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Mini-review

Leptin in the CNS: much more than a satiety signal

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Abstract

The discovery of the obese gene product, leptin has generated enormous interest in how the periphery signals the status of nutritional stores to specific hypothalamic nuclei involved in regulating feeding and energy balance. However it is emerging that leptin, in addition to its role as a circulating satiety factor, is a multi-faceted hormone that plays a key role in a variety of CNS functions. In this review, we summarise recent progress in leptin biology, with particular focus on its diversity of actions within the CNS, ranging from satiety signal, to regulator of bone formation and inhibitor of neuronal excitability.

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1. Introduction

1.1. Leptin and its receptor

Leptin is the product of the obese (*ob*) gene that is synthesised predominantly, although not exclusively, by

white adipose tissue. It circulates in the plasma as a 16 kDa protein and plasma levels of leptin are proportional to body fat content. Anatomical as well as functional data indicate that leptin regulates energy balance mainly by acting in the brain. Leptin enters the brain by a saturable transport mechanism (Banks et al., 1996), possibly by receptor-mediated transport across the blood brain barrier, or it may be transported into the brain via the cerebrospinal fluid (Schwartz et al., 1996a).

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The leptin receptor (Ob-R) was first isolated from the choroid plexus by expression cloning strategies (Tartaglia et al., 1995). Ob-R is encoded by the diabetes (*db*) gene and alternate splicing of the *db* gene generates multiple variants of Ob-R mRNA that encode at least six leptin receptor (Ob-R_{a-f}) isoforms (Lee et al., 1996; Wang et al., 1998). These leptin receptor isoforms share identical extracellular ligand binding domains at the amino-terminus but differ at the carboxy-terminus. With the exception of Ob-R_e, these isoforms are membrane-spanning receptors that fall into two categories. There are short forms of the receptor (Ob-R_{a, c, d & f}), which typically consist of 30–40 cytoplasmic residues and a long form, Ob-R_b, which has an extended intracellular domain (302 cytoplasmic residues) that contains various motifs required for interaction with other proteins and subsequent initiation of signalling pathways. Ob-R_e differs from the other isoforms in that it lacks a transmembrane domain (Lee et al., 1996) and circulates as a soluble receptor. The Ob-R_b isoform plays a pivotal role in the regulation of the obese state. Indeed, it is the absence of this isoform, due to the insertion of a premature stop codon in the cytoplasmic domain of the Ob-R_b mRNA transcript, which results in the obese phenotype of *db/db* mice (Chen et al., 1996). The leptin receptor is a member of the class I cytokine receptor superfamily (Ihle, 1995), which lack intrinsic tyrosine kinase activity and signal via association with janus tyrosine kinases (JAKs). Following leptin binding to Ob-R_b, JAK2 is activated and both proteins are subsequently phosphorylated. These events act as a switch to recruit and activate numerous signalling pathways (Fig. 1). Pathways activated by JAKs include insulin receptor substrate (IRS) proteins (Ihle, 1995) and the p85 subunit of phosphoinositide 3-kinase (PI 3-kinase), which is a common target downstream of IRS proteins (Myers and White, 1996). The STAT (signal transducers and activators of transcription) class of transcription factors can also be activated by JAKs following cytokine receptor activation. In addition, most cytokines also result in activation of the Ras-MAPK (mitogen activated protein kinase) pathway by inducing phosphorylation of the adaptor protein Src homology/collagen (SHC; Ihle, 1995). Recently, a new family of cytokine-inducible inhibitors of signalling have been identified, that include CIS (cytokine inducible sequence) and SOCS-1-3 (suppressor of cytokine signalling). The SH2 domains of SOCS are thought to bind to phosphorylated tyrosine residues on JAKs, to suppress cytokine receptor signalling (Kile and Alexander, 2001).

It was originally thought that the other isoforms of the leptin receptor were signalling incompetent due to their short intracellular domains; a suggestion reinforced by their inability to undergo tyrosine phosphorylation (Bjorbaek et al., 1998) and lack of all the components of the JAK binding motif. However evidence is now

accumulating that the short forms of the receptor may possess some signalling capabilities. For example, leptin has been reported to activate MAPK by interaction with the Ob-R_a isoform (Yamashita et al., 1998). Indeed, leptin antagonises glucagon induced cAMP elevation in hepatocytes lacking Ob-R_b (Zhao et al., 2000). Although a specific function for any of the short isoforms has yet to be defined, Ob-R_a and Ob-R_c are abundantly expressed in microvessels of the brain (Hileman et al., 2002) where they are believed to transport leptin across the blood brain barrier (Tartaglia et al., 1995; Banks et al., 1996; Hileman et al., 2002).

