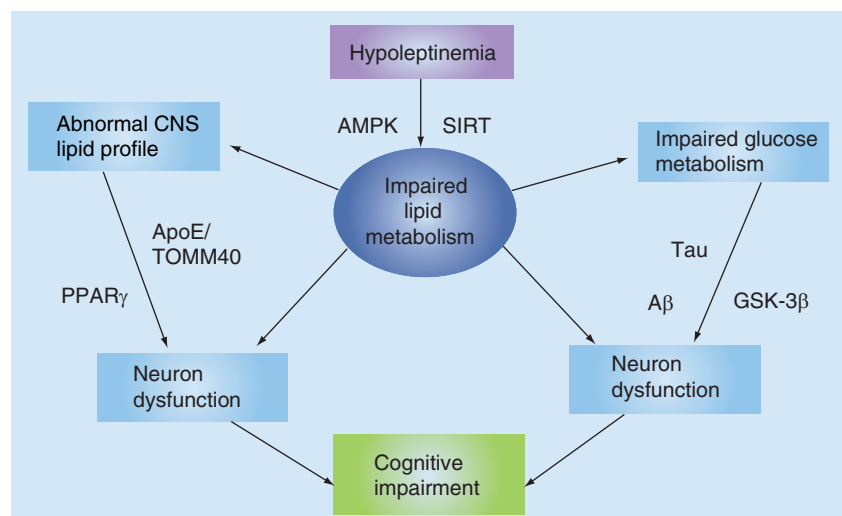


Figure 1. Low circulating leptin levels may lead to cognitive impairment through a number of overlapping pathways. Low leptin levels can lead to energy impairment, affecting AMPK and, consequently, A β processing and tau phosphorylation through a mechanism that involves GSK-3 β . Abnormal CNS lipid profile and/or genetic risk from apolipoprotein E result in abnormal cellular lipid processing and changes in membrane fluidity. These events could change cognitive function independently or through co-operative mechanisms. A β : β -amyloid; AMPK: AMP-activated protein kinase; ApoE: Apolipoprotein E; GSK: Glycogen synthase kinase; PPAR γ : Peroxisome proliferator-activated receptor γ ; SIRT: Sirtuins; TOMM40: Translocase of outer mitochondrial membrane 40 homolog.

activated by both insulin and leptin, and both agents can inhibit tau phosphorylation through AMPK-dependent deactivation of GSK3 β . Leptin, however, was found to be two orders of magnitude more potent than insulin at suppressing tau phosphorylation [16]. The link between energy impairment and neuronal dysfunction is illustrated in FIGURE 1. The studies described above strongly suggest that leptin has the potential to modulate AD pathogenesis.

Recent animal studies have shown that chronic leptin treatment in CRND8 transgenic AD mice has beneficial effects on AD pathology and cognitive decline [17]. Leptin-treated animals showed reduced A β levels in brain and serum, and reduced plaque size and tau phosphorylation compared with saline-treated transgenic controls after 8 weeks of treatment. Furthermore, a battery of behavioral tests showed that leptin treatment improved novel object recognition as well as contextual and cued fear conditioning compared with saline-treated transgenic controls. The cognitive improvements observed may reflect the reduced amyloid burden of the hippocampus in treated transgenic animals. Our results are supported by a study that showed that direct injection of leptin into rodent hippocampus improved memory processing by modulating long-term potentiation and synaptic plasticity [53]. Taken together, these data demonstrate the efficacy of leptin in improving cognitive function in rodents [17,79]. Further, leptin treatment was not associated with any increase in inflammatory markers in the CRND8 mice [17].

Leptin replacement therapy in AD

Leptin has been tested in over a thousand patients in clinical trials in the last 10 years. These studies have assessed safety, dose and pharmacokinetics [2]. It is clear from these studies that leptin has a half-life of approximately 3 h (2.8 ± 0.98 – 4.71 ± 2.16 h) and physiological dose replacement is safe to administer, even to children [30,31]. Reported adverse effects were mild and associated with injection site reactions rather than inflammatory reactions to leptin itself.

Table 2. Recombinant leptin administration and cognitive effects in humans: a summary of studies in which subjects received leptin therapy followed by functional MRI and/or cognitive assessment.

Study	n	Main findings	Ref.
Effects of exogenous leptin on satiety and satiation in patients with lipodystrophy and leptin insufficiency	8	Leptin treatment increased time between eating a meal after fasting to voluntary eating again	[91]
Effect of leptin replacement on brain structure in genetically leptin-deficient adults	3	Sustained gray matter increases in anterior cingulate gyrus, inferior parietal lobule and cerebellum	[49]
Leptin replacement alters brain response to food cues in genetically leptin-deficient adults	3	During food viewing, leptin replacement reduced activation of regions linked to hunger (insula, parietal and temporal cortex) while enhancing activation of regions linked to satiety (prefrontal cortex)	[92]
Leptin replacement improves cognitive development	1	Neurocognitive tests were lower than expected but improved dramatically with leptin	[31]
Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli	6	Functional MRI in obese patients revealed that leptin could change neural activities in response to food cues in the brain stem, parahippocampal gyrus, frontal guri temporal gyrus and frontal gyrus	[93]

Note the beneficial effects of leptin on neural activity.

