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Regulation of glutamate receptor trafficking by leptin

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Keywords

Leptin; hippocampus; synaptic plasticity; AMPA receptor; NMDA receptor; trafficking.

Introduction

Leptin is a 167 amino acid peptide hormone that is predominantly made by adipose tissue and it circulates in the plasma in amounts proportional to body fat content. This hormone is capable of entering the brain by crossing the blood brain barrier via a regulated and saturable transport process [1]. A key central role for leptin is in the regulation of food intake and body weight. Thus leptin signals information about the status of fat stores to leptin receptors located on specific nuclei within the hypothalamus. This information is then relayed from hypothalamic nuclei to higher order regions of the brain, which in turn regulate feeding behaviour and ultimately body weight [2]. However it is now well established that there is widespread expression of leptin receptors within the CNS, with high levels of expression detected in many extrahypothalamic brain regions including the hippocampus, brain stem, cortex, amygdala and cerebellum [3,4,5,6]. Several studies have also detected expression of leptin mRNA and protein throughout the CNS [7,8], suggesting that, in addition to reaching the brain via the blood brain barrier, there may also be localized release of leptin from specific populations of neurons.

Leptin receptors

Leptin mediates its biological actions via activation of leptin receptors which are members of the class I cytokine receptor superfamily [9] that includes interleukin 6 receptors. Leptin receptors signal via association with janus tyrosine kinase (JAKs) and in particular JAK2 is activated following leptin binding to the leptin receptor. Once activated, JAKs promotes the recruitment and subsequent activation of a variety of downstream signaling molecules including phosphoinositide 3-kinase (PI 3-kinase), Ras-Raf-MAPK (mitogen-activated protein kinase) and STAT (signal transducers and activators of transcription) transcription factors. Six splice variants of the leptin receptor (ObRa-f) have been identified. All the leptin receptor isoforms, with the exception of ObRe, have a trans-membrane region which comprises 34 amino acid residues. ObRe is distinct from the other isoforms as it is not membrane-associated and it is thought to act as a carrier for leptin in the plasma. The membrane associated leptin receptor isoforms are subdivided into two groups on the basis of variations in the length of their C-terminal domain. The short isoforms (ObRa, c, d and f) have short C-terminal cytoplasmic domains consisting of 30-40 amino acids, whereas the long isoform (ObRb) contains a long cytoplasmic region (302 amino acids). ObRb is the main signaling-competent form of the leptin receptor as it contains various motifs that are

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necessary for effective signal transduction, within its cytoplasmic domain. Conversely, although the short isoforms are able to activate certain signaling molecules in various cell types, they are generally thought to play a major role in regulating the internalization and degradation of leptin [10].

Evidence is growing that, in addition to regulating energy homeostasis via its hypothalamic actions, leptin modulates numerous other neuronal functions. In particular, several studies have implicated leptin in the regulation of excitatory synaptic transmission and synaptic plasticity in the hippocampus [11]. Indeed, obese rodents with mutations in the leptin receptor (*db/db* mice; *fa/fa* rats) exhibit impairments in both hippocampal long-term potentiation (LTP) and long-term depression (LTD). Leptin-insensitivity also results in deficits in the ability of these rodents (*db/db* mice, *fa/fa* rats) to perform spatial learning tasks in the Morris water maze [12]. Furthermore, administration of leptin directly into the dentate gyrus region of the hippocampus enhances the magnitude of LTP [13]. Moreover the ability of rodents to perform specific memory tasks is significantly improved following direct administration of leptin into the hippocampal CA1 region [14]. Recent cellular studies have demonstrated that application of leptin to acute hippocampal slices results in facilitation of N-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity [11]. Indeed leptin promotes the conversion of hippocampal STP (short term potentiation) into LTP and it facilitates the induction of hippocampal LTP [15, 16]. Leptin also has the ability to reverse established LTP (a process known as depotentiation) and under conditions of enhanced excitability leptin evokes a novel form of *de novo* NMDA-receptor-dependent LTD in the hippocampal CA1 region [17,18]. Furthermore, exposure of hippocampal neurones to leptin results in a rapid increase in the density and motility of dendritic filopodia as well as the number of excitatory synapses [19]; structural changes that are likely to contribute to the regulation of hippocampal excitatory synaptic strength by leptin. It is well documented that the trafficking of glutamate receptors to hippocampal synapses plays a pivotal role in activity-dependent synaptic plasticity [20, 21]. However there is limited information of how glutamate receptor trafficking processes are regulated by hormones such as leptin. In this review we summarize recent evidence showing that leptin has the capacity to modulate glutamate receptor trafficking processes.

