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Leptin signaling in brain: A link between nutrition and cognition?

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Summary

Leptin is a protein hormone that acts within the hypothalamus to suppress food intake and decrease body adiposity, but it is increasingly clear that the hypothalamus is not the only site of leptin action, nor food intake the only biological effect of leptin. Instead, leptin is a pleiotropic hormone that impinges on many brain areas, and in doing so alters food intake, motivation, learning, memory, cognitive function, neuroprotection, reproduction, growth, metabolism, energy expenditure, and more. This diversity of function also means that a dysregulation of leptin secretion and signaling can have far reaching effects. To date research on leptin signaling has focused primarily on the hypothalamus, and the result is a relative lack of information regarding the impact of leptin signaling and leptin resistance in non-hypothalamic areas, despite a growing literature implicating leptin in the regulation of neuronal structure and function in the hippocampus, cortex and other brain areas associated with cognition.

Keywords

hypothalamus; food intake; neuroprotection; hippocampus; cognitive function

Introduction

The discovery of the protein hormone leptin ushered in an era in which a variety of neural circuits, both within and outside the hypothalamus, have been implicated in the regulation of food intake. Like many hormones, the initial description of leptin as a regulator of food intake and body adiposity focused the study of leptin biology, but it is now clear that leptin does not produce a singular effect (i.e, a reduction in food intake). This review will highlight the pleiotropic effects of leptin on the brain, first reviewing the role of hypothalamic leptin signaling in the regulation of energy homeostasis, and then toward more recent data implicating leptin signaling in reward, motivation, learning and memory and neuroprotection. These latter effects appear to reflect leptin action in areas outside the hypothalamus, and indicate that leptin may have effects unrelated to its role as a signal of body adiposity.

Leptin as an adiposity signal that acts in the hypothalamus

In both humans and animals, physiological mechanisms monitor body adipose mass and react to changes in energy balance by altering ingestive behavior and energy expenditure to buffer against drastic changes in body adiposity and restore body weight and adiposity once the nutritional challenge dissipates [1–3]. The protein hormone leptin represents an afferent signal

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within this homeostatic mechanism, with leptin being produced and secreted by adipocytes via mechanisms that are sensitive to both the chronic level of body adipose mass as well as current metabolic status [4–7]. Of the brain areas mediating leptin action, the hypothalamic arcuate nucleus (ARC) is most closely associated with leptin's effects on energy homeostasis. The ARC contains at least two populations of leptin-sensitive neurons. The first population contains the potent orexigenic peptides Neuropeptide Y (NPY) and Agouti-Related Protein (AgRP). Central injection of either NPY or AgRP leads to a profound increase in food intake, and acute ablation of the NPY/AgRP neurons in adult animals leads to significant hypophagia and weight loss [8,9]. Thus NPY/AgRP neurons represent important drivers of food intake, and leptin's action to suppress food intake is mediated, at least in part, by its ability to inhibit these neurons. Adjacent to NPY/AgRP neurons are a population of neurons containing proopiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART). POMC is a large precursor protein which is processed into a variety of smaller products, notably alpha-melanocyte stimulating hormone (α-MSH). Central injection of α-MSH or its stable analog Melanotan II (MTII) produces a marked suppression of food intake, while genetic deletion of POMC results in an obese phenotype [10,11]. Selective deletion of leptin receptors within POMC neurons also results in an obese phenotype [12], although the effect is much less robust than loss of POMC or deletion of leptin receptors in all neurons. Thus POMC neurons exert a tonic inhibitory influence on food intake, and leptin's action to suppress food intake is at least partly mediated by an inhibition of POMC neurons. A model has therefore emerged in which these two populations of neurons exert opposing effects on feeding behavior and energy metabolism, and simultaneously respond in an opposing fashion to leptin.

The mechanism by which leptin regulates these neurons involves changes in both gene expression and acute membrane activity [13–15]. These observations suggest that leptin engages multiple signaling pathways to impact neuronal function, and recent data clearly supports this observation [16]. The leptin receptor is a type 1 cytokine receptor traditionally proposed to signal through the Janus Kinase – Signal Transducer and Activator of transcription (Jak-Stat) pathway. Jak-Stat signaling is critical for leptin action on ARC neurons; leptin induces Stat3 activation in both POMC and NPY neurons [17–19] and loss of leptin's ability to activate Stat3 leads to obesity [20,21]. However, leptin also engages other intracellular pathways, including ERK, PI3K and cAMP/PDE3B [22,23]. Of these, PI3K signaling has received the most attention, as loss of PI3K signaling attenuates leptin-induced inhibition of food intake, regulation of neuropeptide expression, and stimulation of sympathetic nervous system activity [22,24,25].

