Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 8(2025)
https://www.jneonatalsurg.com

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When The Brain Stops Listening: Leptin Resistance As A Driver Of Hippocampal Dysfunction And Cognitive Impairment"- A Systematic Review

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Cite this paper as: Dr. Arijit Mazumdar (2025) When The Brain Stops Listening: Leptin Resistance As A Driver Of Hippocampal Dysfunction And Cognitive Impairment"- A Systematic Review. *Journal of Neonatal Surgery*, 14 (8), 781-796

ABSTRACT

Background: Leptin, a key adipocyte-derived hormone, is essential for maintaining energy homeostasis and also plays a significant neuromodulatory role, particularly within the hippocampus—a brain region critical for learning, memory, and executive function. In obesity and related metabolic disorders, persistent elevation of leptin levels often leads to leptin resistance, a condition marked by reduced sensitivity to leptin signalling. This resistance not only contributes to the progression of obesity but also adversely affects hippocampal function and cognitive performance.

Scope of the Review: This review explores the mechanistic links between hippocampal leptin resistance and the impairment of synaptic plasticity. Special focus is given to its detrimental effects on long-term potentiation (LTP) and long-term depression (LTD), two cellular processes fundamental to memory consolidation and learning.

Major Findings: Emerging evidence reveals that leptin resistance disrupts N-Methyl-D-aspartate (NMDA) receptor signalling and alters hippocampal architecture, resulting in impaired spatial memory and cognitive decline. High-fat diets (HFDs), a major contributor to leptin resistance, further compromise hippocampal synaptic function. Both animal and human studies underline the relevance of these mechanisms in the context of obesity-induced neurocognitive dysfunction.

Conclusions and Future Directions: Therapeutic strategies aimed at restoring leptin signalling, such as the use of leptin sensitizers (e.g., amylin analogs, Celastrol), show promise in alleviating cognitive impairments. Additionally, lifestyle modifications like caloric restriction and regular physical activity can enhance leptin sensitivity and promote synaptic health. This review highlights the potential of targeted interventions in mitigating obesity-associated cognitive decline through restoration of hippocampal leptin signalling.

Keywords:leptin resistance; hippocampal plasticity; cognitive dysfunction; obesity-related memory loss; leptin sensitizers.

1. INTRODUCTION

Leptin, a 16 kDa polypeptide hormone encoded by the ob gene1, serves as a pivotal regulator of energy homeostasis and exerts substantial effects on metabolic processes. Since its initial identification in 1994, the functional repertoire of leptin has been recognized to extend well beyond its canonical roles in appetite regulation and energy expenditure. As a critical neuroendocrine signal, leptin influences a diverse array of physiological processes through its interaction with a wide distribution of receptors present in nearly all tissues.2,3

The biological activity of leptin is mediated via the leptin receptor (ObR), which exists in several isoforms with distinct functional attributes.4 The long isoform, ObRb, is predominantly localized in the hypothalamus and is essential for mediating leptin's anorexigenic effects and for integrating metabolic cues that govern food intake and energy balance.4,5 In contrast, soluble isoforms such as ObRe play a modulatory role by regulating circulating leptin concentrations, thereby buffering against acute hormonal fluctuations.6 Upon ligand binding, leptin activates a complex network of intracellular signalling cascades, notably the Janus kinase/signal transducer and activator of transcription (JAk/STAT) pathway8, as well as the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, which collectively orchestrate metabolic regulation, synaptic plasticity, and neuronal survival.9

In the setting of obesity and related metabolic disorders, leptin's physiological actions are attenuated due to the emergence of leptin resistance. This phenomenon, characterized by diminished leptin signalling despite elevated circulating hormone levels, is implicated in the paradoxical promotion of weight gain and metabolic derangements.10,11 The persistence of leptin resistance in obesity, and its consequential effects on cognitive function—particularly within the hippocampus—underscore a critical nexus between metabolic and neurological health.12

