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Leptin: A Novel Therapeutic Strategy for Alzheimer's Disease

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Abstract

Adipocyte-derived leptin appears to regulate a number of features defining Alzheimer's disease (AD) at the molecular and physiological level. One activity of leptin is the control of AMP-dependent kinase (AMPK). In addition to maintaining lipid levels, AMPK regulates glycogen synthase kinase-3, which modulates tau phosphorylation. Leptin has been shown to reduce the amount of extracellular amyloid-β, both in cell culture and animal models of AD, as well as reduce tau phosphorylation in neuronal cells. Importantly, chronic administration of leptin resulted in a significant improvement in the cognitive performance of transgenic animal models of AD. In humans, weight loss often precedes the onset of dementia in AD and the level of circulating leptin is inversely proportional to the severity of dementia among AD patients. It is speculated that a deficiency in leptin levels or function may contribute to systemic and central nervous system abnormalities leading to AD, suggesting that a leptin replacement therapy may be beneficial for AD. This may be an attractive alternative to the drugs that are currently under development.

Keywords

AICAR; AMP-dependent kinase; amyloid-β; glycogen synthase kinase-3; leptin; tau

INTRODUCTION

Leptin is a protein that was originally discovered as an adipocyte-derived hormone controlling feeding behavior through receptors in the hypothalamus [1]. Since its discovery, it has been shown that leptin has other important physiological roles in the control of fat storage or mobilization, the reproductive system, the immune system, bone homeostasis,

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insulin sensitivity [2–4], and neuronal activity and protection [5]. Leptin receptors have been identified in peripheral tissues, and of importance to this review, in neurons in the brain, including the hippocampus [5–7], which is particularly vulnerable in Alzheimer's disease (AD) [8].

While application of leptin agonists can reduce body weight and glucose levels in obese animals, such molecules have only met with limited success in clinical trials for obesity and diabetes as monotherapies [9]. However, greater success has recently been reported from rat and human studies when used in combination with pramlintide, an analogue of amylin [10]. The lack of efficacy with leptin monotherapy has been suggested to result from the development of leptin resistance, either due to the saturation of the transporter responsible for the movement of leptin from the periphery across the blood brain barrier or because of the desensitization of post-receptor signaling pathways in obese patients. Nonetheless, because of its pleiotropic nature, leptin or leptin agonists/antagonists hold promise as therapeutics in a variety of conditions. Leptin directly stimulates bone growth by inducing osteoblasts to make insulin-like growth factor-I, providing a basis for osteoporosis treatments [11]. The role of leptin in inflammation, may lead to therapies in inflammatory bowel disease, multiple sclerosis, sepsis, and arthritis [12].

In this review, the involvement of leptin in pathological pathways relevant to AD is examined. Specifically, *in vitro* and *in vivo* studies have shown leptin to positively impact amyloid-β (Aβ) homeostasis and tau phosphorylation and to improve, following chronic supplementation, the cognitive ability of animal models of AD. Interestingly, the observations from mechanistic studies suggest that an upstream component possibly linked to metabolic pathways and modulated by leptin precede amyloid plaque and neurofibrillary tangle (NFT) development. Indeed, evidence is provided to suggest that neuronal AMP-dependent kinase (AMPK) may fulfill that role.

An abnormal AMPK activity could potentially translate to abnormal lipid levels and membrane composition in neurons that would affect membrane fluidity and the physiology of lipid rafts, which accommodate many components of the machinery leading to Aβ production. Leptin has been shown to maintain balanced AMPK activity. Also, AMPK is known to regulate glycogen synthase kinase-3β (GSK-3β), a central tau kinase [13], and leptin, like the AMPK activator AICAR, can reduce tau phosphorylation at several sites [14] (Greco et al., unpublished results). Taken together, the mechanistic pathways that are influenced by leptin and that occur prior to amyloid deposition or tau phosphorylation, as well as potential cognitive improvements, highlight the importance of further development of therapies that increase leptin availability in the central nervous system (CNS). These therapies may include leptin supplementation, leptin receptor activation, or controlling the development of leptin resistance, all with the goal of alleviating AD etiology and pathobiology.

