Regulation of hippocampal synaptic function by the metabolic hormone leptin

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Regulation of hippocampal synaptic function by the metabolic hormone leptin: implications for health and disease.

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Abstract.

Significant advances have been made in our understanding of the hormone, leptin and its CNS actions in recent years. It is now evident that leptin has a multitude of brain functions, that extend beyond its established role in the hypothalamic control of energy balance. Additional brain regions including the hippocampus are important targets for leptin, with a high density of leptin receptors (LepRs) expressed in specific hippocampal regions and localised to CA1 synapses. Extensive evidence indicates that leptin has pro-cognitive actions, as it rapidly modifies synaptic efficacy at excitatory Schaffer collateral (SC)-CA1 and temporoammonic (TA)-CA1 synapses and enhances performance in hippocampal-dependent memory tasks. There is a functional decline in hippocampal responsiveness to leptin with age, with significant reductions in the modulatory effects of leptin at SC-CA1 and TA-CA1 synapses in aged, compared to adult hippocampus. As leptin has pro-cognitive effects, this decline in leptin sensitivity is likely to have negative consequences for cognitive function during the aging process. Here we review how evaluation of the hippocampal actions of leptin has improved our knowledge of the regulatory brain functions of leptin in health and provided significant insight into the impact of leptin in age-related neurodegenerative disorders linked to cognitive decline.

Keywords: leptin, hippocampus, synaptic plasticity, long-term potentiation, AMPA receptor, CA1 synapse.

Abbreviations:

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Aβ: amyloid β

GABA: gamma-aminobutyric acid

D-AP5: D-2-amino-5-phosphonovalerate

GSK-3β: glycogen synthase kinase 3β

HFS: high frequency stimulation

JAK2: janus tyrosine kinase 2

KCC2: K^+-Cl^- type 2 co-transporter

LepR: Leptin receptor

LTD: long-term depression

LTP: long-term potentiation

NMDA: N-methyl-D-aspartate

ob: obese

P: postnatal day

PI3-kinase: phosphoinositide 3-kinase

PIP_2: phosphatidylinositol-4,5-bisphosphate

PIP_3: phosphatidylinositol-3,4,5-trisphosphate

PTEN: phosphatase and tensin homolog

SC: Schaffer collateral

STAT3: signal transducer and activator of transcription

STP: short-term potentiation

TA: temporoammonic

VGCC: voltage-gated calcium channel

Leptin and leptin receptor pharmacology.

The endocrine hormone, leptin is the 167 Kda product of the obese (*ob*) gene. White adipose tissue is the primary site for leptin production, and the amount of leptin made and released into the circulatory system is proportional to fat stores within the body [1,2]. It is well established that a transport process located at the blood brain barrier enables leptin to readily enter the brain, where it controls energy homeostasis by acting on specific nuclei located within the hypothalamus. The biological actions of leptin are initiated by leptin binding to the leptin receptor (LepRs), of which six receptor isoforms (LepRa-f) exist. LepRb, which is known as the long form, is the main isoform that can signal due to its extended C-terminal domain containing the necessary motifs required to initiate the complete repertoire of LepR-driven signalling. LepRs are class I cytokine receptors [3] and once leptin binds to the LepR, janus tyrosine kinase 2 (JAK2) is phosphorylated, leading to the activation of downstream signalling cascades that include signal transducers and activators of transcription (STAT3), phosphoinositide 3-kinase (PI 3-kinase) and ERK [4].

In keeping with leptin's role in energy balance, LepRs are highly concentrated in the arcuate nucleus and ventromedial hypothalamus [5,6]. However, LepR distribution extends well beyond the hypothalamus, with the hippocampus, amygdala and cerebellum also expressing a high density of

LepRs, as evidenced from studies that have utilised a combination of *in situ* hybridisation, immunocytochemical and RT-PCR approaches to probe LepR locus [7-9]. Within the hippocampus, LepR expression has been localised to the CA1 and dentate gyrus regions [7]. Dual labelling immunocytochemical studies performed in hippocampal neuronal cultures has also demonstrated LepR distribution at synaptic loci, and in close proximity to the N-methyl-D-aspartate (NMDA) sub-class of glutamate receptors [9,10], suggesting LepR expression at hippocampal synapses. In support of synaptically located LepRs, it is now well documented that synaptic efficacy at hippocampal excitatory and inhibitory synapses is rapidly modulated by leptin [11-15].