2. Leptin receptor signal transduction

Only the long form of the leptin receptor (Ob-R_b) contains intracellular signalling motifs required for activation of the JAK-STAT signalling pathway. Indeed, numerous studies have shown that JAK2 is preferentially activated during leptin receptor signalling (Baumann et al., 1996; Bjorbaek et al., 1997; Ghilardi and Skoda, 1997), although signalling through JAK1 has also been reported (Bjorbaek et al., 1997). Following ligand binding, JAK2 associates with specific binding domains within the C-terminal of Ob-R_b, which results in transphosphorylation to activate JAK2, which in turn phosphorylates tyrosine residues within the cytoplasmic domain of the receptor. One tyrosine residue (Y1138), enables STAT3 binding, followed by JAK phosphorylation, resulting in STAT3 dimerization and eventual translocation into the nucleus. The phosphotyrosine residues are also recognition sites for a number of SH2 domain containing proteins such as SHC and IRS proteins, which recruit further downstream signalling molecules (Fig. 1).

Like other members of the class I cytokine receptor superfamily, leptin receptor activation results in STAT 1, 3 and 5 tyrosine phosphorylation in vitro (Carpenter et al., 1998; Li and Freidman, 1999; Morton et al., 1999). However, in vivo, at least in the hypothalamus, intravenous administration of leptin activates STAT3 specifically (Vaisse et al., 1996), leading to nuclear translocation (Hübschle et al., 2001) and the transcriptional activation of genes, including the immediate-early genes *c-fos* and *c-jun* (Bjorbaek et al., 1998). Recent evidence indicates that leptin can also induce expression of SOCS-3 mRNA in the hypothalamus (Bjorbaek et al., 1998) and in COS cells (Bjorbaek et al., 1999); an action that may be an important feedback mechanism for controlling leptin receptor signalling, at least at the level of transcription (Bjorbaek et al., 2000).

Besides modulating gene transcription, there are numerous reports indicating that leptin can evoke more rapid responses by activating alternative and distinct cell signalling pathways. Indeed, recent studies have clearly