LEPTIN IN OBESITY AND LEPTIN-DEFICIENCY SYNDROMES

Plasma leptin concentrations are highly correlated with amount of body fat, with women having higher concentrations at every level of relative or absolute adiposity [15,16]. This gender dimorphism is maintained even in postmenopausal women, despite a drop in leptin levels (such that levels in premenopausal females > postmenopausal females > males) [16]. The range of leptin serum levels in humans range from 0 ng/ml leptin (in congenital leptin deficiency cases) to more than 100 ng/ml, representing morbidly obese cases. Normally, plasma leptin levels are highest late at night and lowest in the morning.

Leptin has been extensively used in trials for treatment of obesity, but its relatively low therapeutic index as a monotherapy, despite an overall well-tolerated profile, limits its use.

The rather disappointing results, although associated with a clinically significant moderate weight loss, are attributed partially to the fact that obese individuals have hyperleptinemia [15,16] and are generally resistant to further increments of leptin [17]. The dosages of leptin utilized in obesity trials were high, up to 0.4 mg/kg daily. In contrast, in replacement therapies, addressing a number of leptin-deficiency syndromes, clinical efficacy was achieved with doses as low as 0.02 mg/kg [18]. The most dramatic results using leptin as a therapy were obtained with rare genetic cases of obesity with complete leptin deficiency, where patients responded to leptin replacement therapy with reduced appetite and food intake as well as body fat loss [19].

Human testing of leptin as a monotherapy for partially leptin-deficient states has also met with success, among which are trials for lipodystrophy, increasingly common in HIV-infected individuals undergoing highly active anti-retroviral therapy. In addition, trials for hypothalamic amenorrhea, usually reported in women athletes, and for anorexia nervosa, have shown positive results. leptin treatment of patients with these conditions improved metabolic parameters, reduced insulin resistance, and restored reproductive function respectively [20]. From these trials, only mild side effects from injection site complications were reported.

LEPTIN (OB), LEPTIN RECEPTOR (OB-R) AND SIGNALING

The wild-type leptin gene (OB) encodes a 16kDa polypeptide [1]. The primary amino acid sequence of leptin and crystallographic data [21] indicate that leptin adopts a three-dimensional helical structure similar to that of certain cytokines, such as interleukin-2. The human leptin receptor (OB-R) [22] is a member of the class I cytokine receptor (gp130) superfamily [23]. It is present as five alternatively spliced isoforms, among which the expressed OB-Rb is the longest form and the only one responsible for ligand binding-induced signaling. Within the brain, the expression of OB-Rb is highest in the arcuate nucleus and median eminence of the hypothalamus, but is also abundantly expressed in the hippocampus, primarily in the dentate gyrus and CA1 [23,24], areas heavily affected in AD.

Activation of the OB-R triggers the JAK/STAT pathway to induce gene transcriptional changes via activation of Janus tyrosine kinase 2 (JAK2), the signal transducer and activator 3 (STAT3), and the suppressor of cytokine signaling 3 (SOC3). In addition, leptin can evoke an increased response via activation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) [25,26] pathways, which in turn reduce GSK-3 activity and consequently may decrease tau phosphorylation [27].

AMPK may also mediate leptin signaling post OB-Rb binding [28]. Upon phosphorylation, AMPK can be activated when cellular AMP/ATP ratio is high leading to an increase in ATP through a number of pathways that increase glucose uptake, facilitate lipolysis, and inhibit lipogenesis [29]. As such, AMPK may act as an energy management switch, manipulated by leptin levels.