It is interesting to note that in addition to modulating the strength of inhibitory synapses, recent evidence has shown that leptin is also critically involved in the development of gamma-aminobutyric acid (GABA)-mediated inhibitory circuits in the hippocampus. Thus, during the critical stage of postnatal development, exposure of hippocampal neuronal cultures to leptin promotes a shift in $GABA_A$ receptor-mediated responses from depolarising to hyperpolarising via a process involving down regulated expression of the K^+-Cl^- type 2 co-transporter (KCC2) [16].

Hippocampal excitatory synaptic function is regulated by leptin.

The hippocampus is a key brain area involved in higher cognitive functions such as learning and memory. Indeed, activity-dependent hippocampal synaptic plasticity is thought to be the process whereby the brain learns and remembers events. At hippocampal Schaffer-collateral (SC)-CA1 synapses, NMDA receptor-dependent long-term potentiation (LTP) and long-term depression (LTD) are well studied forms of synaptic plasticity that are pivotally involved in spatial learning and memory [17]. CA1 pyramidal neurons are also directly innervated by the temporoammonic (TA) pathway. This input extends from the entorhinal cortex and forms excitatory glutamate synapses on distal dendritic regions of CA1 pyramidal neurons. Like SC-CA1 synapses, synaptic plasticity at TA-CA1 synapses is thought to play a crucial role not only in spatial, but also episodic memory processes [18,19]. Numerous studies have provided evidence that the strength of excitatory synaptic transmission at SC-CA1 and TA-CA1 synaptic connections can be modified by a variety of hormones and growth factors. Indeed, endocrine hormones like insulin and estrogens can influence excitatory synaptic transmission at hippocampal SC-CA1 and TA-CA1 synapses [20-24]. Accumulating evidence indicates that the endocrine hormone leptin is also able to alter hippocampal excitatory synaptic function.

Some of the first reports to postulate a role for leptin at hippocampal synapses, involved studies in obese rodent models that exhibit insensitivity to leptin (*db/db* mice, Zucker *fa/fa* rats). These rodents were found to have impairments in their ability to perform hippocampus-dependent spatial memory tasks in the Morris water maze when compared to wild type littermates [25,26]. On the contrary, administration of leptin directly into the hippocampal CA1 region of wild-type mice

resulted in improved performance in hippocampus-dependent memory tasks relative to control mice treated with vehicle alone [27]. In cellular studies, Shanley and co-workers [11] noted that exposure of acute hippocampal slices to leptin resulted in facilitation of synaptic plasticity such that short-term potentiation (STP) was converted to LTP in leptin-treated slices. *In vivo* studies have also revealed that administration of leptin facilitates LTP, such that the magnitude of LTP is markedly elevated after leptin treatment compared to vehicle treatment alone [28,29].

NMDA receptor activation is known to play an instrumental role in different forms of activity-dependent synaptic plasticity in the hippocampus [30]. Numerous studies have confirmed that activation of NMDA receptors is also necessary for the effects of leptin on hippocampal synaptic function. Thus, leptin treatment leads to enhancement of NMDA receptor-mediated responses in acute brain slices, hippocampal neuronal cultures and in *Xenopus* oocytes expressing recombinant NMDA receptors [11,12,31]. In oocytes co-expressing specific NMDA receptor subunits (GluN1/GluN2A) and LepRb, application of leptin augmented maximal NMDA-induced currents. This suggested that leptin regulates NMDA receptor trafficking such that the density of functional NMDA receptors expressed at the plasma membrane is boosted by leptin [31]. Recent studies support this possibility, as leptin regulates glutamatergic synaptogenesis by increasing the cell surface expression of GluN2B-containing NMDA receptors in hippocampal neurons [32]. The capability of leptin to modify hippocampal NMDA receptor trafficking displays close parallels to the actions of insulin, as exposure to insulin stimulates exocytosis of NMDA receptors, resulting in an increase in NMDA receptor density at the plasma membrane [33].