Regulation of NMDA receptor trafficking by leptin

We and others have shown that leptin facilitates the induction phase of hippocampal LTP [15, 16]. It is well established that activation of NMDA receptors is pivotal for hippocampal LTP induction [22]. In addition, modulation of NMDA receptor function is a predominant way of altering the magnitude of LTP. Thus it is likely that leptin regulates NMDA receptor-dependent synaptic plasticity by modification of NMDA receptor function. In support of this, we have demonstrated previously that application of leptin to acute hippocampal slices results in enhancement of NMDA receptor-mediated excitatory postsynaptic currents (EPSCs) whereas leptin enhances Ca^{2+} influx via NMDA receptor channels in hippocampal cultures [15]. In addition, studies examining the effects of leptin on recombinant NMDA receptors expressed in *Xenopus* oocytes revealed that leptin facilitated NMDA-evoked currents in oocytes expressing NR1a/NR2A-containing NMDA receptors together with ObRb, but not when NR1a/NR2A was expressed alone [15]. This indicates that leptin does not directly modulate NMDA receptors, but rather that leptin receptor activation was required for the enhancement of NMDA responses by leptin. The ability of leptin to enhance NMDA receptor-mediated currents was observed over the entire concentration range of NMDA examined. Thus leptin facilitated inward currents evoked in response to application of maximal as well as sub-maximal concentrations of NMDA. Moreover, leptin promoted an increase in the amplitude of maximal NMDA receptor-mediated currents, in the absence of any changes in NMDA receptor kinetics. These data indicate that leptin is likely to increase

NMDA receptor-mediated currents by increasing the density of NMDA receptors expressed at the cell membrane [23].

There is growing evidence that NMDA receptors, like AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptors, are not static entities. Indeed, the density and molecular composition of synaptically located NMDA receptors can be altered in a synapse-specific manner in response to synaptic activity and certain behaviours [24]. Bi-directional alterations in NMDA receptor trafficking processes have also been implicated in activity-dependent synaptic plasticity [24, 25]. Indeed LTP results in an increase in the surface expression of NMDA receptors in the CA1 region of the adult hippocampus [25]. Recent studies indicate that NMDA receptor trafficking can be modulated by various factors including insulin-like growth factor-1 [IGF-1; 26] and the extracellular matrix protein reelin [27]. Moreover, insulin, a metabolic hormone that activates analogous signaling cascades to leptin, has been shown to facilitate the delivery of new NMDA receptors to the cell surface, by promoting the exocytosis of NMDA receptors [28]. Several lines of evidence support the notion that specific motifs located within C-terminal regions of NR2 subunits play a pivotal role in regulating NMDA receptor trafficking processes [24]. Indeed, IGF-1 promotes protein kinase B (PKB)-dependent phosphorylation of NR2C subunits which in turn increases delivery of NMDA receptors to the cell surface in cerebellar granule cells [26]. However, the precise cellular mechanisms mediating the regulation of NMDA receptor trafficking by the hormone leptin remain to be determined. It also remains to be established if leptin regulates the trafficking of distinct NMDA receptor subunits and if leptin-driven phosphorylation of specific NMDA receptor C-terminal motifs is involved.