It should also be noted that these arcuate neurons respond to a variety of signals in addition to leptin. Insulin also acts in the brain to suppress NPY neurons and stimulate POMC neurons [26,27]. Direct brain insulin injections suppress food intake, while selective deletion of brain insulin receptor leads to obesity [28,29]. Thus insulin and leptin have overlapping physiological effects, and this overlap is mimicked by a degree of overlap in the intracellular signaling pathways they regulate, although this regulation and interaction appears to be highly complex. In addition to leptin and insulin these neuronal populations also detect and respond to a variety of additional nutrient signals, including hormonal signals such at ghrelin and PYY [30,31], as well as fuels such as glucose, fatty acids and amino acids [32–36].

While the arcuate nucleus has received the most attention as a site mediating leptin's regulation of food intake, leptin appears to also act in additional brain areas both within and outside the hypothalamus. Recent work indicates that leptin activates at least one population of neurons (SF-1 containing neurons) within the ventromedial nucleus (VMN), and that specific deletion of leptin receptor in SF-1 neurons increases food intake and body adiposity [37,38]. These data are consistent with previous work demonstrating effects of exogenous leptin on VMN neurons and reductions in food intake in response to local VMH leptin injection [39,40], although the

latter studies are complicated by the close anatomical proximity of the VMN to the ARC. There is also strong evidence that leptin suppresses food intake by acting directly in areas of the caudal brainstem, in particular a population of neurons within the nucleus of the solitary tract (NTS). The NTS is classically associated with satiety and meal termination, and local injections of leptin into the brainstem produce reductions in food intake that are similar in magnitude to injections into the forebrain [41,42].

Lastly, it should it should also be recognized that the suppression of food intake is only one component of leptin's overall effect on energy homeostasis. In essence, the primary effect of brain leptin signaling could be viewed as a reduction in body adiposity, with the suppression of food intake (energy intake) being one component in an array of physiological changes that collectively lead to reduced body adiposity [43,44]. One example is the acute effect of leptin on sympathetic outflow and energy expenditure. Relatively early on in the study of leptin it was recognized that the reduction in body weight induced by leptin involved more than changes in food intake [45], with leptin-deficient animals exhibit increased energy efficiency such that excess adiposity occurs even when hyperphagia is prevented [46]. These observations were extended when it was clearly described that leptin increases energy expenditure and fat oxidation [47–49], at least in part via an activation of the sympathetic nervous system [50, 51], and a resultant activation of brown adipose tissue (BAT) [52–54], although leptin decreases body adiposity and increases energy expenditure even in the absence of BAT-derived UCP1 [55]. These observations are consistent with leptin regulating sympathetic outflow and metabolism in other tissues, particularly skeletal muscle and adipose tissue [49,51,54,56,57].

In addition to an activation of the sympathetic nervous system, leptin also regulates energy homeostasis is via effects on neuroendocrine hormone secretion [58], particularly the secretion of thyroid hormone, gonadotropins, growth hormone, and ACTH. Leptin acts locally in the hypothalamus to stimulate TRH neurons and TRH expression [59] [60,61], indicating that leptin regulation metabolic rate includes a stimulatory effect on the thyroid axis [62]. Although somewhat less direct, leptin also alters energy balance by regulating reproduction. Decreases in body adiposity and periods of negative energy balance are associated with impaired reproductive function in a variety of species [63], and this effect is principally mediated by an inhibition of hypothalamic gonadotropin releasing hormone (GnRH) secretion [64–66]. By acting in the hypothalamus, leptin hastens the onset of puberty in mice [67–69] and improves reproductive function in settings of negative energy balance or leptin deficiency [70–72]. Likewise, leptin acts directly within the brain to stimulate gonadotropin secretion [73–75], possibly via the inhibition of NPY neurons [76–78]. Leptin deficient humans exhibit impaired reproduction and a failure to attain puberty, and this deficit is fully reversed by leptin replacement [79].