Although NMDA receptors are heteromeric complexes comprised of different NMDA receptor subunits, the molecular identity of NMDA receptors that can be trafficked by leptin is not known. As there is differential expression and localisation of GluN2 subunits during development and aging [34], it is feasible that leptin influences the trafficking of distinct NMDA receptor subunits at different ages. The precise cellular mechanisms underlying the regulation of NMDA receptor trafficking by leptin also remain to be determined. Previous studies indicate that the phosphorylation status of GluN2A/GluN2B subunits regulates the surface expression of NMDA receptors, and that tyrosine phosphorylation promotes stabilisation of GluN2B subunits at the plasma membrane and at synapses [35]. As tyrosine kinase inhibitors block the ability of leptin to enhance NMDA-evoked currents in oocytes [31], it is feasible that leptin-driven tyrosine phosphorylation of NMDA receptor subunits contributes to NMDA receptor trafficking to hippocampal plasma membrane by leptin. In support of this possibility, recent studies indicate that exposure to leptin promotes tyrosine phosphorylation and subsequent trafficking of GluN2B subunits during synaptogenesis [32].

Leptin modulates hippocampal SC-CA1 synapses.

In accordance with synaptic expression of LepRs in the hippocampus [9], treatment with leptin is able to rapidly alter excitatory synaptic transmission at SC-CA1 synapses (Figure 1). A short-lasting synaptic depression is evident following acute application of leptin to juvenile (postnatal day (P)14-21) hippocampal slices [11]. By contrast, when excitability is raised, treatment with leptin induces a persistent depression of hippocampal synaptic transmission (long-term depression: LTD) at SC-CA1 synapses at the same age [36]. This novel form of LTD is also NMDA receptor dependent. Interestingly, at earlier stages of postnatal development (P5-8), leptin is also capable of inducing NMDA receptor-dependent LTD at SC-CA1 synapses, but this occurs independently of any change in neuronal excitability [12]. Thus, it is evident that in the early stages of postnatal development, leptin has complex modulatory effects on hippocampal synaptic efficacy that are dependent on the developmental stage and degree of neuronal excitability.

In addition to leptin's effects on basal synaptic transmission, exposure of juvenile hippocampal slices to leptin can reverse established LTP at SC-CA1 synapses and this process is known as depotentiation [37]. The ability of leptin to depotentiate SC-CA1 synapses is prevented following blockade of NMDA receptors with D-aminophosphovaleric acid (D-AP5), indicating that activation of NMDA receptors is also required for this leptin-driven process. Interestingly, leptin-induced depotentiation was found to be highly concentration-dependent, with application of 25nM or 50nM leptin readily able to reverse established LTP, whereas 10nM leptin was without effect [37]. Furthermore, the ability of leptin to reverse LTP displayed a distinct temporal profile, such that leptin was effective when applied 30 min, but not 50 min, after the induction of LTP [37]. The failure of leptin to reverse LTP 50 min after induction, points towards some persistent change occurring between 30-50 min, that renders potentiated synapses insensitive to leptin. However, the precise nature of this synaptic alteration remains to be determined.