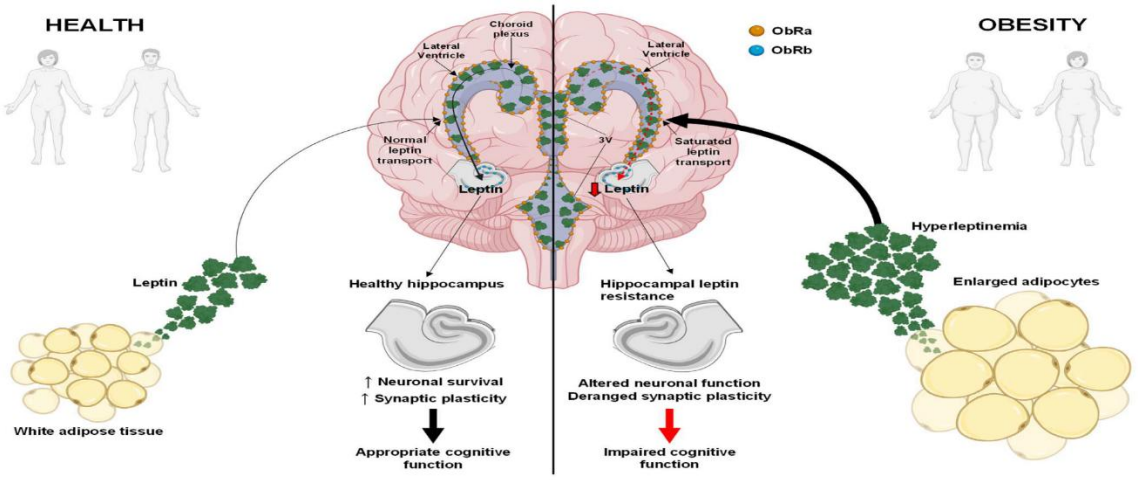

Figure 1: Impact of Leptin Signalling on Hippocampal Function in Health and Obesity

Left Panel: Normal Physiology: White adipose tissue secretes physiological levels of leptin. Leptin is transported efficiently through the choroid plexus into the brain, encountering functional ObRa and ObRb receptors. Hippocampus: Adequate leptin signalling promotes neuronal survival and enhances synaptic plasticity. Outcome: Normal neuronal activity supports healthy cognitive function.

Right Panel: Obese State Pathophysiology: White adipose tissue becomes hypertrophic, releasing excessive leptin, leading to hyperleptinemia. Transport Dysfunction: Saturated leptin transport at the choroid plexus reduces leptin's entry into the brain, even as plasma leptin levels are elevated. Hippocampal Resistance: Impaired leptin signalling (hippocampal leptin resistance) disrupts neuronal function and synaptic plasticity. Outcome: Results in cognitive impairment, characterized by deficits in learning and memory. Summary Description: This figure illustrates the contrasting effects of leptin signalling on hippocampal integrity in health versus obesity. In healthy individuals, adequate leptin transport supports hippocampal neurons and cognition. In obesity, leptin resistance—despite high circulating leptin—results in impaired hippocampal function and cognitive decline, highlighting the neurobehavioral consequences of metabolic dysregulation.

The hippocampus, situated in the medial temporal lobe, is indispensable for spatial navigation and declarative memory formation. Its laminar architecture processes information via specialized neuronal circuits, including the perforant pathway, mossy fibers, and Schaffer collaterals.[13] These circuits enable spatial encoding and consolidation of short- to long-term memories. Hippocampal-dependent learning and memory rely fundamentally on synaptic plasticity mechanisms, notably long-term potentiation (LTP) and long-term depression (LTD), which are evolutionarily conserved from rodents to humans.[14]

Preclinical studies indicate that leptin resistance disrupts hippocampal synaptic plasticity and compromises cognitive performance, exacerbating learning and memory impairments[15]. Experimental models demonstrate that high-fat diets (HFDs) and metabolic dysregulation impair central leptin signalling, adversely affecting cognitive function and revealing potential therapeutic targets (Figure 1). Leptin analogues and sensitizers show promise in rescuing cognitive deficits in rodent models, though translational applicability is hindered by leptin resistance pathophysiology.[16]

Despite advances, critical knowledge gaps persist:

Molecular mechanisms linking leptin resistance to synaptic plasticity and cognitive deficits remain incompletely defined.