When taken together, these data provide a model for the neural basis of leptin-dependent regulation of energy homeostasis. The traditional view is thus one in which leptin, acting as an adiposity signal, regulates a defined populations of neurons in the hypothalamus to alter food intake and other components of energy homeostasis. While an abundant literature supports the core of this model, it is also apparent that leptin has a more diverse effect on the brain, with implications not only on the regulation of food intake, but on brain areas and neural systems that might be independent of the regulation of energy homeostasis.

Leptin and food intake: Reward and motivation

It is well recognized that nutritional status influences motivated behavior. For instance, food deprivation increases motivation to attain rewarding stimuli, including food, drugs of abuse, and electrical stimulation of specific brain areas [80–82]. These observations collectively demonstrate that negative energy balance enhances the desire for rewarding stimuli.

Interestingly, leptin attenuates the effects of negative energy balance in these models [83–85], indicating that leptin does not simply act in the brain to reduce the consumption of food, but that it also acts more generally to reduce the motivation to acquire rewards. Although areas of the hypothalamus (i.e. lateral hypothalamus) are associated with these responses, areas outside the hypothalamus are also involved. The mesolimbic dopamine system is critical for the motivation to obtain pleasurable stimuli [86,87]. Dopaminergic projections from the ventral tegmental area to the nucleus accumbens are particularly important, as manipulation of this dopamine system powerfully influences instrumental performance for and consumption of drugs or food [88–90]. Leptin directly impinges on this system, acting in the VTA to suppress food intake and modulate dopamine neurons [91–93], and also may indirectly influence this system via effects in the hypothalamus. Thus leptin-dependent suppression of food intake involves brain areas associated with the anticipation, memory or motivation, as supported by available data indicating that leptin alters behaviors related to food intake but independent of the actual consumption of food [83,94]. Lastly, brain imaging studies in leptin deficient humans have highlighted the profound effect that the absence of leptin has on the brain, with leptin deficient humans responding more strongly to food cues (i.e., images of foods) than normal individuals [95], and leptin treatment altering the neuronal response to food cues in a variety of brain areas [96,97]. Collectively, these data provide a unique view of the expanding role for leptin, and demonstrate that leptin exerts significant effects on food intake via actions via mechanisms that occur prior to and separate from the actual consumption of food, and that these effects are mediated by brain areas that are distinct from the hypothalamus.

Leptin as a signal promoting neuronal survival and cognition

Upon its discovery, leptin was heralded as a hormone acting in the brain as a signal of body adipose mass. Yet in addition to regulating food intake and body weight homeostasis, leptin also acts within brain areas that are unrelated (at least directly) to an effect on energy homeostasis. Within these brain areas leptin alters neuronal/synaptic function and structure, and influences neuronal survival and proliferation. The result of these effects appears to be an improvement in learning, memory and other forms of cognition and a resistance to insults which impair cognitive performance.

Perhaps the first evidence for a role for leptin in cognition is the recognition that leptin receptors are expressed widely throughout the brain. Although leptin receptors, particularly the signaling form of the receptor (Long form – LepRb) are densely expressed within medial areas of the hypothalamus, leptin receptors are also expressed in many brain areas, including regions associated with learning and memory, such as various cortical regions and the hippocampus [98–102]. Another clue to the role of leptin in the regulation of these brains areas stems from the clear effects that both diet and obesity have on cognitive function. Variations in caloric intake or diet composition can produce changes in gene expression within areas of the hippocampus and cortex [103], indicating that these brain areas are not insulated from variations in nutritional or metabolic status. Similarly, it is increasingly apparent that alterations in nutritional status can alter cognitive function, and in particular that settings of obesity are associated with decreases in cognitive function [104]. Based on these and other observations, the key question therefore is whether variations in leptin signaling contribute to changes to metabolic or nutritionally induced alterations in neuronal or cognitive function within areas outside the hypothalamus.

