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Leptin

A Multifaceted Hormone in the Central Nervous System

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Abstract

It is well established that the adipocyte-derived hormone leptin is an important circulating satiety factor that regulates body weight and food intake via its actions on specific hypothalamic nuclei. However, there is growing evidence that leptin and its receptors are widely expressed throughout the brain, in regions not generally associated with energy homeostasis, such as cortex, cerebellum, brainstem, basal ganglia, and hippocampus. In this review the author discusses recent advances made in leptin neurobiology, with particular emphasis on the role of this endocrine peptide in normal and pathophysiological hippocampal function.

Index Entries: Leptin; hippocampus; PI 3-kinase; MAPK; BK channels; NMDA receptor.

Leptin and Its Receptor

Leptin, the obese *(ob)* gene product is a 16 Kda protein that is synthesized predominantly, although not exclusively, by white adipose tissue. It circulates in the plasma at levels proportional to body fat content and is partially bound to plasma proteins *(1)*. Leptin expression is influenced by the status of energy stores as demonstrated by the increased levels of adipose tissue *ob* mRNA and serum leptin in obese humans and animals *(2–4)*. Functional as well as anatomical data indicate that leptin regulates energy homeostasis mainly via its actions in the brain *(5)*. Leptin may be transported into the brain via a saturable transport mechanism *(6,7)*, possible by receptor-mediated transport across the blood–brain barrier. Indeed, leptin can enter most regions of the central nervous system (CNS)—not only the hypothalamus—via the blood–brain barrier and with uptake and saturation transport rates that vary amongst different brain regions *(8)*. Evidence is also accumulating that the brain is

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a source of leptin, as leptin immunoreactivity as well as leptin mRNA and protein are expressed throughout the CNS *(9,10).*

Using expression-cloning strategies, Tartaglia et al. *(11)* first isolated the leptin receptor (Ob-R) from the choroid plexus. Ob-R is encoded by the diabetes gene *(db)* and alternate splicing generates multiple variants of Ob-R mRNA that encode at least 6 isoforms of the leptin receptor (Ob-$R_{a–f}$; *12,13*) in rodents. The extracellular-binding domains (at the amino terminus) of these isoforms are identical, whereas differences exist in their intracellular domains (at the carboxy terminus). The isoforms (with the exception of Ob-R_e) are all membrane-spanning receptors that fall into 2 categories: short forms of the receptor (Ob-$R_{a,c,d,f}$) that have short intracellular domains consisting of 30–40 cytoplasmic residues, and a long form of the receptor (Ob-R_b) that has a large intracellular domain (302 residues) with various motifs required for both the initiation of cell-signaling processes and interaction with other proteins. The Ob-R_b isoform is thought to play a vital role in body weight regulation as insertion of a stop codon in the cytoplasmic domain of Ob-R_b mRNA results in the obese phenotype of *db/db* mice *(14).* Ob-R_e is distinct from the other leptin receptor isoforms as it has no transmembrane domain *(15)* and it is thought to circulate as a soluble receptor.

Genetically Obese Rodent Models

In recent years, significant progress has been made to determine the role of leptin in energy homeostasis, by evaluation of the natural recessive mutations in rodents (primarily *ob/ob* and *db/db* mice and Zucker *fa/fa* rats). These rodents display phenotypes similar to type 2 diabetes, with early onset obesity, hyperinsulinaemia, and hyperglycaemia *(15).* Administration of leptin can correct the defects associated with *ob/ob* mice, whereas higher concentrations of leptin can induce significant weight loss in normal mice *(16–18).* In contrast, neither peripheral nor central administration of leptin causes weight loss in the diabetic mouse *(db/db; 17,18).* Zucker *fa/fa* rats have a single point mutation in the extracellular domain of all leptin receptor isoforms which results in attenuation of the affinity of the receptor for leptin as well as the receptor-driven signal transduction capability *(19).* In humans, mutations in leptin and its receptor have been found *(20),* which result in hyperphagia, early onset obesity, and hypogonadism. However, these mutations are extremely rare and are unlikely to underlie the resistance to leptin associated with most obese humans.