The synaptic effects of leptin in adult or aged hippocampus completely oppose its actions at earlier stages of postnatal development. Thus, a persistent increase in excitatory synaptic transmission (leptin-induced LTP) is observed in adult (3-4 month old) hippocampal slices in response to leptin [12,38], and like leptin-induced LTD, activation of NMDA receptors is a pre-requisite for the induction of leptin-induced LTP in adulthood (Figure 1). Although a common feature of leptin-driven changes in synaptic efficacy at SC-CA1 synapses is the dependence on NMDA receptors, pharmacological analysis has identified differing roles for GluN2 subunits at different ages. Thus, GluN2B subunits play a pivotal role in the synaptic depression induced by leptin during early postnatal development, whereas GluN2A-containing NMDA receptors are necessary for leptin-induced LTP in adulthood [12]. Divergent signalling events also mediate the bi-directional effects of

leptin on synaptic efficacy such that ERK activation is required for the synaptic depression induced by leptin, whereas PI 3-kinase activity is crucial for leptin-induced LTP at SC-CA1 synapses [12,38].

The cellular mechanisms underlying leptin-induced LTP have been explored in depth and like activity-dependent hippocampal synaptic plasticity [39], significant evidence points to alterations in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking playing an essential role in leptin-driven increase in synaptic efficacy at SC-CA1 synapses [38]. Thus, studies in cultured hippocampal neurons demonstrate that treatment with physiological concentrations of leptin result in insertion of the AMPA receptor subunit, GluA1 into synapses, with little effect on the GluA2 subunit. Biotinylation studies have also identified selective upregulation in the surface expression of GluA1, but not GluA2, in leptin-treated hippocampal slices [38]. Furthermore, electrophysiological analysis revealed that leptin-induced LTP is associated with an increase in the rectification properties of synaptic AMPA receptors, indicating a role for the synaptic incorporation of GluA2-lacking AMPA receptors in leptin-induced LTP. Reversal of leptin-induced LTP by addition of philanthotoxin, an inhibitor of GluA2-lacking AMPA receptors, also provides pharmacological verification that AMPA receptors that lack GluA2 subunits are inserted into SC-CA1 synapses during this process [38].

Insertion of AMPA into synapses is known to be vital for activity-dependent LTP induced at hippocampal SC-CA1 synapses [39], and PI 3-kinase has been identified as a key enzyme that regulates AMPA receptor trafficking events during NMDA-dependent LTP [40]. As a key function of PI 3-kinase is to promote phosphorylation of phosphoinositide 4,5-bisphosphate (PIP_2) into phosphoinositide 3,4,5-bisphosphate (PIP_3), one key indicator of PI 3-kinase activity is an elevation in the intracellular levels of PIP_3. In hippocampal neurons, treatment with leptin resulted in increased trafficking of the AMPA receptor subunit, GluA1 to the plasma membrane, and this effect was accompanied by a rise in intracellular PIP_3 levels, suggesting the involvement of a PI 3-kinase-driven process. However, inhibition of PTEN (phosphatase and tensin homolog), the phosphatase that opposes the actions of PI 3-kinase [41], also leads to a rise in the levels of PIP_3. Indeed, leptin is reported to elevate PIP_3 levels in hypothalamic neurons via inhibition of PTEN, rather than via direct activation of PI 3-kinase [42]. Similarly, in hippocampal neurons, the ability of leptin to increase GluA1 surface expression was mirrored by treatment with either pharmacological inhibitors of PTEN or dominant negative PTEN mutants [38]. Direct application of PTEN inhibitors to acute hippocampal slices also leads to a sustained increase in synaptic efficacy which closely mirrored the actions of leptin. Collectively these findings indicate that leptin-driven inhibition of PTEN is likely to drive movement of GluA2-lacking AMPA receptors into hippocampal synapses, which culminates in an increase in excitatory synaptic strength.

How the leptin-driven elevation in PIP_3 levels drives movement of GluA2 subunits into hippocampal synapses is not entirely clear. However, one reasonable downstream target for PIP_3 is the serine-threonine kinase Akt, which is known to inhibit glycogen synthase kinase-3 (GSK-3) activity by phosphorylating GSK-3. In accordance with this, Akt-dependent inhibition of GSK-3β is associated with the synaptic incorporation of AMPA receptors [38]. Consequently, it is possible that leptin-driven inhibition of PTEN, generates an increase in intracellular PIP_3 levels, which then leads to activation of Akt. This in turn promotes the phosphorylation and thus inhibition of GSK-3β activity, which ultimately drives AMPA receptors into synapses.