Leptin depotentiates hippocampal CA1 synapses

Recent studies indicate that leptin can also reverse (depotentiate) established LTP at hippocampal CA1 synapses [17]. Thus application of leptin to acute hippocampal slices, 10-30 min after the induction of LTP caused a reversal of excitatory synaptic transmission to baseline levels (i.e. pre-LTP). The ability of leptin to depotentiate hippocampal CA1 synapses occurred within a specific time window after LTP induction, as application of leptin 50 min after the induction of LTP failed to reverse hippocampal LTP. It is well documented that activity-dependent synaptic plasticity is dependent on prior synaptic activity and this process is known as metaplasticity [29]. Thus, the failure of leptin to alter the magnitude of LTP, 50 min after LTP induction, suggests that a metaplastic alteration has occurred at potentiated synapses that renders them insensitive to modulation by leptin. However it is not clear what time-dependent changes occur at potentiated synapses which alter their sensitivity to leptin. The capacity of leptin to depotentiate hippocampal CA1 synapses is also dependent on the concentration of leptin. Thus, application of low concentrations of leptin (10 nM) had no effect on the magnitude of LTP, whereas higher concentrations of leptin (25nM-50 nM) readily reversed LTP.

Leptin-induced depotentiation has a postsynaptic locus of expression as concurrent analyses of the paired-pulse facilitation ratio (PPR) and coefficient of variation (CV) during experiments demonstrated that leptin-induced depotentiation was not associated with any changes in either parameter. Furthermore, the ability of leptin to depotentiate CA1 synapses was completely prevented in the presence of the competitive NMDA receptor antagonist, D-AP5, indicating the involvement of an NMDA receptor-dependent mechanism. The role of an NMDA receptor-driven process in mediating leptin-induced depotentiation is similar to the NMDA receptor-dependence of the reversal of LTP by either LFS or the metabotropic glutamate receptor (mGluR) agonist, DHPG [30, 31]. The involvement of NMDA receptors in leptin-induced depotentiation also displays parallels to the effects of leptin on other forms of hippocampal synaptic plasticity [15, 18, 19] as leptin-induced *de novo* LTD, leptin-

dependent facilitation of LTP and the structural changes in dendrites induced by leptin all require NMDA receptor activation.

Leptin-induced depotentiation involves removal of GluR2-lacking AMPA receptors from hippocampal synapses

Previous studies have shown that internalization of AMPA receptors underlies low-frequency stimulation (LFS)-induced depotentiation of hippocampal CA1 synapses [32]. Removal of AMPA receptors from hippocampal synapses also mediates the reversal of LTP by mGluR activation or neuregulin [33, 34]. In a similar manner, the reversal of potentiated synapses by leptin is associated with removal of AMPA receptors from hippocampal CA1 synapses. It is known that polyamines block the channel pore of GluR2-lacking AMPA receptors in a voltage-dependent manner resulting in pronounced inward rectification [35]. Thus, the rectification properties of synaptic AMPA receptors can be readily assessed during whole cell recordings using pipettes containing the polyamine, spermine. Using this approach, Moult et al [17] found that, in agreement with previous studies [36, 37], the induction of LTP was associated with an increase in the rectification of synaptic AMPA receptors and thus insertion of GluR2-lacking AMPA receptors. However, contrary to previous findings [36], this alteration in AMPA receptor rectification was maintained for at least 30 min after LTP induction. Moreover, subsequent application of leptin to potentiated synapses, 30 min after LTP induction, resulted in a reduction in the rectification of AMPA receptors suggesting that removal of GluR2-lacking AMPA receptors from synapses plays a role in the synaptic depotentiation induced by leptin. This finding was further supported by the ability of the selective inhibitor of GluR2-lacking AMPA receptors, philanthotoxin, to reverse hippocampal CA1 LTP, thereby mirroring leptin-induced depotentiation. Moreover, like leptin, addition of philanthotoxin to potentiated synapses resulted in a reduction in synaptic AMPA receptor rectification.