Cytokine Receptor Signal Transduction

The leptin receptor shows sequence homology with the class I cytokine receptor superfamily that includes receptors for interleukin 6, granulocyte-colony stimulating factor, and leukemiainhibitory factor *(21).* This family of receptors signal via association with janus tyrosine kinases (JAKs). Indeed, high-affinity binding of leptin (at nanomolar concentrations) to an Ob-R_b homodimer causes JAK2 activation and subsequent phosphorylation of both proteins. This in turn acts as a switch to recruit and stimulate a variety of downstream-signaling pathways. The STAT (signal transducers and activators of transcription) family of latent transcription factors is recruited to activated cytokine receptor/JAK complexes, where the STAT proteins are tyrosine phosphorylated and activated. Recently, a novel family of cytokine-inducible inhibitors of signaling have been identified that include CIS (cytokine inducible sequence) and SOCS1-3 (suppressor of cytokine signaling); the latter of which is thought to suppress cytokine signaling by binding to phosphorylated residues on JAKs *(22).* Another target for JAKs, following cytokine-receptor stimulation, is the insulin receptor substrate (IRS) proteins *(23),* and a common downstream target of IRS proteins is the p85 subunit of the lipid kinase, phosphoinositide 3-kinase (PI 3-kinase; 24). Most

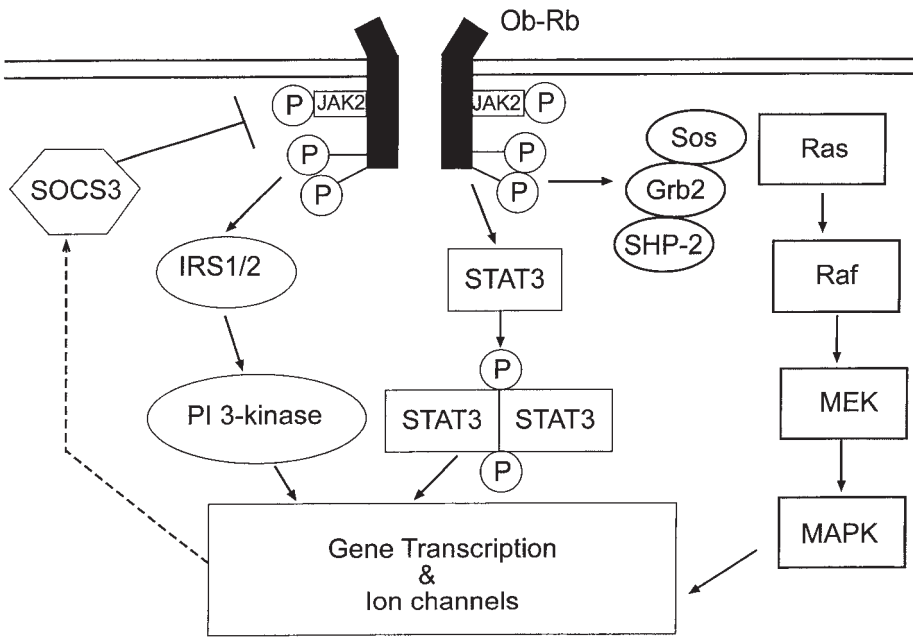

Fig. 1. Potential signal-transduction pathways stimulated by leptin receptor (Ob-R_b) activation. Grb2, growth factor receptor bound 2; IRS, insulin receptor substrate protein; JAK2, janus tyrosine kinase 2; PI 3-kinase, phosphoinositide 3-kinase; MAPK, mitogen activated protein kinase; MEK, MAP kinase kinase; SOCS3, suppressors of cytokine signaling 3; Shc, Src homology and collagen; STAT, signal transducers and activators of transcription; Sos, son of sevenless.

cytokines can also stimulate the Ras-MAPK (mitogen-activated protein kinase) pathway. This pathway involves the tyrosine phosphorylation of the adaptor protein, Src homology collagen (Shc), which in turn interacts with Grb2, resulting in the recruitment of the Son-of-sevenless (Sos) exchange protein to the plasma membrane for activation of Ras. Once activated, Ras operates as a molecular switch, stimulating a serine kinase cascade through the step-wise activation of Raf, MEK, and ERK.