Regulation of TA-CA1 synapses by leptin.

In addition to regulating SC-CA1 synapses, evidence is mounting that hippocampal CA1 synapses that are directly innervated by the TA input are also modulated by the hormone leptin, but crucially in a manner distinct to that observed at SC-CA1 synapses [43]. At juvenile TA-CA1 synapses, application of leptin results in the induction of a novel form of LTP that requires selective activation of NMDA receptors comprised of GluN2B subunits and stimulation of the PI 3-kinase signalling cascade [44]. AMPA receptor trafficking also plays a pivotal role in leptin-induced LTP at TA-CA1 synapses, as the ability of leptin to increase synaptic efficacy was blocked by selective inhibition of GluA2-lacking AMPA receptors with philanthotoxin. From these findings it can be concluded that leptin-induced LTP in juvenile hippocampus requires insertion of GluA2-lacking AMPA receptors into TA-CA1 synapses (Figure 2).

Previous studies have identified that delivery of a high frequency stimulation (HFS) paradigm results in induction of an NMDA receptor-dependent form of LTP at juvenile TA-CA1 synapses [45]. TA-CA1 LTP can be generated in hippocampal slices where the hippocampal CA3 region is physically removed, indicating that a functional SC-CA1 synaptic connection is not required for TA-CA1 LTP [44,45]. Distinct cellular mechanisms have been found to underlie TA-CA1 LTP, at different ages. For instance, in adult hippocampus (6-7 weeks old), stimulation of both NMDA receptors and voltage-gated Ca^{2+} channels (VGCCs) is required for LTP induction [46], whereas NMDA receptor activation alone is required for HFS-induced TA-CA1 LTP in juvenile (p11-18) hippocampus, as VGCCs are not implicated in this process [44]. Recent evidence indicates that at juvenile stages of development, insertion of GluA2-lacking AMPA receptors into synapses contributes to HFS-induced LTP at TA-CA1 synapses [44]. Moreover, there are parallels between activity-dependent synaptic plasticity at TA-CA1 synapses, and the novel form of LTP evoked by leptin. Thus, in electrophysiological studies, the ability of leptin to induce LTP is occluded by prior induction of HFS-induced LTP. Additionally, prior induction of LTP by exposure to leptin, occludes subsequent induction of LTP by HFS. Together these findings suggest that these two forms of synaptic plasticity at TA-CA1 synapses share similar expression mechanisms [44].

Leptin induces LTD at adult TA-CA1 synapses.

Electrophysiological studies in adult hippocampal slices discovered that exposure to leptin leads to a long-lasting reduction (LTD) in excitatory synaptic transmission at TA-CA1 synapses [47]. In a similar manner to other synaptic effects of leptin, activation of NMDA receptors is pivotal for leptin-induced TA-CA1 LTD, as the ability of leptin to depress synaptic transmission is completely blocked by pharmacological inhibition of NMDA receptors with D-AP5. Moreover, treatment of slices with selective inhibitors of GluN2A, but not GluN2B, subunits prevented the actions of leptin suggesting that activation of NMDA receptors consisting of GluN2A subunits is required for leptin-induced LTD at adult TA-CA1 synapses (Figure 2).

Detailed analyses of the signalling pathways involved in leptin-induced LTD have revealed a key role for the JAK-STAT pathway. Indeed, studies utilising a range of broad spectrum and selective inhibitors of this signalling pathway revealed that selective activation of JAK2 and STAT3 was required for leptin-induced LTD [47]. In agreement with the proposed involvement of JAK2-STAT3 signalling, recent studies pinpointed that the JAK2-STAT3 pathway is also a key element of NMDA-dependent LTD evoked at SC-CA1 synapses [48]. However, in contrast to the non-canonical role proposed for JAK-STAT signalling at SC-CA1 synapses, gene transcriptional changes have been found to play a crucial part in leptin-induced TA-CA1 LTD [47]. Thus, treatment with specific inhibitors that block the nuclear actions of STAT3, prevent STAT3-DNA interactions and inhibit protein synthesis all prevented the ability of leptin to induce LTD at TA-CA1 synapses. Consequently, leptin-induced TA-CA1 LTD involves activation of JAK2-STAT3 signalling that ultimately leads to gene transcriptional changes. The genes that are regulated by leptin and play a role in leptin-induced LTD have yet to be determined. However, as recent evidence indicates that leptin regulates hippocampal BDNF gene expression via an epigenetic mechanism [49], it is feasible that the leptin-driven changes in gene transcription linked to LTD, also involve an epigenetic process.