Blood brain barrier

Although there is some evidence that leptin could be synthesized within the brain [30], it is believed that the majority of leptin in the CNS is derived from peripheral white adipose tissue [31]. Evidence has been provided for a specific transport system for leptin to cross the blood brain barrier and enter the brain of mice, rats, and humans. The rate of transport can be decreased by high plasma concentrations of leptin. Thus, reduced entry of leptin to the brain may be one of the mechanisms of reduced sensitivity of the leptin pathway in obese individuals [31]. Nonetheless, accumulating data suggest that AD patients bear low plasma

leptin levels, similarly to other patients with lipodystrophies, making them good candidates for a leptin replacement therapy.

LEPTIN AND THE NEUROBIOLOGY OF ALZHEIMER'S DISEASE

Several studies to date have addressed the correlation between reduced levels of circulating leptin and risk for AD. In the initial reports, only a limited number of cases were examined [32,33] but have since been corroborated with larger patient populations. More interestingly, a negative correlation between leptin levels and severity of dementia has been observed [34]. Furthermore, a large prospective study involving about 3,000 older persons followed over more than four years showed that those with the lowest leptin levels had a greater decline in their cognitive ability than those with the highest levels [35,36]. Additionally, a large longitudinal analysis showed that central obesity in midlife increases the risk of dementia independent of diabetes and cardiovascular co-morbidities later in life [37]. These observations indicate that leptin deficiency is common in AD and is somehow associated with mid-life obesity, characterized by leptin “resistance” or “inefficiency”.

A high concentration of leptin receptors in the hippocampus [24] (central for cognition and memory) underscores the possibility of a multifaceted role for leptin. Early work by Harvey's group demonstrated that leptin was capable of inhibiting hippocampal neurons' excitability via activation of large conductance calcium-activated K+ channels [38]. More recently it was shown that direct injection of leptin into the hippocampus of rodents can improve memory processing and modulate long term potentiation and synaptic plasticity [39]. Improved memory following leptin administration was also found in SAMP-8 mice, an accelerated senescence rodent model that develops amyloid plaques [40].

Amyloid

Although historically the “amyloid cascade” and “tau and tangle” hypotheses have largely been considered distinct proposals to explain AD pathobiology, accumulating data indicate multiple factors, many of which interconnect between the Aβ and tau molecular pathways, must come into play to exacerbate the progression of pathogenesis and cognitive decline. Exposure of neurons to Aβ can promote tau phosphorylation at sites identical to those found in paired helical filaments [41,42].

The extracellular accumulation of Aβ is a hallmark pathological feature of AD and the amount clearly depends on the rates of its production, secretion, and clearance. Based on our previous data [43], neurons depend on the interaction between presenilin-1 (PS1) and Cytoplasmic-Linker Protein 170 (CLIP-170) to generate Aβ. Further to this requirement, formation of Aβ depends on the assembly of key proteins in lipid rafts (LRs) [44]. LRs are membrane microdomains enriched in cholesterol, glycosphingolipids, and glucosylphosphatidylinositol-(GPI)-tagged proteins, implicated in signal transduction, protein trafficking, and proteolysis. Within the LRs, it is believed that the amyloid-β protein precursor (AβPP) is cleaved by β-secretase (BACE) to generate the intermediate fragment, CAPPβ. The latter is subsequently processed by γ-secretase, a high molecular weight multi-protein complex containing PS1 fragments [45]. Once outside the neuron, Aβ can: 1) exert a biological activity by binding and activating specific receptors, including the receptor for advanced glycation-end products (RAGE) [46] and scavenger receptors [47]; 2) be removed by mechanisms of endocytosis involving apolipoprotein E (ApoE) and lipoprotein receptor-like protein (LRP) or scavenger receptors; and 3) be degraded by extracellular proteases including insulin-degrading enzyme and neprilysin [48].