Leptin-Receptor Driven Gene Transcriptional Changes

During leptin-receptor signaling, the janus tyrosine kinase JAK2 is preferentially stimulated *(25–27)*. JAK2 appears to associate with Ob-R_b both before and after leptin binding. This constitutive interaction involves 2 motifs: the conserved Box1 motif and a specific binding domain (amino acids 31–36; *28*) located within the Ob-R_b C-terminal. Leptin binding to Ob-R_b results in transphosphorylation of JAK2 and the subsequent phosphorylation of tyrosine residues on the receptor. The tyrosine residue (Y1138) allows binding of STAT3, which in turn causes STAT3 dimerization and its subsequent translocation to the nucleus (Fig. 1). In contrast, phosphorylation of Tyr985 enables recruitment of SHP-2, which in turn initiates the Grb2-Ras-MAPK signaling cascade. The phosphotyrosine residues are also potential recognition sites for a range of proteins with SH2-domains which can recruit a number of downstream-signaling molecules (*see* Fig. 1).

In parallel with other members of the class I cytokine receptor superfamily, Ob-R_b activation induces tyrosine phosphorylation of STAT1, 3,

and 5 in vitro *(29–31).* Administration of leptin intravenously also specifically activates STAT3 in the hypothalamus *(32),* which in turn leads to nuclear translocation *(33).* Moreover, leptin-induced STAT3 signaling is required for its actions on energy balance *(35).* In hypothalamic neurons and COS cells, leptin can also induce expression of SOCS3 mRNA *(34,36),* which may be a potential mechanism of regulating leptin receptor-driven signal transduction at the transcriptional level *(37).*

Leptin Receptor-Driven PI 3-Kinase Stimulation

In addition to inducing gene transcriptional changes, leptin can evoke more rapid responses (within minutes) by activation of alternative signaling pathways. For instance, leptin inhibits hypothalamic glucose-responsive neurons *(38)* and insulin-secreting cells *(39,40)* via rapid PI 3-kinase-driven effects on K_{ATP} channels *(41,42).* Intracerebroventricular infusion of PI 3-kinase inhibitors also prevents leptin-induced anorexia *(43),* indicating that PI 3-kinase is a central enzyme linking hypothalamic leptin to reduced food intake. PI 3-kinase is also a key element of the signaling pathways driven by leptin-receptor activation in other peripheral cells *(44,45)* and in hippocampal neurons *(46–48).* PI 3-kinase consists of a p110 catalytic subunit and a p85 regulatory subunit that possesses 2 SH2 domains that interact with tyrosine phosphorylated motifs in IRS proteins. At least 8 isoforms of the regulatory subunits have been identified which display differences in potency for enzyme activation and tissue distribution. However, the exact roles of the different regulatory subunits of PI 3-kinase in leptin action are unclear. Activation of PI 3-kinase can stimulate multiple signaling cascades. One of the main functions of PI 3-kinase is to promote the phosphorylation of phosphoinositides on the 3-position, resulting in phosphatidylinositol-3-phosphates, in particular PtdIns(3,4,5)P_3. There is also accumulating evidence that the lipid products of PI 3-kinase closely associate with the actin cytoskeleton where they can modulate a variety of proteins *(49).* Indeed, leptin-induced activation of K_{ATP} channels in CRI-G1 insulinoma cells is prevented by the actin filament stabilizer, phalloidin. Actin disrupters also increase K_{ATP} channel activity in a phalloidin-dependent manner. Furthermore, the ability of leptin to induce rapid disassembly of actin filaments involves a PI 3-kinase-dependent process, consistent with leptin-activating K_{ATP} channels via PI 3-kinase-driven actin filament disruption *(50).*