While the presence of plasma antibodies to leptin has been reported [82], these were not neutralizing and did not interfere with leptin action over long-term administration. In addition, healthy individuals are unaffected in any adverse way by leptin administration [83]. Thus, we believe that the cognitive improvement, observed in other patients receiving leptin therapy (TABLE 2), would be significant in Alzheimer's patients, who appear to represent an additional leptin-deficient group [72]. Leptin replenishment may be disease modifying, affecting both amyloidogenic and fibrillary tangle pathways and may have an added benefit as an insulin sensitizer.

As with all novel therapies, leptin replacement as an AD therapy will require rigorous testing. Leptin has been administered chronically in previous clinical studies, and such a protocol is expected to be required for AD therapy. Mild cognitively impaired patients will be recruited and screened for low circulating leptin levels and disease-related biomarkers in the cerebrospinal fluid such as $A\beta_{(1-42)}$ and total and/or phosphorylated tau. In addition, study participants will be selected for at least one APOE4 allele, because

homozygotes of the E4 allele are 15-times more likely to develop AD than noncarriers [84]. While carriers of the E3 allele have the same risk of AD as other elderly individuals, carriers of the E2 allele have a progressively decreased risk of AD. Recent studies have shown that the *TOMM40* gene has two polymorphic variants that could define E3 carriers into two risk forms: one that may be associated with E4 and one that may be associated with E2 [85]. We suggest that trial participants should additionally be genotyped for *TOMM40* [GRECO SJ, UNPUBLISHED DATA].

Whether the disease-modifying properties of leptin therapy will produce a clinically relevant reduction in cognitive decline remains to be seen. Previous studies suggest that low-dose leptin administration to healthy individuals is safe with negligible weight loss [86], but it is unknown whether leptin will have a safe/efficacious profile in mild cognitively impaired patients and AD patients who are advanced in age and commonly have other comorbidities that could affect $A\beta$ levels and safety. Additional concerns regarding the correlation between leptin levels and the growth of some cancers, including esophageal [87] and

Executive summary

Overview of leptin biology

- Leptin is a 16 kDa human peptide originally implicated in feeding behavior. Other roles include fat storage, metabolism, immune and reproductive function, insulin sensitivity and neuronal protection.
- The leptin receptor is highly expressed in the hypothalamus, the hippocampus and cortex.
- Leptin deficiency has been implicated in congenital obesity, lipodystrophy, amenorrhoea and Alzheimer's disease.

Leptin in clinical studies

- Congenital leptin-deficient subjects benefit from leptin replacement with physiological doses with weight loss and glycemic control. Other obese cases have high circulating leptin levels and leptin therapy has not been successful.
- Congenital lipodystrophy can be treated with leptin therapy at physiological doses. The resulting benefits include reduced triglyceride levels and liver volume, along with improved glycemic control and menstrual profile in females.
- Partial lipodystrophies, such as anorexia and HIV infection, have shown less clear results owing to disease heterogeneity. However, leptin replacement may be of particular benefit to HIV-induced lipodystrophy where no adverse effects on viral control were noted.

Leptin, the hippocampus & the cortex

- Leptin has pleiotropic effects on the brain and is critical for brain development.
- Leptin increases neurogenesis, axonal growth and hippocampal synaptogenesis.
- Leptin replacement has resulted in improved cognition in four subjects with congenital leptin deficiency.
- Leptin has an important role in cognitive processes.

Leptin & Alzheimer's disease

- Low levels of leptin have been linked to Alzheimer's disease in four independent studies with over 3000 patients.
- Leptin reduced neuronal tau phosphorylation and amyloid β accumulation/secretion, hallmarks of Alzheimer's pathology, in cell cultures *in vitro*.
- Leptin injection improved cognitive performance and brain pathology in transgenic mouse models of Alzheimer's disease.

Leptin replacement therapy in Alzheimer's disease

- Circulating leptin levels are inversely correlated with Alzheimer's disease severity.
- Disease modifying effects of leptin in cell and animal cultures will benefit Alzheimer's patients and improve cognition.
- Rigorous testing is required because aging patients have comorbidities that may be of concern.

Future perspective

- Previous studies indicate that leptin is safe, even for use in children, at the proposed physiological doses.
- Long-term use is indicated and no immunological reaction to leptin has been reported.
- Leptin may have an additional benefit as an insulin sensitizer.

breast [88], in cell and animal models await further investigation, although these adverse effects have not been described in subjects receiving long-term leptin replacement to date [8,31,44].

Future perspective

Increasing evidence suggests that AD is a progressive cognitive disorder with underlying metabolic disturbances [89], associated in some cases with low leptin, the hormone controlling energy homeostasis, as well as insulin-resistance and lipid dysregulation. Such disruptions overwhelm neurons, preventing adaptability to metabolic stress and, eventually, lead to cognitive impairment. Interventions that restore energy balance may be effective therapeutics for AD, including leptin therapy. Leptin is a natural hormone that can modify both the amyloid processing and tau hyperphosphorylation pathways of AD. This property of leptin is unique in that

existing therapies target either amyloidogenic or tau phosphorylation pathways, but not both. The pluripotent profile of leptin, as well as the low physiological dose required for replacement therapy and the established safety profile, support the study of leptin replacement in AD populations and those at risk presenting with low leptin levels.

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