BACE is known to be imbedded in membranes where it targets AβPP, the precursor of Aβ within lipid rafts. Our previous *in vitro* studies have demonstrated that leptin treatment of

neuronal cells reduces the amount of Aβ secreted into the medium in a time- and dose-dependent fashion [49]. This was coincident with the subcellular redistribution of membrane lipids, BACE, and AβPP, and may be attributed to the lipolytic action of leptin. In accord, inhibitors of lipogenesis (i.e., TOFA, targeting Acetyl coenzyme A Carboxylase, and Cerulinin, targeting Fatty-acid Synthase) also inhibited Aβ production, whereas inhibitors of lipolysis (i.e., Etomoxir, targeting Carnithine palamitoyl transferase-1) had the opposite effect of leptin, increasing Aβ production [49]. Overall, an abnormal accumulation of lipids in non-adipocytes (neurons specifically) may favor amyloidogenic pathways, which can be prevented if sufficient leptin is present.

The uptake of lipoprotein-like particles by neural cells [50] may be a mechanism by which neurons acquire lipids for membrane remodeling as well as an avenue that supplies neurons with precursors for other lipid metabolites and second messengers essential for function. Finally, the uptake of ApoE/Aβ complexes may serve as a mechanism for clearing Aβ from the brain interstitium. Interestingly, the uptake of the ApoE/Aβ complexes by neurons appears to be allele specific and a more efficient uptake of Aβ was achieved with ApoE3 compared to ApoE4 [49]. Leptin is one compound that facilitates the uptake of ApoE/Aβ complexes via LRP [49].

Tau phosphorylation

NFTs are intraneuronal aggregates of highly phosphorylated tau protein that correlate closely with cognitive loss in AD [51]. Tau is expressed predominantly in axons where it acts to stabilize microtubules, a function that is regulated by phosphorylation. Highly phosphorylated tau shows decreased binding to microtubules [52,53]. The abnormal phosphorylation of tau protein leads to disrupted microtubule function, abnormal protein trafficking, the formation of NFTs, and eventual neuronal death. Furthermore, increased phosphorylation of tau promotes self-aggregation suggesting that in AD a misregulation of tau phosphorylation would result in loss of microtubule stability and loss of function, and aggregation of tau into the paired helical filaments that form NFT [54]. Since NFT density correlates reasonably well with the clinical scale of dementia severity [55], and is increased in subjects with dementia and psychosis [56], therapies blocking this cascade may have therapeutic potential in AD.

Considerable evidence points to GSK-3β as a predominant tau kinase in brain. Overexpression of GSK-3β in animal models induces neurodegeneration [57,58] and overexpression of GSK-3β in Drosophila induces aggregation of tau into tangles similar to those of AD [59]. Although both known mammalian GSK-3 isotypes (α and β) can induce paired helical filament-like phosphorylation of tau, active GSK-3β is co-expressed in tangle-bearing neurons [60], suggesting that GSK-3β activity is likely to contribute to tau abnormalities in AD.

Recently, it was demonstrated that leptin can phosphorylate GSK-3β at Ser-9 and deactivate it, contributing to the development of mouse cortical neurons [61]. Our laboratory has demonstrated that leptin treatment can lead to a reduction in tau phosphorylation. Specifically, leptin, in a time- and concentration-dependent fashion, reduced the amount of phosphorylation of tau at Ser^{202}, Ser^{396}, and Ser^{404} [14], all sites which are phosphorylated in NFTs [62,63]. A similar activity has been reported for insulin [64–66]. Most interestingly, as determined by IC50 values for the Ser^{396} phosphorylation reaction of tau, leptin was two orders of magnitude more potent than insulin [14]. This finding is particularly important because brain insulin resistance has long been thought as a possible cause for sporadic AD [67].

Thus leptin is capable of modulating both the production of Aβ and phosphorylation of tau [14], the building blocks of two pathological hallmarks of AD. Further, leptin-deficient mice have distinctly different synaptic profiles from wild-type mice [68], documented by electron microscopy and electrophysiology. Administration of leptin rapidly, within six hours, normalized synaptic function, a time well ahead of appetite, food intake, or weight changes. Loss of synapse function is indeed another feature related to the cognitive decline in AD.