PI 3-kinase also possesses serine kinase activity and both the regulatory and catalytic domains of the enzyme can interact with other signaling molecules, including the AGC family of serine/threonine protein kinase, the TEC family of tyrosine kinases, and Rho GTPases. Indeed, there is evidence that leptin stimulates PI 3-kinase-dependent activation of cyclic nucleotide phosphodiesterase 3B, a cAMP-degrading enzyme in pancreatic beta cells *(51)* and hepatocytes *(44).* This pathway may also be an important signaling cascade involved in the hypothalamic action of leptin on feeding as ICV administration of a selective phosphodiesterase 3B inhibitor reversed leptin action on food intake and body weight *(52).*

As well as stimulating PI 3-kinase, activation of the Ras-MAPK pathway following leptin-receptor activation has been observed in peripheral cell lines, including the MIN6 insulin-secreting cell line *(53),* C3H10T1/2 cells *(54),* and HEK293 cells heterologously expressing Ob-R_b *(55).* There is also evidence that leptin signals via the Ras/MAPK-signaling cascade in rat preadipocytes *(56)* and porcine chromaffin cells *(57).* Furthermore leptin promotes proliferation of human blood mononuclear cells via a MAPK-driven process *(58).* In central neurons, leptin is also capable of signaling via the Ras-MAPK pathway *(46).* In contrast to leptin-induced JAK-STAT signaling, phosphorylation of Tyr (985) on Ob-R_b appears to be required for leptin receptor-driven activation of the Ras-MAPK signaling pathway *(55).*

The long form of the leptin receptor, Ob-R_b was originally thought to be the only leptin-receptor isoform capable of signaling as the short leptin receptor isoforms are unable to be tyrosine phosphorylated *(34).* However, the short forms of the receptor possess some signaling capabilities, as leptin antagonizes glucagon-induced cAMP accumulation in hepatocytes lacking Ob-R_b *(44).* Furthermore, activation of Ob-R_a can stimulate the Ras-MAPK pathway in CHO cells *(59)* and HEK293 cells *(34).* Although no specific function has been assigned to the short isoforms, it is possible that they play a role in the blood-to-brain transport of leptin, as Ob-R_a and Ob-R_c are abundantly expressed in brain microvessels *(7,11,60).*

Convergence of Leptin and Insulin Signaling Networks

Evidence is emerging that, at least in peripheral tissues, leptin and insulin receptor-driven signaling pathways are interconnected at a number of levels. For example, in human hepatic cells the ability of insulin to tyrosine phosphorylate IRS-1 and downregulate gluconeogenesis is attenuated by leptin *(61).* Leptin treatement also enhances insulin-induced tyrosine phosphorylation and PI 3-kinase binding to IRS-1 in a hepatic cell line *(62).* Furthermore, insulin occludes leptin-induced activation of ATP-sensitive K^+ (K_{ATP}) channels in CRI-G1 insulinoma cells *(63).* Insulin also inhibits leptin-receptor signaling at the level of JAK2 in HEK 293 cells *(64).* In contrast, in hypothalamic glucose-responsive neurons insulin mimics K_{ATP} channel activation induced by leptin *(65),* and leptin and insulin both activate hypothalamic PI 3-kinase-signaling pathways *(66).* However, insulin modulates leptin-induced STAT3 activation in rat hypothalamus *(67).* Thus, it still needs to be established whether insulin and leptin stimulate parallel but distinct signaling pathways or whether their signaling pathways converge in central neurons.