Significant parallels have been identified between leptin-induced LTD and activity-dependent LTD induced at adult TA-CA1 synapses [47,50]. Thus, LTD induced by low frequency stimulation (LFS) at TA-CA1 synapses is also NMDA receptor-dependent and it requires activation of the canonical JAK2-STAT3 signalling pathway which in turn leads to AMPA receptor endocytosis [50]. Consequently, it is likely that similar expression mechanisms underlie both forms of synaptic plasticity at this synapse. In accordance with this possibility, occlusion studies have shown directly that leptin-induced LTD occludes LFS-induced LTD, and vice versa, at adult TA-CA1 synapses [47].

Collectively these studies demonstrate that leptin has directly opposing actions on synaptic efficacy at the anatomically distinct inputs onto CA1 pyramidal neurons and the polarity of leptin action at SC-CA1 and TA-CA1 synapses is highly age-dependent. Moreover, the available evidence indicates that divergent cell signalling cascades and molecularly distinct NMDA receptors mediate the leptin-

driven changes in synaptic efficacy at different ages. The differing roles of NMDA receptor subunits with age is in line with the alterations in hippocampal NMDA receptor subunit expression that occurs during postnatal development, and with the reported differential expression of NMDA receptor subunits at SC-CA1 and TA-CA1 synapses. Consequently, this has fuelled the possibility that the molecular identity of NMDA receptors at SC-CA1 and TA-CA1 synapses determines not only the specific signalling cascades that are stimulated, but is also likely to be key for determining the direction of leptin's effect on synaptic efficacy.

***F*unctional implications of leptin's actions at hippocampal synapses.**

It is widely accepted that SC-CA1 synapses play a role in spatial memory processes [17,51], and in accordance with leptin's role in regulating the strength of synaptic transmission at SC-CA1 synapses, behavioural studies have demonstrated that leptin can influence hippocampal spatial memory [25,26]. As TA-CA1 synapses are involved in memory consolidation, control of place cell firing, as well as episodic memory function [18,19,45], the ability of leptin to modify TA-CA1 synaptic strength, is likely to influence episodic memory processes and memory consolidation. Recent evidence from behavioural studies support this possibility as the ability of mice to perform object-place-context recognition tasks, which mirror key features of human episodic memory, is better after peripheral administration of leptin [52]. Consequently, there is now good evidence from animal-based studies that leptin, via its ability to regulate the strength of hippocampal excitatory synaptic connections and thus learning and memory processes, has pro-cognitive actions. Furthermore, cognitive enhancing effects of leptin have also been demonstrated in human clinical studies. Thus, cognitive impairments in individuals with rare mutations in the leptin (*ob*) gene improve after treatment with leptin [53], and leptin treatment markedly elevates grey matter volume in those with congenital deficiencies in leptin [54].

On the flip side, lack of or disruption to the endogenous leptin neuromodulatory system is likely to have negative consequences for cognitive function. It is already known from studies in leptin-deficient or insensitive rodents that these rodents display poorer performance in hippocampal-dependent memory tasks relative to wild-type animals [25,26]. Additionally, it is known that age-related changes occur in the leptin system, with a decline in neuronal responsiveness to leptin reported in many studies [12, 55,56]. Indeed, the ability of leptin to induce LTP at hippocampal SC-CA1 synapses is significantly reduced with age [12], suggesting that there is a decline in the potential cognitive enhancing actions of this hormone with age. Similarly, the modulatory effects of leptin at TA-CA1 synapses are altered during the aging process as leptin fails to induce TA-CA1 LTD in aged hippocampus which contrasts with the capability of leptin at inducing LTD at TA-CA1 synapses in adulthood [47].