METABOLIC PATHWAYS AND ALZHEIMER'S DISEASE

There is overwhelming evidence underlying the importance of metabolic pathways in the course of AD. First, from several genetic studies, it has been established that carriers of the ApoE4 allele are an order of magnitude more likely to get AD [69]. Second, the effect of diet and nutrition on the prevalence of AD has been documented [70–72] and weight loss is frequently observed in AD patients prior to the onset of dementia [73,74]. Further, central obesity is associated with an increased risk for dementia [37]. Third, in cell culture and animal models it has been demonstrated that lipids play an important role in amyloidogenic pathways [75]. Fourth, the majority of AD patients have some form of insulin resistance or hyperinsulinemia or type II diabetes [76].

Thus, it is not surprising that modulators of cholesterol (i.e., statins) and glucose (i.e., rosiglidazone) [77] are being developed as potential AD therapeutics. In fact, cholesterol-reducing therapies such as statins have been shown to reduce Aβ deposition both *in vivo* and *in vitro* [78]. These are in agreement with epidemiological studies documenting a decreased prevalence of AD with the use of statins [79]. Interestingly, the rosiglidazone studies have revealed an important association between the drug's efficacy as a cognitive enhancer in AD patients and their ApoE genotype [80]. As the mechanism of action for leptin appears to be substantially unique compared to any of the approved drugs and any of those under development, increasing the availability of leptin in the CNS holds promise as an AD therapy (Figure 1).

AMPK is an important enzyme for regulation of cellular metabolic activity. AMPK acts as a master switch regulating several intracellular systems including the cellular uptake of glucose, the β-oxidation of fatty acids and the biogenesis of glucose transporter 4 (GLUT4) and mitochondria [81]. AMPK may be important for CNS development as supported by the phenotype of the Drosophila mutant löchrig which has a defective AMPK [82] and abnormal cholesterol levels that results in extensive neurodegeneration.

It has been shown that leptin directly activates AMPK [83] and our laboratory has demonstrated that the ability of leptin to modulate both tau phosphorylation and Aβ production are mediated through AMPK [14] (Greco et al., unpublished results). By utilizing a panel of known inhibitors and activators of candidate leptin signaling molecules, in addition to the employment of recombinant expression and siRNA technology, it became apparent that a number of targets upstream, but not downstream, of AMPK could simultaneously modulate Aβ and tau phosphorylation.

Thus based on the available data, perhaps in AD, select neuronal populations may have a deficient/defective AMPK system for one or more of the following reasons: low leptin/insulin levels, low leptin/insulin sensitivity, hyperactive GSK-3β, abnormal cholesterol and fatty acid membrane composition, and low glucose uptake. This can then lead to changes in synaptic properties, an increase in amyloid deposition, an increase in tau phosphorylation, and finally death.

Other pharmacological agents known to modulate AMPK, such as metformin, an insulin-sensitizing antidiabetic drug [28], and 5-aminoimidazole-4-carboxamide ribonucleoside, an

adenosine analogue (AICAR) could in principal at least partially replace the biological activity of leptin in pathways leading to AD pathology. To this end, rosiglitazone, a thioglitazone, and PPARγ agonist (see above), may also act through AMPK [84].

IMMUNE SYSTEM AND ALZHEIMER'S DISEASE

The immune system has been implicated in the pathobiology of neurodegeneration in AD. Amyloid plaques accumulate proteins of the complement system, eicosanoids and cytokines, which are integral components of ongoing inflammatory processes that augment the harmful effects of Aβ [85]. Important regulators of the immune system include the cytokines and chemokines, which are secreted by leukocytes (B or T cells, normally scarce in the brain) or antigen presenting cells (APC) (microglia, perivascular macrophages, astrocytes in the brain). In the AD brain, both pro-inflammatory cytokines (IFN-γ, TNF-α, IL-12, IL-1, IL-2, IL-15, IL-16, IL-17, IL-18) and anti-inflammatory cytokines (IL-4, IL-5, IL-10, IL-13, IL-14, TGF-β) are expressed [86]. In addition to participating in immune response, cytokines may also directly affect the processing of AβPP [87].