Leptin Receptor Expression in the CNS

In the CNS, the primary target for leptin action with respect to food intake and body weight regulation is the hypothalamus. Indeed, several hypothalamic nuclei including the arcuate nucleus (ARC), ventromedial hypothalamus (VMN), and dorsomedial hypothalamus (DMN) display particularly high levels of Ob-R_b expression in rodents *(6,68–70).* In human hypothalamus, high levels of leptin receptor mRNA as well as Ob-R_b protein have also been identified *(71,72).* This expression pattern and the localization of the strongest signals in the ARC correlate well with this region being the hypothalamic centre that converts leptin signals from the periphery into neuronal responses *(73).* The expression of Ob-R_b in the hypothalamus appears to be sensitive to circulating leptin levels as *ob/ob* mice or fasted rats display increases in Ob-R_b expression *(74,75).* In addition to the hypothalamus, high levels of leptin-receptor immunoreactivity and Ob-R_b mRNA expression have been detected in brain regions not generally associated with energy balance, including the thalamus, cerebral cortex, cerebellum, pyriform cortex, hippocampus, substantia nigra, brainstem, olfactory tract, and amygdala *(69,70,76,77).* Within the hippocampal CA1/CA3 regions and the dentate gyrus in particular, there is widespread expression of leptin-receptor mRNA *(76,78)* and leptin-receptor labeling *(69).* In a manner similar to the hypothalamus, the hippocampus of fasted rodents also displays alterations in the levels of leptin receptor-gene expression *(79).* In hippocampal cultures (prepared from CA1/CA3 regions), leptin-receptor immunoreactivity is evident on somata, dendrites, and axons *(47).* Furthermore, leptin-receptor labeling is concentrated at points of synaptic contact and growth cones *(47),* suggesting a potential role for leptin in modulating synaptic function.

As well as leptin receptors, leptin mRNA, leptin immunoreactivity and *ob* protein are all expressed in specific regions of the brain including hippocampus, hypothalamus, cor-

tex, and cerebellum *(9,10).* Leptin labeling is not only differentially distributed throughout the CNS, but also the subcellular localization varies between neuronal populations. For example, in the dentate gyrus region of the hippocampus leptin labeling is localized to perinuclear and nuclear sites. In contrast, labeling is restricted to nuclear regions in CA2/CA3 hippocampal neurons *(10).* Moreover, leptin immunoreactivity appears to be confined to specific neuronal populations, as demonstrated by labeling specifically localized to oxytocin- and vasopressin-containing neurons within the supraoptic nucleus and paraventricular nucleus. These findings support the possibility that leptin may be made and released from specific neuronal populations and regions of the brain. However, further investigations are required to determine if centrally derived leptin fulfills the criteria of being a neurotransmitter or cotransmitter. Evidence is also emerging that leptin is transported across the blood–brain barrier to extrahypothalamic sites, such as the hippocampus, cortex, and cerebellum *(8).* In the absence of clear proof that leptin is a neurotransmitter, the blood-to-brain transport of leptin would certainly negate the need for leptin production in these brain regions.

The widespread distribution of leptin and its receptors throughout the brain, however, suggests that leptin functions as more than just a satiety signal in the CNS. As the hippocampus is one region of the brain that expresses high levels of leptin and leptin receptors, the remainder of this review focuses on the role of leptin in modulating hippocampal function.

Leptin: A Potential Cognitive Enhancer?

It is well established that in the CNS, the hippocampus plays a central role in learning and memory processes. Indeed, the phenomenon of long-term potentiation (LTP), which is a long-lasting enhancement of synaptic transmission, is thought to be a cellular correlate of certain aspects of learning, memory, and habituation. In particular, *N*-methyl-D-aspartate (NMDA) receptor-dependent LTP evoked at hippocampal CA1 synapses may underlie the processing of spatial memory in this brain region *(80).* It is well-documented that the phenomenon of LTP can be modulated at a number of levels by other hormones.