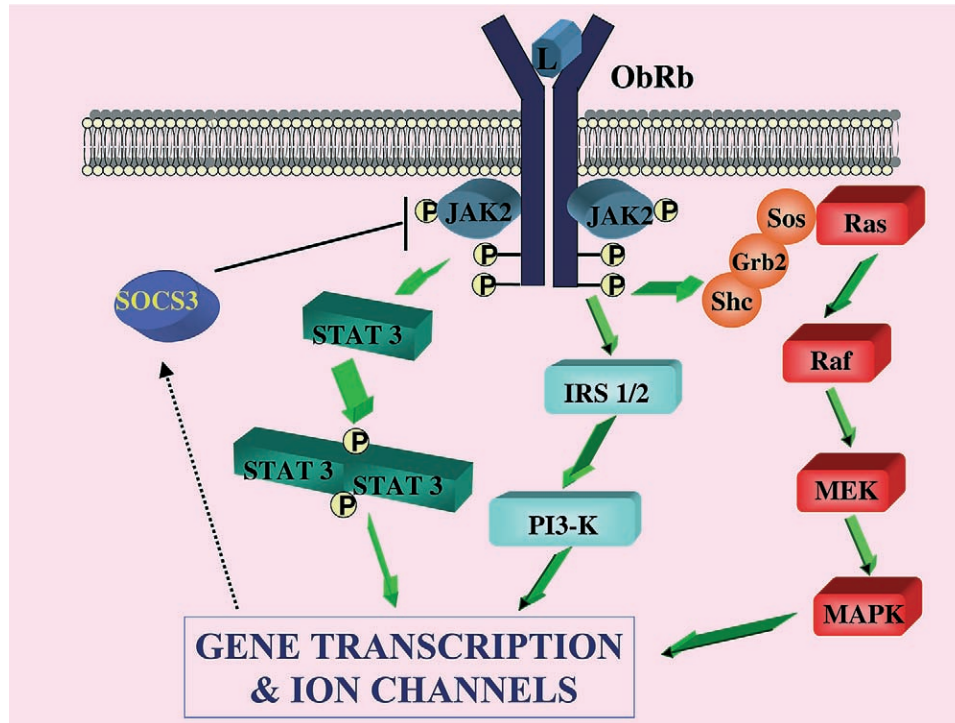


Fig. 1. Signal transduction pathways activated following the binding of leptin to its receptor (ObRb form). Grb2, growth factor receptor bound 2; IRS, insulin receptor substrate; JAK, janus kinase; MAPK, mitogen-activated protein kinase; MEK, MAP kinase kinase; PI3-K, phosphatidylinositol 3 kinase; Shc, Src homology and collagen; SOCS, suppressors of cytokine signalling; Sos, son of sevenless; STAT, signal transducers and activators of transcription.

implicated the lipid kinase, PI 3-kinase as a key component of leptin receptor-driven signalling pathways in peripheral cell types, including insulin-secreting cells (Harvey et al., 2000a), hepatocytes (Zhao et al., 2000) and myocytes (Berti et al., 1997). Leptin receptor activation has also been reported to stimulate the Ras-MAPK signalling pathway in various peripheral cell types (Tanabe et al., 1997; Takahashi et al., 1997; Banks et al., 2000).

There is growing evidence in peripheral tissues that leptin and insulin signalling networks are connected at a number of levels. For instance, leptin facilitates the actions of insulin on hepatic glucose metabolism (Aiston and Agius, 1999; Harvey et al., 2000b). Leptin also attenuates insulin-induced tyrosine phosphorylation of IRS-1 and downregulation of gluconeogenesis in human hepatic cells (Cohen et al., 1996). Furthermore, insulin occludes leptin-induced activation of ATP-sensitive K^+ (K_{ATP}) channels in insulinoma cells (Harvey and Ashford, 1998), but mimics leptin-induced K_{ATP} channel activation in hypothalamic GR neurones (Spanswick et al., 2000).

3. Genetically obese rodents

Investigations into the importance of leptin in the regulation of body weight have been significantly aided

by studying natural recessive mutations associated with certain obese syndromes, most notably *ob/ob* and *db/db* mice and Zucker *fa/fa* rats. The obese phenotypes in mice arise from mutations in the *ob* and *db* genes, respectively, and exhibit phenotypes similar to type 2 diabetes including early onset obesity, hyperglycaemia and hyperinsulinaemia (Zhang et al., 1994). In C57B1/6J *ob/ob* mice, a Cys to Thr substitution results in a stop codon at position 105 and the synthesis of a truncated protein that cannot be secreted. In contrast in the *ob²¹/ob²¹* mouse mutant, a transposon inserted into the first intron prevents synthesis of mature *ob* mRNA (Zhang et al., 1994). Both *ob/ob* mouse mutants result in leptin deficiency (Pellemounter et al., 1995; Halaas et al., 1995; Campfield et al., 1995) and the *ob* phenotype. Administration of recombinant leptin to these mice corrects the associated defects and at higher doses induces significant weight loss in normal mice (Pellemounter et al., 1995; Halaas et al., 1995; Campfield et al., 1995). The diabetic *db/db* mouse displays phenotypic characteristics indistinguishable from the *ob/ob* mouse. This mutation resides in the *db* gene, and renders the animal insensitive to leptin. However, unlike *ob/ob* mice, neither peripheral nor central administration of leptin leads to weight loss (Halaas et al., 1995; Campfield et al., 1995). Zucker fatty rats have a single point mutation in the extracellular domain of the leptin receptor (resulting in a Gln to Pro substitution at position

269), and this appears to induce both a reduced affinity for leptin and reduced signal transduction capability (Da Silva et al., 1998). Mutations in leptin and its receptor have also been identified in humans (Clement et al., 1998), but are rare and therefore are presumably not the cause of the putative leptin resistance associated with the majority of obese humans.