Leptin has similar structural and functional characteristics to the cytokines [23], sharing post-receptor pathways and participating in the immune response to pathogens and infections. Leptin deficiency is associated with impaired T cell immunity [88] and increased sensitivity to the lethal effects of bacterial endotoxin and TNF-α. Importantly, these effects can be reversed by leptin administration which attenuates inflammatory cytokine and neuroendocrine responses to infection [89]. Further, in critically ill septic patients, higher leptin levels are positively correlated with survival [90]. Although, previous trials have not reported any inflammatory side-effects from leptin treatments, monitoring of inflammatory markers in leptin trials is important.

BEHAVIORAL STUDIES

Mouse models of AβPP overexpression (Tg2576) have proven to be valid models for testing these leptin hypotheses. Chronic leptin supplementation to the Tg2576, using implanted miniosmotic pumps, significantly reduced brain amyloid levels [49]. From this study and others [91], leptin is known to cross the blood brain barrier. However, it is currently unknown how leptin passage to the CNS in AD patients is affected, ultimately affecting its bioavailability.

More recently, studies were conducted using the CRND8 mice which overexpress an AβPP gene containing the Swedish (K670N and M671L) and Indiana (V717F) FAD mutations. These mice show an age-related increase in Aβ production, as well as an early onset of plaque deposition in the cortex and hippocampus [92] and develop pathology at a younger age (6 months) [93] compared to the Tg2576 mouse (10 months) [94]. Preliminary data suggests that chronic leptin supplementation, starting at a pre-plaque age and continuing through to post-plaque age, can significantly improve the performance of these mice in cognitive and memory tests (Tezapsidis et al., unpublished results). Leptin treatment was associated, as determined by pathological examination, with reduced plaque density and tau phosphorylation. Furthermore, biochemical analysis showed that leptin treatment reduced levels of solubilized Aβ and phospo-tau in brain, and reduced plasma Aβ. Significantly, no changes in the levels of plasma inflammatory markers (CRP, TNF-α, cortisol) were recorded.

CLINICAL TRIALS FOR ALZHEIMER'S DISEASE

The preclinical data obtained from our and other laboratories, the ample safety data from leptin human trials, and the epidemiological data, favorably support a clinical trial for leptin

as a novel therapy for AD. However, we lack adequate evidence of a biological signal indicative of a therapeutic effect in patients. Some concerns are related to side effects, along with uncertainty about dosing. A pilot study in patients with AD that is sufficient in scope to assess the impact of leptin on biomarkers selected for their relevance to the mechanism of action of leptin and the pathobiology of AD (i.e., in CSF: Aβ, tau, phospho-tau, leptin; in plasma: Aβ, leptin, insulin) may be a prudent first step. Such a pilot trial will also help to clarify tolerability, safety, and feasibility issues relevant for consideration of a larger subsequent trial.

CONCLUSION

The mechanistic and animal study data presented, as well as the ample clinical data using leptin, suggest that increasing leptin availability is a valid target for a novel treatment for AD. While the potential side effects of increased leptin to an already susceptible population are currently unknown, the intriguing biological activities of leptin, especially inhibition of Aβ production, upregulation of Aβ uptake, and inhibition of GSK-3β, hold promise for long-term therapeutic benefit for AD patients. Its unique mode of action in the CNS can positively sway disease pathways and may be utilized as a desirable complementation to other strategies. Future projects involving the evaluation of a number of other products capable of modulating the AMPK system, including novel leptin and AICAR products, in combination with various formulations allowing alternative deliveries could provide further opportunities to widen the portfolio of products addressing AD.