These alterations in leptin-sensitivity parallel the age-related decline in functionality that has been reported for other metabolic systems, like insulin [57,58]. As age-related deterioration in metabolic function is associated with an increased risk of neurodegenerative disorders like Alzheimer's disease (AD), functional decline in the leptin system is also likely to have important implications for cognitive health during the ageing process. It is known that hippocampal and cortical regions of the brain are principally affected in AD, and that marked histological alterations, including accumulation of tau, occurs in the TA pathway in the pre-clinical stages of AD [59,60]. Moreover, impairments in synaptic plasticity at TA-CA1 synapses have been uncovered in rodent models expressing mutant forms of human tau [61]. As the TA-CA1 synaptic connection is implicated in episodic memory processes [18] and key pathological changes emerge in this pathway in pre-clinical AD, it is likely that TA pathway pathogenesis is a factor involved in development of episodic memory impairments in early AD. Consequently, as leptin enhances episodic-like memory [52], and it markedly influences TA-CA1 synaptic efficacy, there is every likelihood, that leptin also displays neuroprotective actions at TA-CA1 synapses, although this remains to be demonstrated experimentally.

However, evidence is growing that leptin has powerful protective actions against the acute synapto-toxic effects of amyloid β (Aβ) at SC-CA1 synapses. It is well documented that exposure to oligomeric Aβ leads to disruption of hippocampal SC-CA1 synaptic function, such that induction of LTP is blocked whereas LTD is facilitated in slices treated with Aβ [62,63]. The mobility of AMPA receptors is also impacted, with exposure to Aβ associated with increased endocytosis of GluA1 and GluA2 AMPA receptor subunits [64]. Recent evidence reveals that leptin hinders the aberrant synaptic effects of Aβ, by counteracting the effects of Aβ on hippocampal LTP and LTD and preventing removal of GluA1-containing AMPA receptors from synapses [52,65,66]. The neuroprotective actions of leptin also extend to the chronic actions of Aβ, with leptin limiting neuronal cell death associated with long-term exposure to Aβ [65,67,68]. Recent studies utilising rodent models of AD, indicate that treatment with leptin not only promotes Aβ clearance, but it also leads to enhanced neurogenesis [69]. The ability of leptin to counteract the aberrant acute and chronic effects of Aβ at hippocampal CA1 synapses suggests that boosting the hippocampal levels of leptin may be beneficial in AD. However, further studies are required to establish fully, the therapeutic potential and clinical efficacy of this hormone.

Conclusions.

In summary, leptin is suggested to be a key endogenous modulator of synaptic plasticity at both SC-CA1 and TA-CA1 synapses, whose effects on the molecular and cellular process that underly changes in hippocampal synaptic strength is likely to represent an important target for intervention in correcting deficits in cognitive function associated with ageing and dementia.