One of the main targets for modulation is the NMDA receptor, which is a key component of the induction phase of LTP. For example, insulin, which stimulates similar signaling pathways to leptin *(81),* can modulate both native and recombinant NMDA receptor-dependent responses in hippocampal neurons and *Xenopus* oocyte expression systems *(82–84).* Moreover, in diabetic (Streptozotocin-induced) rodent models and diabetic humans, deficits in learning and memory processes have been identified which are presumably attributable to either insulin deficiency or resistance *(85).* Thus, as high levels of leptin receptors are expressed throughout the hippocampal formation, and leptin and insulin share similar signal-transduction capabilities, it is feasible that hippocampal synaptic plasticity may also be modulated by leptin. This possibility is supported by recent studies using genetically obese leptin receptor-deficient rodents (Zucker *fa/fa* rats and *db/db* mice), that have impairments in both LTP and long-term depression (LTD) that are not alleviated by leptin administration. These rodents also show impaired performance in spatial memory tasks in the Morris water maze *(86).* A role for leptin in modulating hippocampal synaptic plasticity is also further implicated by its ability to convert short-lasting potentiation (STP) of synaptic transmission (induced by primed burst stimulation of the Schaffer collateral commissural pathway) into LTP *(46).* The mechanisms underlying this action of leptin involve enhancement of NMDA receptor function as leptin rapidly potentiated pharmacologically isolated NMDA receptor-mediated EPSCs and NMDA-induced

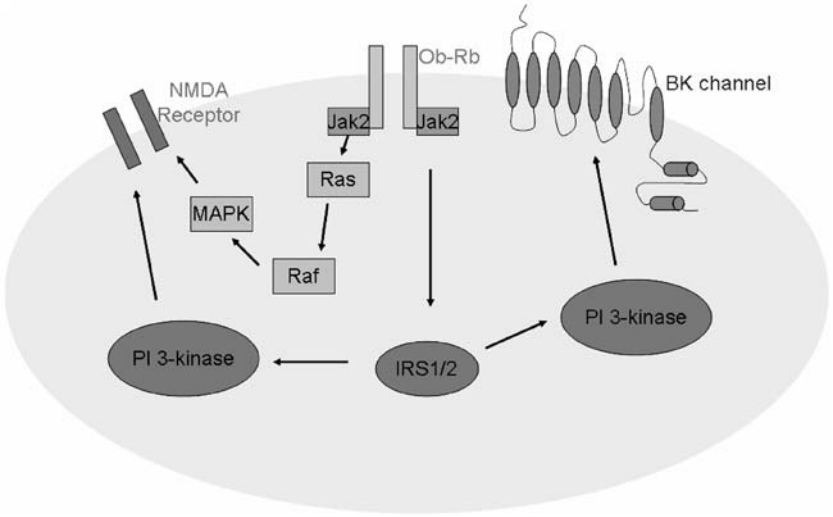

Fig. 2. Schematic representation of leptin receptor-driven signaling pathways at hippocampal CA1 synapses. Leptin-receptor activation enhances NMDA receptor-mediated responses via activation of PI 3-kinase and MAPK-dependent pathways. Leptin inhibits hippocampal neurons via PI 3-kinase-driven activation of BK channels.

increases in $[Ca^{2+}]_i$ *(46).* This process was selective for NMDA receptors as leptin had no effect on the Ca^{2+} rise induced by administration of either α-amino-3-hydroxy-5-methyl-isoxazole (AMPA) or high $[K^+]$.

Leptin also depressed, rather than facilitated, AMPA-receptor mediated synaptic transmission evoked at CA1 hippocampal synapses. In parallel with leptin action on hypothalamic neurons *(42)* and peripheral cells *(41,44),* a PI 3-kinase-dependent process underlies leptin action as 2 different PI 3-kinase inhibitors (LY 294002 and wortmannin) attenuated leptin-induced facilitation of NMDA responses. Selective inhibitors of MAPK activation (PD98059) and Src tyrosine kinases (PP1 and lavendustin A) also inhibited leptin action on NMDA responses, suggesting that MAPK- and Src-tyrosine kinase-driven pathways play a role in leptin action (Fig. 2). However, as there is no direct evidence that leptin can stimulate these signaling pathways in hippocampal neurons, the possibility that the leptin action requires stimulation of these pathways by another agent/neurotransmitter cannot be excluded.