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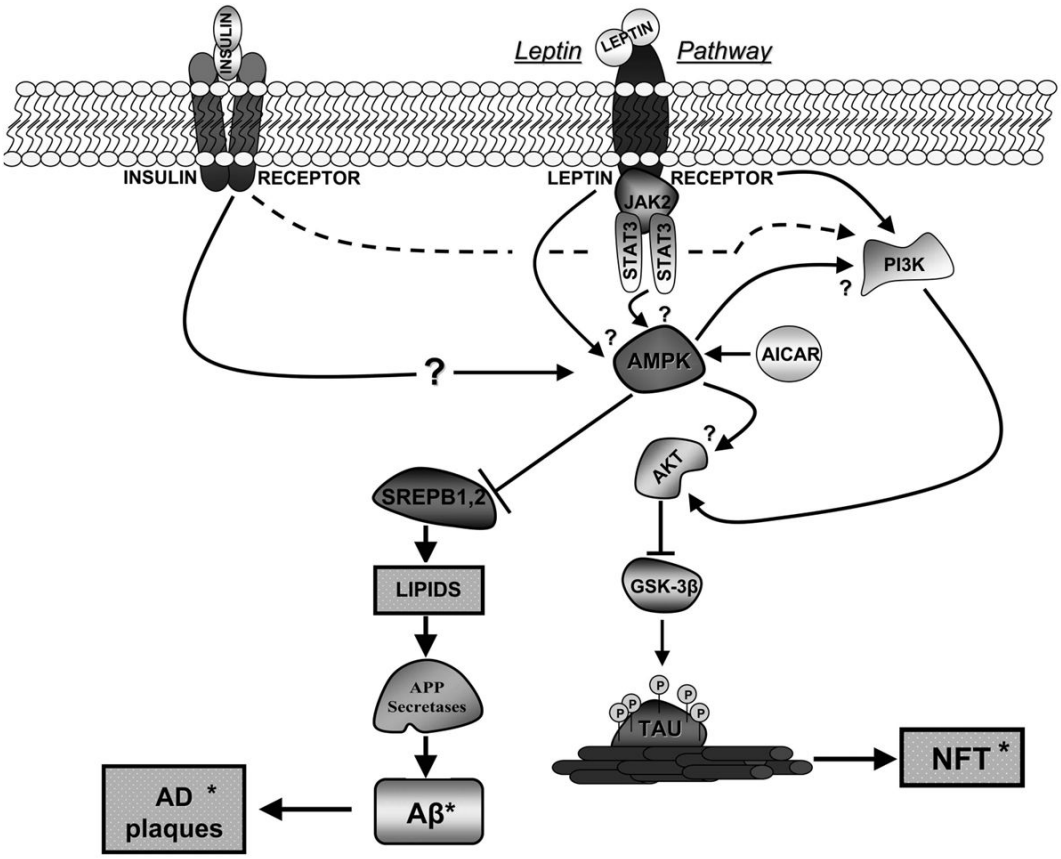

Figure 1.

Leptin can modulate AMPK activity following binding to the leptin receptor. The precise mechanism is currently unknown but there is some evidence that this may involve STAT3. There is considerable information regarding events downstream of AMPK leading to tau phosphorylation, which involves modulation of GSK-3β via Akt. In contrast, the cascade from AMPK to Aβ homeostasis is less defined. Activated AMPK may turn-off the transcriptional factors SREBP1,2, known to regulate lipid metabolism (fatty acid synthase, palmitoyl transferase etc.), previously shown to be downregulated by leptin [40]. There is some evidence that insulin is also capable of modulating AMPK. In addition to AMPK, insulin and leptin may share another common target, PI3K, which also regulates GSK-3β through Akt. Activation of Akt by AMPK leads to the phosphorylation of GSK-3β at Ser-9 which deactivates it. GSK-3β is the major kinase for tau.

Based exclusively on our studies, AMPK is emerging as a central modulator of major pathological pathways in AD. We propose that leptin deficiency in AD contributes to the downregulation of the AMPK system. This in turn causes increases in Aβ and phosphorylated tau. A lower AMPK activity may also be associated with a general low metabolic activity within neurons, an overall neuronal “fatigue”. Infusing leptin in the AD brain may improve the outlook, boosting metabolic pathways and reducing Aβ and phospho-tau. A better understanding of the AMPK system as it relates to AD pathways can provide more targets for future drug discovery efforts.