The developmental trajectory of leptin resistance across life stages and its specific impact on hippocampal function are poorly characterized.

Translational challenges from animal models to human's limit clinical progress; while leptin sensitizers exhibit preclinical efficacy, their utility for human cognitive decline requires rigorous validation.[17]

This review comprehensively examines leptin resistance–mediated hippocampal dysfunction, with emphasis on:

Disruption of glutamatergic neurotransmission

Impairment of synaptic plasticity in obesity contexts. By synthesizing molecular pathways underlying leptin resistance and their cognitive sequelae, we aim to identify novel therapeutic targets for obesity-associated cognitive deficits.

Materials and Methods

Literature Search and Selection

A comprehensive literature review was performed to synthesize current knowledge regarding the molecular, synaptic, and cognitive effects of leptin resistance, with a particular focus on hippocampal function and pathophysiology in the context of obesity and high-fat diets. Scientific publications were sourced from peer-reviewed journals using indexed databases such as PubMed, Scopus, and Web of Science, as well as references within seminal review articles published from 1994 to 2024.

Search terms included combinations of:

"leptin resistance"

"hippocampus"

"synaptic plasticity"

"long-term potentiation" (LTP)

"long-term depression" (LTD)

"high-fat diet" (HFD)

"obesity"

"NMDA receptor"

"cognitive impairment"

"leptin sensitizers"

"clinical trials"

Relevant preclinical and clinical studies were included based on the following criteria:

English language

Original data on leptin signalling, hippocampal plasticity, or cognitive assessments

Utilization of rodent models (with genetic or diet-induced obesity) and/or human cohorts

Data Extraction and Integration

Extracted data comprised:

Molecular pathways (Jak/STAT, PI3K/Akt, MAPK) underlying leptin action and resistance

Central and peripheral physiological roles of leptin

Impact of leptin resistance on neuronal survival, synaptic plasticity (LTP, LTD), neurogenesis, and dendritic morphology

Behavioral assessments of learning and memory, particularly hippocampal-dependent tasks (e.g., Morris water maze in rodents)

Interventions utilizing leptin analogs, sensitizers (e.g., amylin analogs, Celastrol), and lifestyle strategies (caloric restriction, exercise)

Clinical data on metabolic and cognitive endpoints in relevant populations

Methodological Synthesis

Findings from included studies were critically evaluated for methodological rigor, relevance to the reviewed hypothesis, and translational significance. Both mechanistic and interventional data were incorporated, with special attention paid to translational barriers between animal and human research.

Where possible, convergence and divergence between preclinical and clinical results were noted. Limitations and knowledge gaps were identified, especially regarding the developmental trajectory of leptin resistance and mechanisms linking leptin signalling with synaptic and cognitive function. Recommendations for future research were formulated based on this integrative analysis.

Biological Role and Mechanisms of Action of Leptin

As already mentioned the hormone, leptin is a 167-amino acid polypeptide hormone encoded by the ob gene and belongs structurally to the class I cytokine family, sharing a similar tertiary structure. The hormone is synthesized as a pre-protein with a 21-amino acid signal peptide, which is cleaved before secretion into the circulation, resulting in a mature protein of 146 amino acids with an approximate molecular mass of 16 kDa. A functional disulphide bond is essential for its biological activity, underscoring the importance of its tertiary configuration in receptor binding and downstream signalling.[19]

Evolutionary conservation of leptin is high, particularly between human and murine species, with human leptin sharing approximately 84% and 83% sequence homology with mouse and rat leptin, respectively. This high degree of conservation

emphasizes its critical physiological role across mammalian species. Leptin is primarily secreted by white adipose tissue, but it is also synthesized by a range of other tissues, including brown adipose tissue, brain, skeletal muscle, gastric mucosa, mammary glands, ovaries, and the placenta during gestation.[20] This broad tissue distribution illustrates its involvement in both energy homeostasis and a variety of peripheral physiological processes.