It is well established that Src can directly phosphorylate NMDA-receptor subunits, including NR2A *(87)* and NR2B *(88).* Furthermore, during the induction phase of LTP, it is thought that Src is rapidly activated, which in turn leads to enhancement of NMDA-receptor function *(89).* Thus, the involvement of Src in leptin action may have important implications for hippocampal synaptic plasticity. Although the mechanisms responsible for stimulation of Src during LTP are not known, it is possible that during high frequency stimulation and the induction phase of LTP, leptin that is released at CA1 synapses stimulates a Src-dependent process and subsequently facilitates NMDA responses. Alternatively, hormonally released leptin (from adipocytes) may be transported from the periphery to the brain *(7,8)* where it acts to modulate the threshold for LTP induction, by selective enhancement of NMDA-receptor function. As NMDA receptors contribute little to basal levels of synaptic transmission at CA1 synapses, but are activated during high frequency stimulation *(90),* it is likely that modulation of NMDA receptor

function by leptin only occurs under conditions that promote synaptic plasticity.

Leptin Is a Potential Anticonvulsant

As facilitation of NMDA-receptor function by leptin is only likely to occur during periods of high-frequency synaptic activity, what does leptin do under resting (low frequency) conditions? In the periphery, leptin inhibits insulin-secreting cells via activation of K_{ATP} channels *(39,40)*. K_{ATP} channels are also the molecular target for leptin in GR hypothalamic neurons *(91)*. Thus, it is feasible that leptin modulates K^+ channel function in hippocampal neurons. Indeed, leptin hyperpolarizes rat hippocampal neurons by increasing a K^+ conductance *(48)*. However, in contrast to these other cell types, the hyperpolarization and increased K^+ conductance induced by leptin are not sensitive to the sulfonylurea tolbutamide, indicating that K_{ATP} channels are not the end-point for leptin action in hippocampal neurons *(48)*. However, the effects of leptin were prevented and reversed by the Ca^{2+}- and voltage-dependent K^+ channel blocker, TEA. Furthermore, leptin increased the activity of a charybdotoxin-sensitive K^+ channel in single-channel recordings, consistent with the activation of large conductance Ca^{2+}-activated K^+ (BK) channels. In a manner similar to leptin modulation of NMDA receptors, this process required activation of PI 3-kinase.

It is well known that in hippocampal pyramidal neurons, the activity of BK channels, which are located at postsynaptic sites, is crucial for regulating action potential firing rates as well as burst-firing patterns. Indeed, BK channels have also been implicated in regulating epileptiform-like activity *(92,93)*. Thus, it is conceivable that leptin receptor-driven activation of BK channels may control the level of neuronal excitability in hippocampal neurons. In one model of epileptiform-like activity, perfusion of hippocampal slices with Mg^{2+}-free medium for 2–3 h results in the generation of spontaneous interictal epileptiform-like activity *(94)*. Application of leptin to slices bathed in Mg^{2+}-free medium, reduced the frequency of interictal discharges in a readily reversible manner. This action of leptin was absent in slices from leptin-receptor deficient (Zucker *fa/fa* rats) rodents, indicating that leptin-receptor activation was required for this process *(47)*. Animals with leptin receptor/signaling deficits also display increased levels of neuronal excitability as demonstrated by the increased frequency of interictal firing in slices from Zucker *fa/fa* rats compared to lean controls.