The signaling pathways coupling leptin receptor activation to the removal of GluR2-lacking AMPA receptors and subsequent depotentiation were also examined. In contrast to previous studies that have implicated the stress activated protein kinase, JNK (c-jun NH2-terminal kinase) in LFS-induced depotentiation of CA1 synapses [32], the synaptic depotentiation induced by leptin was unaffected by inhibition of JNK [17]. However, leptin-induced depotentiation was markedly attenuated in the presence of the protein phosphatase 2B (calcineurin) inhibitor, cypermethrin, indicating the involvement of calcineurin in this process. Recent studies have identified a role for calcineurin in the endocytosis of GluR2-lacking AMPA receptors following NMDA receptor activation [38, 39]. In addition, NMDA receptor-driven removal of AMPA receptors from hippocampal synapses involves dephosphorylation of GluR1 on serine 845 [40]. Thus it is feasible that leptin, via the activation of calcineurin and subsequent dephosphorylation of GluR1, promotes endocytosis of GluR2-lacking AMPA receptors from hippocampal CA1 synapses.

Several studies have indicated that depotentiation and *de novo* LTD are likely to be distinct phenomenon. For instance, NMDA receptor-dependent *de novo* LTD is readily evoked in calcineurin Aα-knockout mice whereas the ability of LFS to reverse LTP is absent in mice lacking calcineurin Aα [41]. In a similar manner, leptin-induced *de novo* LTD and leptin-induced depotentiation involve the activation of divergent signaling cascades suggesting that these leptin-driven processes are also distinct phenomenon [17]. Thus, inhibitors of calcineurin readily block the depotentiation of hippocampal synapses by leptin, but fail to influence the magnitude of leptin-induced LTD [17]. It is known that NR2 subunits dictate the pharmacological and biophysical properties of NMDA receptors [42]. Moreover, distinct NR2-containing NMDA receptors are reported to be involved in different forms of activity-dependent synaptic plasticity in adult forebrain [31, 43]. Thus NR2B-containing NMDA

receptors have been implicated in *de novo* LTD whereas NMDA receptors comprising NR2A subunits underlie LFS-induced depotentiation. A number of recent studies also support the proposal that activation of molecularly distinct NMDA receptors leads to the activation of divergent signaling pathways which in turn mediate bi-directional activity-dependent synaptic plasticity. Thus it is feasible that molecularly distinct NMDA receptors mediate leptin-induced depotentiation and leptin-induced LTD, respectively. However this possibility remains to be determined.

Conclusion

It is well established that the trafficking of glutamate receptors to and away from excitatory synapses is pivotal for activity-dependent synaptic plasticity. Evidence is growing that glutamate receptor trafficking processes can be regulated by various factors, including the hormone leptin. Indeed, leptin has the capacity to regulate the trafficking of both NMDA and AMPA receptors, which in turn contributes to the alterations in excitatory synaptic strength induced by leptin. It is known that leptin plays an important role in normal brain function, however recent evidence indicates that alterations in the leptin system is also linked to a number of CNS-driven diseases and neurodegenerative disorders. Thus the ability of leptin to regulate glutamate receptor trafficking is likely to have important implications not only in health but also in diseases associated with leptin dysfunction.

Abbreviations

AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
calcineurin	protein phosphatase 2B
CNS	central nervous system
EPSC	excitatory postsynaptic current
JAK	janus tyrosine kinase
IGF-1	insulin-like growth factor-1
LFS	low frequency stimulation
LTD	Long-term depression
LTP	Long-term potentiation
MAPK	mitogen-activated protein kinase
mGluR	metabortropic glutamate receptor
NMDA	N-methyl-D-aspartate
ObR	leptin receptor
PI 3-kinase	phosphoinositide 3-kinase
STAT	signal transducers and activators of transcription
STP	short term potentiation

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