Effects on neuronal/synaptic function

Within these non-hypothalamic areas, leptin acts in part by directly regulating neural function, including local effects at the synapse [105]. In rodent models of genetic leptin or leptin receptor deficiency, hippocampal neurons (CA1) exhibit impaired development of long term potentiation (LTP) and depression (LTD), and an associated reduction in CaMK II activity

[106]. Consistent with this observation, leptin treatment of hippocampal neurons stimulates CaMK II phosphorylation and facilitates the development of LTP [107]. These changes in LTP and LTD are influenced by leptin dependent regulation of NMDA receptor function [108, 109], as leptin enhances NMDA-induced increases in intracellular calcium levels and facilitates NMDA receptor-mediated synaptic transmission [108]. Leptin treatment in neonatal animals altered the expression of NR1, NR2B, synapsin 2A and synaptophysin in the hippocampus [110]. In addition to altering NMDA receptors, there is also evidence that leptin regulates the function of large-conductance, calcium activated K+ channels (BK channels) [111,112]. Lastly, these effects of leptin are not limited to hippocampal neurons, as leptin receptors are expressed in cerebellar neurons at the both the somatic plasma membrane and the synapse, and treatment of these neurons with leptin facilitated NR2B NMDA receptor mediated calcium influx [113].

Just as leptin regulates hypothalamic neurons via a variety of signaling pathways, evidence suggests that leptin uses multiple signaling pathways to regulate non-hypothalamic neurons. For leptin dependent effects on synaptic function and activity, a large abundance of data implicates leptin-dependent activation of phosphotidylinositol 3-kinase (PI3K) signaling. PI3K is implicated in leptin-dependent regulation of LTP and LTD, NMDA receptors, and actin cytoskeleton dependent clustering of BK channels [108,109,111,112]. Yet other signaling systems are also implicated, including leptin activation of MAPK and Src signaling [108, 113]. Taken together, the above data indicates that leptin directly regulates the signaling and synaptic activity of neurons within the hippocampus, cortex and cerebellum. It is thus highly likely that these signaling effects contribute to the cognitive and behavioral effects of leptin that will be discussed below.

Effects on neuronal structure and plasticity

In addition to direct effects on neuronal/synaptic function, leptin also appears to influence neurons by altering their structure and plasticity. Initial evidence for this effect stemmed from the observation that rodent models of leptin deficiency exhibit smaller brains, that these alterations in brain development are evident in utero, and that leptin replacement in these models serves to increase brain size, protein and DNA [114–117]. More recent studies provide evidence for neuroproliferative effects within the fetal cortex, and indicate that leptin is associated with a maintenance and differentiation of neural stem cells, glial-restricted progenitor cells and/or neuronal lineage cells [118]. Interestingly, similar observations have been made in humans, where fasting plasma leptin levels in normal humans are correlated with grey matter volume in several brain areas [119], and leptin replacement in leptin deficient humans leads to gross changes in brain structure, particularly an increase in grey matter volume in discrete areas [120]. These very provocative observations thus provide strong evidence that leptin, and particularly the absence of leptin, has fundamental effects on brain structure.

In addition to these general effects of leptin, there have been more specific observations of leptin dependent changes in neuronal structure in a variety of brain areas, including the hypothalamus. Leptin deficiency appears to reduce the density of axonal projections from leptin sensitive neurons, and this structural defect can be restored by leptin treatment during a critical period of neonatal life [121]. Consistent with this observation, leptin acts on arcuate nucleus explants to promote neurite outgrowth [121]. Similar observations have also been made within areas of the hippocampus, cortex and cerebellum. Leptin was shown to act in cerebellar neurons to promote neurite outgrowth and increase the complexity of the neurite arbor [122], in hippocampal cells to enhance the motility and density of dendritic filopodia [123], and in cortical neurons to stimulate growth cone morphogenesis [124]. Lastly, there is also evidence in the hypothalamus that leptin influences the number of both inhibitory and stimulatory synaptic inputs onto neurons within the arcuate nucleus. Mice that are deficient for leptin

exhibit a skewed distribution of synaptic input onto feeding related neurons, and leptin treatment induces a relatively rapid reorganization of the synaptic input to these ARC neurons [125]. In summary, these data collectively support a model in which leptin acts to influence neuronal structure and plasticity. As such, these changes provide an additional means by which leptin might regulate neuronal function.