Similarly, leptin is also capable of reducing the level of aberrant synaptic activity in a neuronal culture model of epilepsy. In this model system, perfusion of hippocampal cultures with Mg^{2+}-free medium evoked a rise in intracellular $[Ca^{2+}]$ levels that was accompanied by the induction of spontaneous Ca^{2+} oscillations. These phasic elevations in $[Ca^{2+}]$ are associated with recurrent bursts of synaptic activity *(95,96)*. Following exposure to Mg^{2+}-free medium, subsequent application of leptin induced a rapid and reversible depression of the Mg^{2+}-free induced enhancement in global Ca^{2+} levels. In contrast, however, leptin failed to affect the basal levels (in Mg^{2+}-containing medium) of $[Ca^{2+}]$ in the hippocampal cultures. This action of leptin was mimicked by a selective BK-channel opener and was prevented by the BK-channel blockers, iberiotoxin and charybdotoxin, implicating leptin receptor-driven activation of BK channels in this process. In a manner similar to leptin action on BK channels, the signaling mechanisms underlying leptin inhibition of the enhanced $[Ca^{2+}]_i$ levels involved activation of a PI 3-kinase-, but not MAPK-dependent process *(47)*. Thus, leptin-induced modulation of epileptiform-like activity in hippocampal cultures and slices is likely to involve PI 3-kinase driven stimulation of BK channels (*see* Fig. 2). This coupling of leptin receptors to BK channels may be a useful therapeutic target in the treatment of epilepsy.

Leptin and CNS Development

A potential role for leptin in developmental processes has been suggested by the high lev-

els of leptin expression in placenta *(97).* There is also widespread expression of leptin and its receptors in fetal tissues *(98)* and human umbilical cord *(99),* implicating a potential role for this peptide in the regulation of *in utero* development. In support of this possibility, leptin receptor gene expression is detected in various embryonic mesoderm-derived tissues, such as cartilage/bone primordial and musculoaponeurotic laminae *(100).* Evidence is also emerging that leptin can promote angiogenesis in human endothelial cells *(101)* and induce endothelial cell migration *(102)* as well as expression of matrix metalloproteinases *(103).* Developmental changes in both the expression levels and localization of Ob-Rb have also been detected in rodent brains, implicating leptin receptor-driven systems in CNS development *(104–106).* For example, in mouse embryos (at embryonic d 11.5; E11.5) Ob-R_b mRNA was detected in the ventricular zone of the rhombencephalon, whereas from E14.5 Ob-R_b mRNA expression was localized to the ventricular zone of the thalamus. However, Ob-R_b mRNA was not detected in the arcuate nucleus and ventromedial hypothalamus until E18.5 *(107).* Moreover, reductions in brain weight *(108,109)* and protein content *(108)* have been reported in leptin deficient or insensitive (*ob/ob* and *db/db* mice) rodents when compared with control mice, which also supports a role for leptin in CNS development. *Ob/ob* and *db/db* mice also display reduced levels of a variety of synaptic proteins including syntaxin-1, synaptosomal-associated protein-25, and synaptobrevin in hippocampal and neocortical regions of the brain. The expression of glial fibrillary acidic protein as well as the myelin basic protein, proteolipid protein is also attenuated in the hippocampus, neocortex, and striatum of *ob/ob* and *db/db* mice. However, the levels of these proteins and brain weight in *ob/ob* mice can be normalized by postnatal administration of leptin *(108).* The possibility that leptin deficiency affects development of the CNS is also supported by reports of deficits in brain myelin *(110),* altered dendritic orientation *(111),* and attenuated neuronal soma size *(112)* in *ob/ob* mice compared to control mice. However, it still needs to be clarified that exposure of neurons to leptin can directly induce developmental changes in the CNS.

Conclusions

In conclusion, the adipocyte-derived hormone, leptin plays an important role in controlling feeding behavior and energy expenditure via its actions on specific hypothalamic nuclei. However, evidence is emerging that within the CNS, leptin is a multifaceted hormone that plays a key role in a wide variety of neuronal functions. For instance in the hippocampus, an area of the brain that is particularly important in learning and memory processes, leptin is a potential cognitive enhancer as it facilitates synaptic plasticity via selective augmentation of NMDA receptor function. In contrast, when NMDA receptors are quiescent (usually during basal or low-frequency synaptic transmission) leptin can potently regulate hippocampal hyper-excitability by stimulating BK channel activation—a process that may have important implications for developing novel drug therapies for the management of hyper-excitable states such as temporal lobe epilepsy. Evidence is accumulating that leptin may also play a vital role in the development of both the central and peripheral nervous systems.

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