4. Role of leptin in the hypothalamus

Within the CNS, the hypothalamus is the main site of leptin action with respect to controlling food intake and energy expenditure. High levels of the ObR_b receptor isoform are expressed in several hypothalamic nuclei including the arcuate nucleus (ARC), ventromedial hypothalamus (VMN) and dorsomedial hypothalamus (DMN), with the strongest signals localised to the ARC (Schwartz et al., 1996b; Hakansson et al., 1996; Hakansson et al., 1998; Elmquist et al., 1998a). Intravenous or intraperitoneal injection of leptin results in the activation of ARC, VMN, DMN and paraventricular nucleus (PVN) hypothalamic neurones; all areas implicated in regulating feeding behaviour and energy balance (Ahima, 2000). Furthermore, intracerebroventricular (icv) administration of leptin to *ob/ob* mice and wild type mice inhibits food intake and decreases body weight (Ahima and Flier, 2000; Elmquist et al., 1999).

The ARC is the hypothalamic centre that transduces peripheral leptin signals into neuronal responses and behavioural changes associated with alterations of food intake and body weight regulation (Dawson et al., 1997; Tang-Christensen et al., 1999). The ARC is also rich in neurones that contain neuropeptides implicated in CNS anabolic and catabolic effector pathways (Elmquist et al., 1998b). Two neuronal subtypes are critical targets for leptin in the ARC, an orexigenic pathway comprising neuropeptide-Y (NPY) and agouti-related protein (AGRP)-containing neurones and an anorexigenic pathway consisting of proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART)-containing neurones. Mice deficient (*ob/ob*) or unresponsive (*db/db*) to leptin, or fasted rats, are characterised by increased levels of NPY/AGRP mRNA and decreased levels of POMC/CART mRNA, and direct administration of leptin to fasted rats or *ob/ob* mice reverses these changes (Ahima et al., 2000). Thus, ARC neurones transduce information on body energy stores, as supplied by circulating levels of hormones such as leptin, into neuronal responses. These neurones subsequently innervate various second order neurone centres where further integration of satiety/adiposity signalling occurs. Outputs from these second order centres descend through hindbrain regions where there is additional integration before output to spinal neurones and peripheral organs.

There is widespread acceptance that leptin-induced gene transcription changes (via JAK-STAT3 pathway) are an important driver for the anorexigenic actions of leptin. However, leptin also has acute actions on ARC neurones. Electrophysiological examination has shown that a sub-population, defined as glucose-responsive (GR) neurones, whereby removal of glucose elicits neuronal hyperpolarisation, are also inhibited by leptin (Spanswick et al., 1997). Both glucose removal and leptin application hyperpolarise these neurones by activation of ATP-sensitive K⁺ (K_{ATP}) channels. Although not proven, these effects are consistent with GR neurones being NPY/AGRP-containing neurones, whereby inhibition of electrical activity results in decreased transmitter output and hence reduced food intake. Furthermore, activation of GR neurone K_{ATP} channels by leptin is defective in the Zucker (*fa/fa*) model of obesity and type 2 diabetes, consistent with the lack of effect of icv leptin on *fa/fa* rat food intake and body weight (Seeley et al., 1996). In contrast, there is no defect in the ability of leptin to reduce food intake in K_{ATP} channel (Kir 6.2^{-/-}) knockout mice (Miki et al., 2001), suggesting that activation of K_{ATP} channels is possibly not the only mechanism underlying leptin receptor-driven regulation of food intake. However, the possibility that leptin activates Kir 6.1-containing K_{ATP} channels cannot be excluded as GR neurones also express functional K_{ATP} channels comprising Kir 6.1 and SUR1 (Lee et al., 1999).

The opening of K_{ATP} channels by leptin in GR neurones is membrane delimited as demonstrated by leptin activation of channel activity in patches isolated from GR neurones (Spanswick et al., 1997). These actions of leptin are rapid, with channel activation occurring within 10 minutes of hormone application. Consequently, this action of leptin is not driven by gene transcription changes. A number of studies have demonstrated direct interactions between leptin and insulin signalling pathways in peripheral tissues (Harvey and Ashford, 1998; Szanto and Khan, 2000; Zhao et al., 2000), with the insulin signalling intermediate, PI3-kinase, being strongly implicated. Indeed, leptin modulation of K_{ATP} channel activity in GR hypothalamic neurones requires activation of PI 3-kinase (Mirshamsi and Ashford, 2001) in a manner similar to leptin receptor-driven activation of K_{ATP} channels in insulinoma cells (Harvey et al., 2000b). Furthermore, icv infusion of PI 3-kinase inhibitors prevents leptin-induced anorexia (Niswender et al., 2001), indicating that PI 3-kinase is a key enzyme linking hypothalamic leptin to reduced food intake. One function of PI 3-kinase is to promote the conversion of phosphatidylinositol biphosphate (PtdIns(4,5)P₂) into phosphatidylinositol trisphosphate (PtdIns(3,4,5)P₃; Shepherd et al., 1998) and there is evidence that the lipid products of PI 3-kinase are closely associated with the actin cytoskeleton where they can modulate the activity of a variety of