Effects on neuronal survival and proliferation

It has long been known that various growth factors act on neurons to protect against neurodegeneration and cell death [126], and a rather large literature has accumulated specifically implicating leptin as a neuroprotective signal [127]. Within a variety of non-neural cells, including cancer cells, leptin has been show to inhibit apoptotic cell death [128–132]. In neurons in vitro, leptin appears to attenuate cell death induced by the removal of serum or neurotrophines [133,134], to improve cell survival in models of ischemic stroke [135,136], to protect against glutamatergic excitotoxicity [133,137], to protect against oxidative stress [133], and to promote the proliferation of hippocampal progenitor cells [138]. These in vitro effects of leptin are replicated by in vivo experiments demonstrating that leptin attenuates the loss of dopamine neurons in a chemically induced model of Parkinson's disease [139], that leptin deficient mice are more sensitive to middle cerebral artery occlusion (MCAO) but that leptin treatment decreases infarct volume and animal recovery following MCAO [135,140], and that leptin reduces symptoms of chemically induced epileptic seizures [141]. These effects of leptin appear to stem from leptin's activation of intracellular signaling pathways associated with growth factor signaling, including the activation of Stat3, PI3K/Akt and ERK/MAPK [133–136,138,139,141]. Interestingly some evidence also implicates an effect of leptin on the NF-KappaB/c-Rel signaling pathway, as the ability of leptin to improve function following MCAO was attenuated in c-Rel deficient mice, and leptin stimulated the antiapoptotic Bcl-xl in cortical neurons via a c-Rel dependent mechanism [140]. Taken together, these data provide compelling support for leptin as a neuroprotective signal, although the physiological implications of this relationship are not fully clear. Are physiological increases (or decreases) in leptin relevant to neuronal health? Are these effects in any way related to leptin's role as a nutritional signal? Additional work is clearly required to test whether leptin's neuroprotective actions have any role in neurodegenerative processes, particularly those related to nutrition and metabolism.

Effects on cognition and behavior

The above observations provide strong support for a role for leptin in a variety of brain areas and signaling systems that appear, at least on the surface, to be unrelated to its role in energy homeostasis. In addition, these molecular and cellular examples for leptin-dependent effects on synaptic function, neuronal structure, and neuroprotection also provide a mechanistic basis for the remarkable observation that leptin acts within the brain to support and promote cognitive function. The relationship between leptin and cognitive function exists on multiple levels. First, correlational evidence provides a link between altered, particularly reduced, circulating leptin levels and impaired cognition in humans [142–144], with examples including a correlation between high leptin and improved cognition in the elderly and an association between low leptin levels and impaired learning and memory in HIV infected men. Secondly, genetic models of leptin suggest that leptin deficiency impairs cognitive performance [106,145–147]. The most provocative of these is the human example, where a leptin deficient individual with reduced cognitive performance at baseline exhibited a marked improvement in neurocognitive tests following leptin treatment [145]. Lastly, there is also direct evidence for an effect of leptin treatment to improve cognitive performance in rodents [107]. These experiments particularly implicate the hippocampus, as local injections of leptin into the hippocampus improved memory retention [148], although at least one experiment has failed to detect an effect of hippocampal leptin on spatial memory [149].

While these observations provide a direct link between leptin and cognition, it is currently unclear whether these behavioral effects of leptin are mediated by discrete brain regions (hippocampus vs cortex), or whether these cognitive changes are mediated by any or all of the diverse effects of leptin on synaptic function, neuronal structure and plasticity, and neuroprotection. Nevertheless, these observations provide an exciting new direction for leptin research, and clearly indicate that leptin is much more than an adiposity signal that acts within the hypothalamus to regulate food intake.

Implications for leptin resistance

Shortly after the discovery of leptin, it was recognized that leptin deficiency was not a common cause of obesity. Instead, most obese individuals exhibit high circulating leptin levels coincident with ongoing hyperphagia [5]. Obese humans and animals are also relatively unresponsive to exogenously administered leptin, and this syndrome of reduced sensitivity to endogenous and exogenous leptin has been termed leptin resistance [150]. Leptin resistance appears to occur on at least two fronts, with the first being a reduced relative transport of circulating leptin across the blood brain barrier [151], and the second a reduction in intracellular signaling downstream of the leptin receptor. The existence of leptin resistance, at least within the hypothalamus, is thus well accepted, and considerable research effort continues to focus on hypothalamic resistance, both to define the cellular mechanisms underlying leptin resistance and to determine the role of hypothalamic leptin resistance in the development of obesity [152–155]. Yet absent within this discussion is the consideration that leptin resistance within non-hypothalamic areas might also occur, and that this resistance, by altering neuronal function within brain areas such as the cortex and hippocampus, might also alter behavior and cognition.