The synthesis and secretion of leptin are tightly regulated by a variety of internal and external cues. Its production is positively modulated by factors such as age, high-fat diets (HFDs), insulin, and glucocorticoids.[21] In contrast, conditions associated with negative energy balance, such as fasting, physical activity, exposure to heat, and adrenergic stimulation, significantly reduce leptin expression. Leptin secretion exhibits a pulsatile profile and is modulated by hormonal signals including insulin and cholecystokinin, both of which enhance its release.[22] Furthermore, leptin demonstrates a circadian rhythm in its secretion: human leptin levels typically peak during the day, while in nocturnal rodents, peak levels are observed during the night, aligned with their respective activity patterns.

In the circulation, leptin exists in both free and protein-bound forms, with plasma concentrations ranging from approximately 5 ng/mL in individuals of normal body weight to 25–100 ng/mL in individuals with obesity. The hormone is characterized by a relatively short plasma half-life—endogenously produced leptin has a half-life of approximately 25 minutes,[26] while recombinant forms exhibit an extended half-life of around 90 minutes. Clearance of leptin is predominantly renal in nature.

Functionally, leptin plays a pivotal role in regulating food intake, energy expenditure, and maintaining energy balance through its central and peripheral actions. It acts via leptin receptors (Ob-R), members of the class I cytokine receptor family,[27] which are widely distributed throughout nearly all body tissues, enabling its pleiotropic effects. Centrally, leptin acts primarily on the hypothalamus, where it influences neuroendocrine circuits that regulate appetite and metabolic rate. Peripherally, leptin modulates numerous physiological processes, including glucose metabolism, immune function, reproductive health, and thermogenesis.[28]

Structure, Isoforms, and Biological Significance of Leptin Receptors

The leptin receptor, first discovered in 1995, belongs to the class I cytokine receptor superfamily and is integral to mediating the biological actions of leptin. This transmembrane protein exists in multiple isoforms, generated via alternative mRNA splicing from the db gene. To date, six distinct isoforms have been identified in mammals: ObRa, ObRb, ObRc, ObRd, ObRe, and ObRf.[29-33] All isoforms share a conserved architecture comprising an N-terminal extracellular domain responsible for leptin binding, a single 34-amino acid transmembrane segment that anchorage the receptor within the plasma membrane, and various C-terminal intracellular domains that determine their downstream signalling capacities.

Based on the length and composition of the cytoplasmic domain, leptin receptor isoforms are functionally classified into three main categories: short, long, and soluble forms. The short isoforms (ObRa, ObRc, ObRd, and ObRf) possess relatively short intracellular domains of 30–40 amino acids. The long isoform (ObRb), distinguished by an extended intracellular domain of approximately 302 amino acids, is the only variant competent for full intracellular signalling. The sixth isoform, ObRe, lacks both the transmembrane and cytoplasmic domains, functioning as a soluble receptor that circulates in plasma.[34]

The soluble receptor isoform ObRe has a key role in modulating leptin bioavailability in the bloodstream. It binds circulating leptin, thereby acting as a dynamic buffer and likely extending leptin's half-life while regulating its access to membrane-bound signalling receptors.[35] In contrast, the long isoform ObRb is the principal mediator of leptin's physiological actions, particularly within the central nervous system. ObRb is most abundantly expressed in the hypothalamus, a critical brain region for energy balance regulation.[36] It is the only isoform containing the full intracellular motifs necessary for initiating intracellular signalling cascades, notably the Janus kinase/signal transducer and activator of transcription (Jak/STAT) pathway. Ligand binding induces receptor dimerization and activation of Jak2, which in turn phosphorylates specific tyrosine residues on the receptor, leading to recruitment and phosphorylation of STAT proteins and subsequent transcriptional activation of leptin-responsive genes.[37]