proteins (Janney, 1998). Indeed, leptin activation of K_{ATP} channels in insulinoma cells involves PI 3-kinase driven-disruption of the actin cytoskeleton (Harvey et al., 2000a). Thus, it is possible that the ability of leptin to activate K_{ATP} channels in GR hypothalamic neurones also involves a change in the dynamics of the actin cytoskeleton (Fig. 2).

As well as inhibiting GR hypothalamic neurones, leptin activates POMC-containing neurones of the ARC inducing depolarisation and increased firing. This excitation is caused by a combination of depolarisation through activation of a non-specific cation channel and by reducing GABA release from the NPY-containing neurones onto POMC-containing neurones (Cowley et al., 2001). Leptin also excites hypothalamic PVN neurones (Powis et al., 1998) by increasing a non-selective cation conductance. Thus, there are at least two distinct populations of neurones in the hypothalamus that are sensitive to leptin: those that are depolarised by leptin with the subsequent release of appetite-reducing peptides, such as α -MSH and those that are hyperpolarised or inhibited by leptin with the resultant reduction in release of appetite stimulating factors (NPY and AGRP). In addition to directly modulating the activity of specific hypothalamic neurones, leptin can also interact with other neurotransmitter systems that are involved in maintaining food intake. For instance, endocannabinoids

(Di Marzo et al., 2001), melanin concentrating hormone (MCH; Sahu, 1998a) and orexins (Tritos et al., 2001) are all part of an expanding group of orexigenic mediators that are regulated by leptin in the hypothalamus. Furthermore, leptin may reduce food intake by modulating the actions of secreted neuropeptides such as MCH and NPY (Sahu, 1998b; Smith et al., 1996).

5. Other hypothalamic actions of leptin

There is accumulating evidence that leptin plays an important part in regulating neuroendocrine function, in addition to conveying the status of energy stores to the CNS. For instance in the reproductive system, leptin deficiency and resistance in animal models are associated with reproductive dysfunction (Swerdloff et al., 1976), which can be rescued by leptin treatment (Barash et al., 1996). Leptin also accelerates the onset of puberty in normal (wild type) mice (Ahima et al., 1997; Chehab et al., 1997), whereas mutations of *ob* and *db* genes result in hypothalamic hypogonadism in humans (Montague et al., 1997; Strobel et al., 1998). Leptin may be a crucial link between sufficient energy stores and normal reproductive function as transgenic mice overexpressing leptin display accelerated puberty (Yura et al., 2000) and administration of leptin to rodents reverses the