The study of leptin resistance has focused primarily on the failure of exogenous leptin reduce food intake and activate key signaling molecules (Stat3) within neurons of the hypothalamic arcuate nucleus. This ARC-specific leptin resistance is well described, and occurs in response to high fat diets, age, pregnancy and lactation, seasonal variations, and even chronic leptin exposure [153,156–161]. But does leptin resistance occur in brain areas besides the arcuate nucleus? In addressing the question of region-specific leptin resistance, Munzberg et al., [162] compared leptin-induced phosphorylation of Stat3 in a variety of brain areas in mice fed a high diet, while Ladyman et al., [163] conducted a similar study in pregnant, leptin resistant rats. These experiments detected a marked reduction of leptin-dependent Stat3 phosphorylation in the ARC in leptin resistant animals, but persistent leptin signaling within other brain areas both within and outside the hypothalamus. The conclusion was therefore that leptin resistance occurs specifically in the hypothalamic arcuate nucleus, and to date few if any studies have followed up on these observations by focusing on leptin resistance in non-hypothalamic areas. However, it should be noted that these anatomical studies were based solely on leptin activation of Stat3, and did not account for changes in other signaling pathways. Yet the majority of studies indicate that leptin-dependent changes in neuroprotection, proliferation, synaptic function and structural plasticity are mediated by pathways such as the PI3K/Akt pathway and ERK/MAPK signaling [108,109,111–113,123,133–136,138,139,141]. Thus, it remains possible that leptin signaling is altered within these brain areas, despite a normal or persistent regulation of Stat3. Available evidence already exists to suggest that leptin resistance may vary based on biological endpoint. For instance, there is evidence that leptin-dependent effects on sympathetic outflow may persist despite an attenuation of leptin's suppression of food intake [164,165]. These data therefore provide support for the hypothesis that leptin signaling and leptin resistance vary across brain areas.

Although virtually no work has specifically tested whether leptin resistance develops within brain areas associated with learning, memory or other aspects of cognitive function, a collective consideration of the work reviewed above provides a foundation for this hypothesis. First,

increasing age, obesity and metabolic dysfunction each negatively impact these brain areas and lead to impaired cognitive function. Second, leptin signaling, at least within the hypothalamus, is impaired coincident with age, obesity and metabolic dysfunction. Third, animals with genetically impaired leptin signaling show defects in cognitive function. Fourth, exogenous leptin administration improves cognitive function and protects neurons against damage and degeneration, including an effect of leptin when directly administered into the hippocampus. Taken together, these observations indicate that leptin signaling (or the loss thereof) in the cortex or hippocampus is well positioned to contribute to age and/or diet-associated declines in cognitive function. However, future studies must be designed to clearly test whether and when leptin resistance develops in these non-hypothalamic areas, and then to determine if maintenance of leptin signaling ameliorates the effects of diet or age.

Conclusions

Leptin has received considerable attention as a nutritional signal acting in the hypothalamus to suppress food intake. Yet leptin is a pleiotropic hormone, impinging on a variety of brain areas to influence satiety, motivation, learning, memory, cognitive function, reproduction, growth, metabolism, and additional effects not discussed here [166–168]. This diversity of function indicates that the dysregulation of leptin secretion and signaling that occurs in settings of both undernutrition and obesity can have far reaching effects. While to date research on leptin resistance has focused primarily on the hypothalamus and emphasized obesity and diabetes, it is increasingly apparent that leptin also acts within areas such as the cortex and hippocampus to influence neuronal function and promote cognition. As such, alterations in leptin signaling within these non-hypothalamic brain areas may provide a unique mechanism linking obesity and diabetes to impaired cognitive function.