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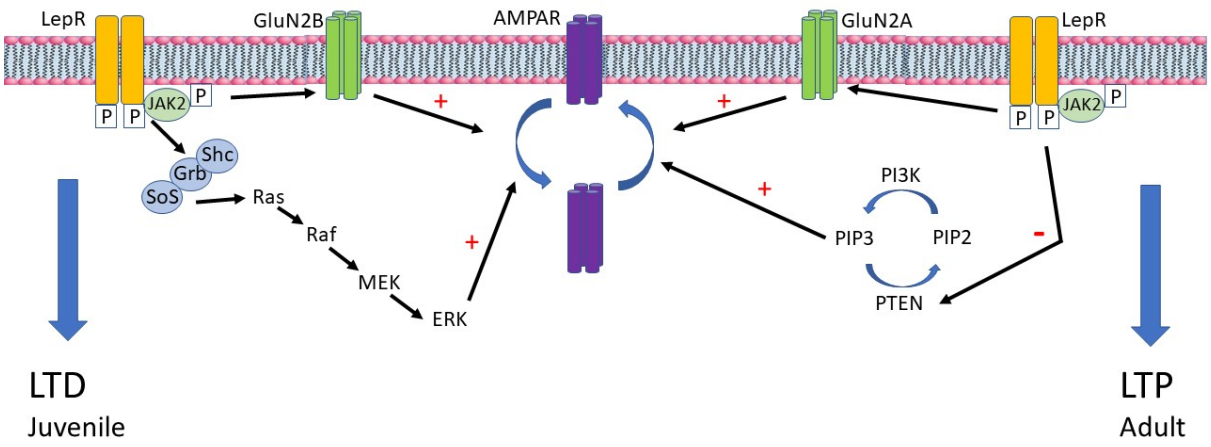
Figure 1. Bi-directional effects of leptin at SC-CA1 synapses.

Scheme demonstrating the opposing actions of the hormone leptin at SC-CA1 synapses with age. In juvenile slices treatment with leptin results in a transient or persistent depression in synaptic transmission (LTD) and this process involves activation of GluN2B subunits, and stimulation of ERK. Conversely, at adult SC-CA1 synapses, leptin induces a novel form of NMDA-dependent LTP, that requires selective activation of GluN2A-containing NMDA receptors. Leptin-induced LTP involves inhibition of PTEN which leads to a rise in PIP_3 levels and the subsequent synaptic insertion of GluA2-lacking AMPA receptors.

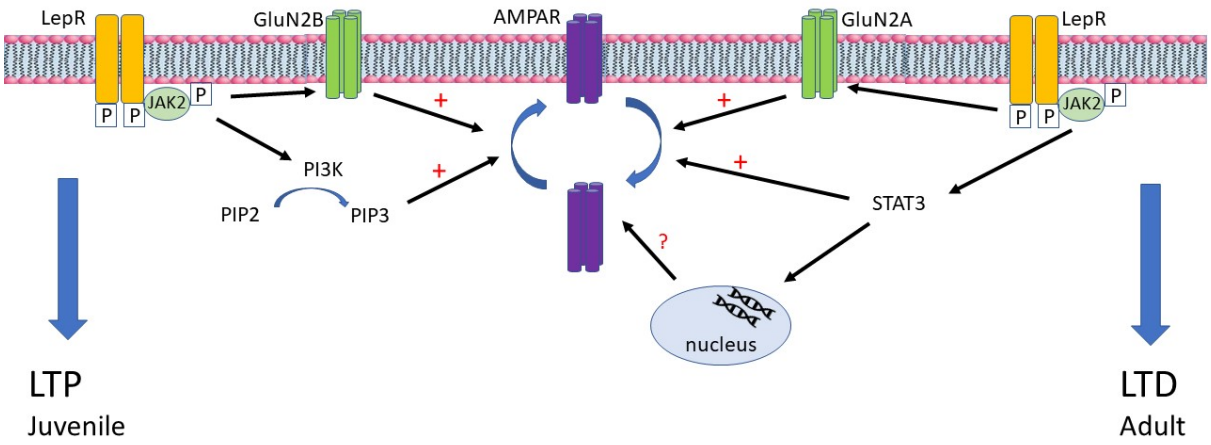
Figure 2. Age-dependent regulation of TA-CA1 synapses by leptin.

Scheme illustrating the bi-directional age-dependent effects of leptin on TA-CA1 synaptic efficacy. In juvenile hippocampus, leptin induces a novel form of LTP that requires stimulation of GluN2B NMDA receptor subunits and involves PI 3-kinase-driven synaptic insertion of GluA2-lacking AMPA receptors.

Conversely, at adult TA-CA1 synapses, treatment with leptin induces LTP that is GluN2A-dependent and involves canonical JAK2-STAT3 signalling and removal of GluA2-lacking AMPA receptors from synapses.



SC-CA1
synapses



TA-CA1
synapse