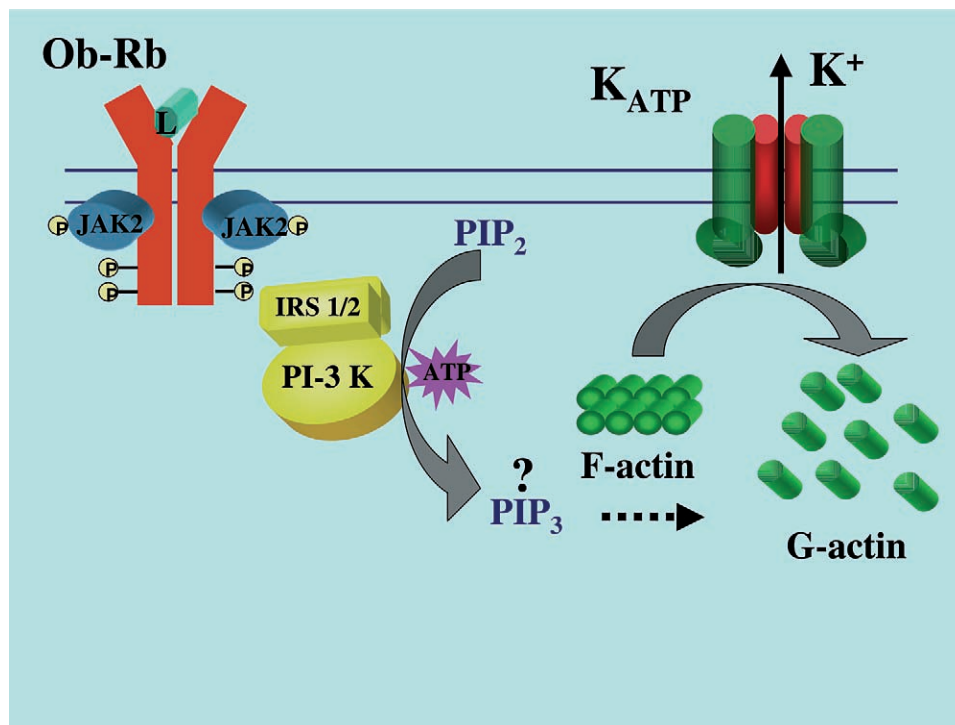


Fig. 2. Activation of K_{ATP} channels on GR neurones by leptin. Binding of leptin to its receptor (ObRb) induces a signalling cascade that involves activation of PI3-kinase, which leads to the conversion of phosphatidylinositol bisphosphate (PtdIns(4,5)P₂ (PIP₂)) to phosphatidylinositol trisphosphate (PtdIns(3,4,5)P₃ (PIP₃)), or some other processed 3' phosphatidylinositol lipid. This lipid intermediate appears to cause an alteration in cytoskeletal dynamics converting filamentous actin (F-actin) to the disaggregated, globular, (G-actin) form. The actin structural re-arrangement provokes, by an as yet unknown mechanism, K_{ATP} channel opening and increase K^+ efflux, resulting in membrane hyperpolarization.

suppression of sexual maturation induced by fasting. In a variety of animal models, leptin can restore the pulsatile release pattern of luteinising hormone (LH) which is attenuated during fasting (Gonzalez et al., 1999). This action of leptin is likely to occur in hypothalamic neurones as LH pulsatility is controlled by gonadotrophin-releasing hormone (GnRH) and leptin can directly stimulate hypothalamic GnRH secretion in vivo (Wanatobe, 2002). Thus, it is likely that when nutritional stores are adequate, leptin acts in concert with GnRH and the growth hormone axis to initiate the complex process of puberty.

It is also emerging that another important function of leptin is to regulate bone formation. The observations that gonadal failure induces bone loss, whereas obesity prevents it have suggested that bone mass, body weight and reproduction could all be controlled by the same hormone(s) (Karsenty, 2001). Indeed leptin- and leptin receptor-deficient mice have increased bone formation, leading to high bone mass (HBM) despite being obese and hypogonadic (Ducy et al., 2000). The HBM phenotype in *ob/ob* mice has been shown to exist prior to the development of obesity indicating that the absence of leptin signalling, rather than obesity, causes the HBM phenotype. In addition, there is no evidence of leptin expression or signalling in osteoblasts, but icv infusion of leptin causes bone loss in both *ob/ob* and wild type mice (Ducy et al., 2000). Thus, leptin, via its actions in the hypothalamus, is a potent inhibitor of bone formation.

6. Leptin actions in the hippocampus

Recent studies indicate that leptin receptor immunoreactivity and mRNA are expressed in areas of the CNS that are not directly associated with the regulation of energy balance, such as the cerebellum, pyriform cortex, cerebral cortex, thalamus, hippocampus, amygdala, olfactory tract and substantia nigra (Elmqvist et al., 1998a; Hakansson et al., 1998; Mercer et al., 1996; Baskin et al., 1999). Thus, it is likely that leptin has additional functions in these brain regions.