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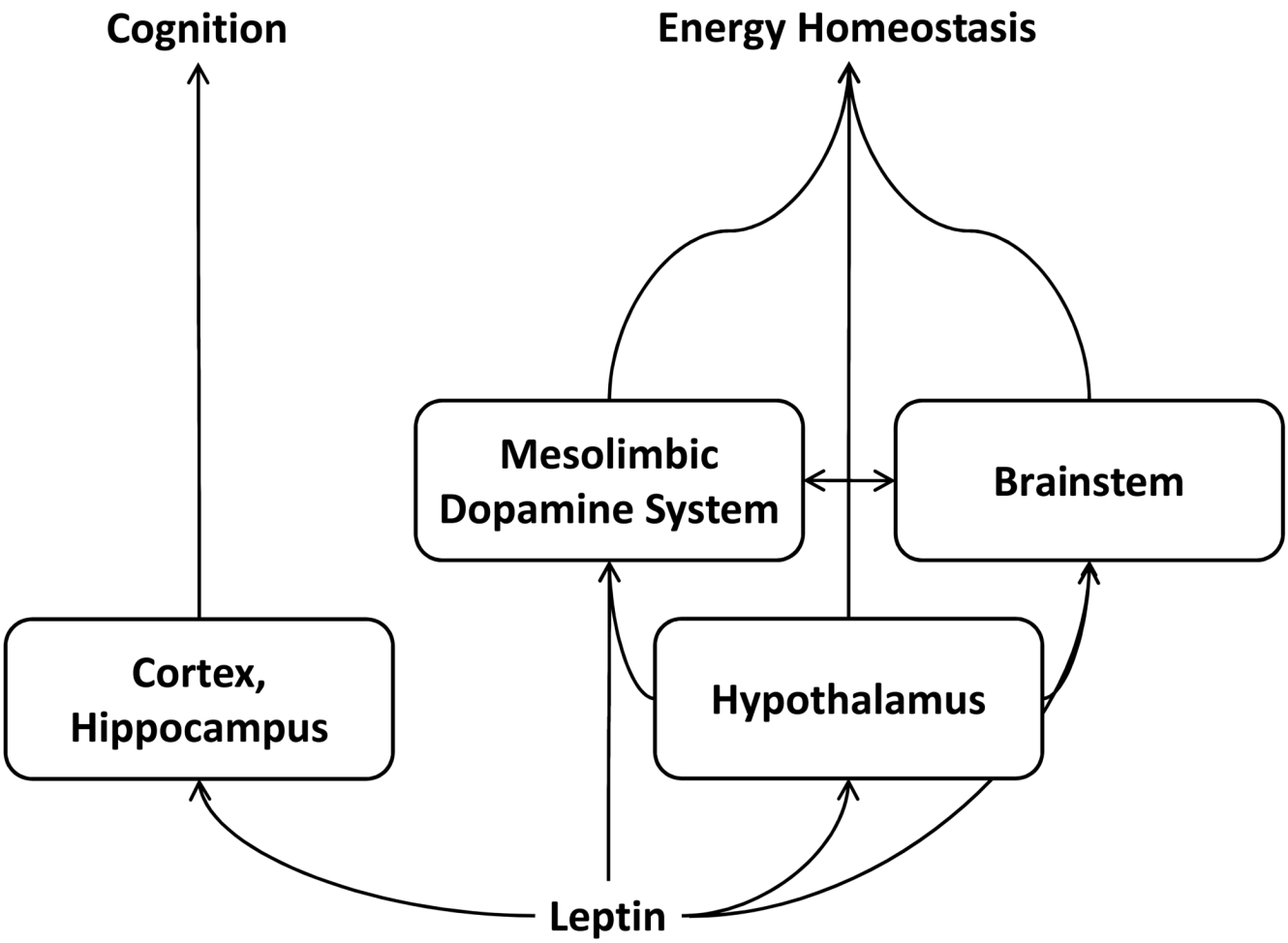

Figure 1. Leptin sensitive brain areas in the regulation of energy homeostasis and cognition

Leptin-dependent regulation of energy homeostasis is mediated by a complex interaction of brain areas which contribute to leptin's suppression of feeding behavior and stimulation of energy expenditure. Contrastingly, relatively little is known about leptin's potential role in the regulation of cognition, but there is clear evidence for a direct effect of leptin within areas of the cortex and hippocampus. It remains unclear whether an interaction exists between those areas influencing energy homeostasis and those influencing cognition, but the existence of well established neuroanatomical connections indicate that such interactions are likely.