In the hippocampus, an area of the brain that is critically involved in learning and memory, N-methyl-D-aspartate (NMDA) receptors are necessary for the induction of long-term potentiation (LTP) in most pathways (Bliss and Collingridge, 1993). Indeed, leptin converts short-term potentiation (STP) of synaptic transmission induced by primed burst stimulation of the Schaffer-collateral commissural pathway into LTP. Furthermore, leptin receptor-deficient rodents (Zucker rats and *db/db* mice) display impairments in both long-term potentiation and long-term depression (Li et al., 2002); actions that are not reversed by leptin treatment. The performance of these animals in spatial memory tasks in the

Morris water maze are also impaired (Li et al., 2002). The mechanisms underlying the facilitatory effects of leptin on STP involve enhancement of NMDA receptor function as leptin rapidly enhanced NMDA-induced increases in $[Ca^{2+}]_i$ and facilitates NMDA, but not AMPA, receptor mediated synaptic transmission (Shanley et al., 2001). The signalling processes underlying these effects involve activation of a PI 3-kinase-dependent process as the ability of leptin to facilitate NMDA responses was prevented by the PI 3-kinase inhibitors, wortmannin and LY 294002 (Fig. 3). Furthermore, roles for the activation of MAPK and Src tyrosine kinases are also implicated in this process as selective inhibitors of Src tyrosine kinases and MAPK activation inhibited the actions of leptin on NMDA responses. It is well established that NMDA receptors contribute little to basal synaptic transmission, but are activated during periods of high frequency stimulation. Thus, it is likely that leptin modulation of NMDA receptor function only occurs under such conditions. There is growing evidence that diabetic patients and diabetic animal models display cognitive deficits (Gispén and Biessels, 2000), actions thought to be associated with insulin resistance and/or insulin deficiency. Another common feature of diabetes is obesity that is attributed to leptin resistance, even under hyperleptinaemic conditions (Sinha et al., 1996). As leptin resistance is, at least in part, likely to be due to compromised intracellular signalling cascades, impairments in this process would limit the potential for synaptic plasticity. Thus, leptin resistance may also be a crucial factor associated with the cognitive deficits observed in diabetics.

But what does leptin do under resting conditions? In glucose-responsive hypothalamic neurones (Spanswick et al., 1997) and insulin secreting cells (Harvey et al., 1997; Kieffer et al., 1997), leptin inhibits cellular function by activating K_{ATP} channels. In contrast, however, leptin inhibits rat hippocampal neurones via activation of large conductance Ca^{2+} -activated K^+ (BK) channels (Shanley et al., 2002b). In the hippocampus, BK channels are activated during an action potential when the membrane potential depolarises and there is a subsequent rise in $[Ca^{2+}]_i$. Thus, the activity of these channels is critical in determining action potential firing rates, as well as burst firing patterns. Indeed, using a simple model of epileptiform activity in hippocampal cultures, leptin inhibits spontaneous Ca^{2+} oscillations evoked following Mg^{2+} -removal, also by stimulating BK channel activity (Shanley et al., 2002a). Furthermore, leptin receptor-driven BK channel activation results in inhibition of spontaneous epileptiform burst firing induced in hippocampal slices. In parallel with the actions of leptin on K_{ATP} channels (Harvey et al., 2000b), the ability of leptin to modulate BK channel activity requires stimulation of a PI 3-kinase-driven process (Shanley et al., 2002a) as the ability of leptin to increase BK channel

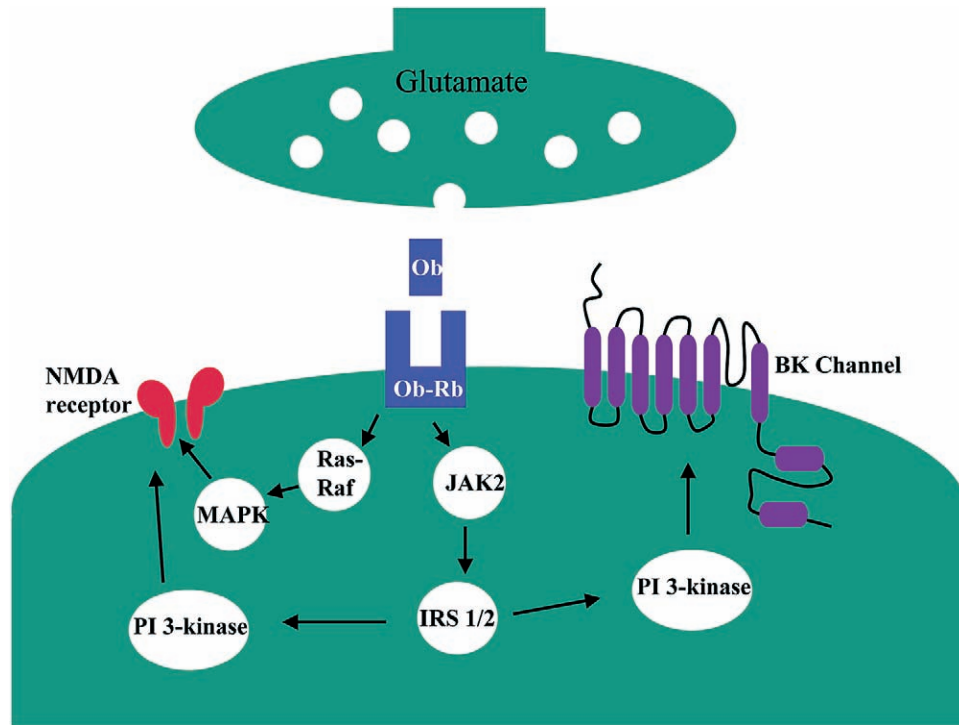


Fig. 3. This scheme illustrates the signalling mechanisms underlying leptin receptor driven modulation of NMDA receptor-mediated responses and BK channel activity at hippocampal CA1 synapses. Leptin receptor activation induces facilitation of NMDA receptor function via a signalling cascade involving activation of PI 3-kinase and/or MAPK. Leptin receptor driven PI 3-kinase stimulation also underlies modulation of BK channels by leptin.

activity is reversed by the PI 3-kinase inhibitors, wortmannin and LY294002 (Fig. 3). In conclusion, leptin hyperpolarises CA1 pyramidal neurones thereby moving the membrane potential of these neurones away from their firing threshold and by priming BK opening associated with action potential activity limits high frequency discharges. Leptin also reversibly reduces the amplitude of evoked EPSCs, an action unaccompanied by any change in input resistance (Shanley et al., 2001). Thus, it is likely that these actions of leptin on CA1 pyramidal neurones act in concert to inhibit hyper-excitability and may reduce the spread of seizure-like events throughout the hippocampus.

7. Leptin and CNS development

Recent evidence indicates that leptin may play an important role in development. For instance, placenta expresses high levels of leptin (Masuzaki et al., 1997), and there is wide spread synthesis of leptin and leptin receptors in foetal tissues (Hoggard et al., 1997). A role for leptin in CNS development has also been implicated by recent studies. Comparison of *ob/ob* and *db/db* mice with control mice indicated that leptin deficiency or insensitivity to its action leads to decreased brain weight (Ahima et al., 1999; Stepan and Swick, 1999) and protein content (Ahima et al., 1999). Reductions in the lev-

els of several synaptic proteins (syntaxin-1, synaptosomal-associated protein-25 and synaptobrevin) as well as elevations in growth-associated protein in the neocortex, striatum and hippocampus have also been reported. However, postnatal administration of leptin normalises the levels of these proteins and brain weight in *ob/ob* mice (Ahima et al., 1999). *Ob/ob* mice are also reported to display deficiencies in brain myelin (Sena et al., 1985), reduced neuronal soma size (Bereiter and Jeanrenaud, 1979) and altered dendritic orientation (Bereiter and Jeanrenaud, 1980) compared to control mice, supporting the view that leptin deficiency affects CNS development.

8. Conclusions

In conclusion, the *ob* gene product leptin is predominantly a circulating satiety factor that exerts its effects through a number of CNS pathways. In the hypothalamus, leptin can trigger responses to counteract the adverse effects of either starvation or obesity, and the specific neuro-anatomical, as well as signalling pathways that underlie these responses are now being identified. In the hypothalamus there are at least two distinct populations of neurones sensitive to leptin: those that are depolarised by leptin with the subsequent release of anorexigenic peptides and those hyperpolarised or inhibited

by leptin with the resultant reduction in release of orexigenic peptides.

However, there is growing evidence that leptin functions as more than just a satiety signal in the CNS. Indeed, leptin, via its actions in the hypothalamus, is an important regulator of reproductive function as well as bone formation. In the hippocampus, under conditions where NMDA receptors are activated, leptin acts as a potential cognitive enhancer as it facilitates synaptic plasticity via selective enhancement of NMDA responses. In contrast, at rest or during low frequency stimulation, leptin inhibits hippocampal neurones via activation of BK channels; a process that may be an important mechanism for regulating hippocampal excitability. Leptin is also an important hormonal signal in the developing CNS.

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