The short isoforms, although incapable of full signal transduction, are believed to facilitate alternative functions such as leptin transport across the blood–brain barrier (particularly via the choroid plexus), receptor-mediated internalization, and ligand degradation. Additionally, they may play supporting roles in modulating leptin sensitivity and availability in peripheral tissues.[38]

Leptin receptors exhibit widespread expression across both central and peripheral tissues. In the central nervous system, receptor isoforms—particularly ObRb—are found in regions such as the hypothalamus, cerebral cortex, hippocampus, nucleus of the solitary tract, and ventral tegmental area, implicating leptin in the modulation of not only energy homeostasis but also neuroendocrine and cognitive functions.[39,40] Peripherally, leptin receptors are expressed in the liver, spleen, skeletal muscle, heart, and adipose tissue, reflecting leptin's systemic involvement in processes including immune responses, glucose metabolism, cardiovascular regulation, and reproductive function.[41]

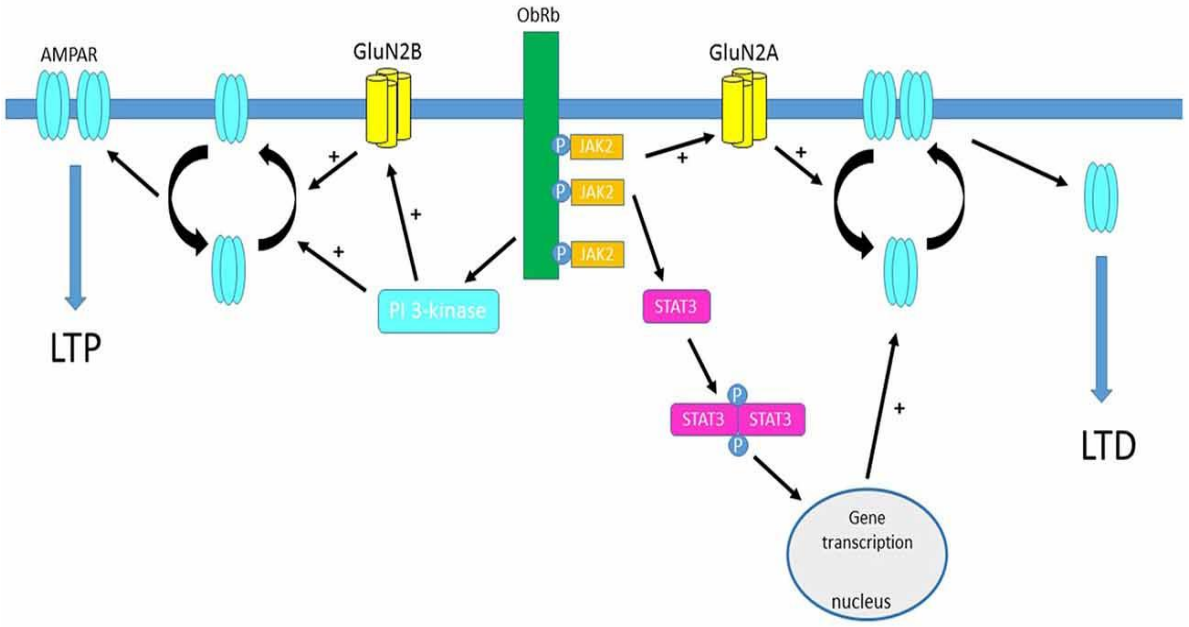

Fig:2: The image depicts leptin signalling (ObRb/JAK2/STAT3 pathway) and synaptic plasticity (AMPAR/LTP, GluN2A/GluN2B NMDA subunits), linking metabolic regulation to neuronal gene transcription and long-term potentiation (LTP).

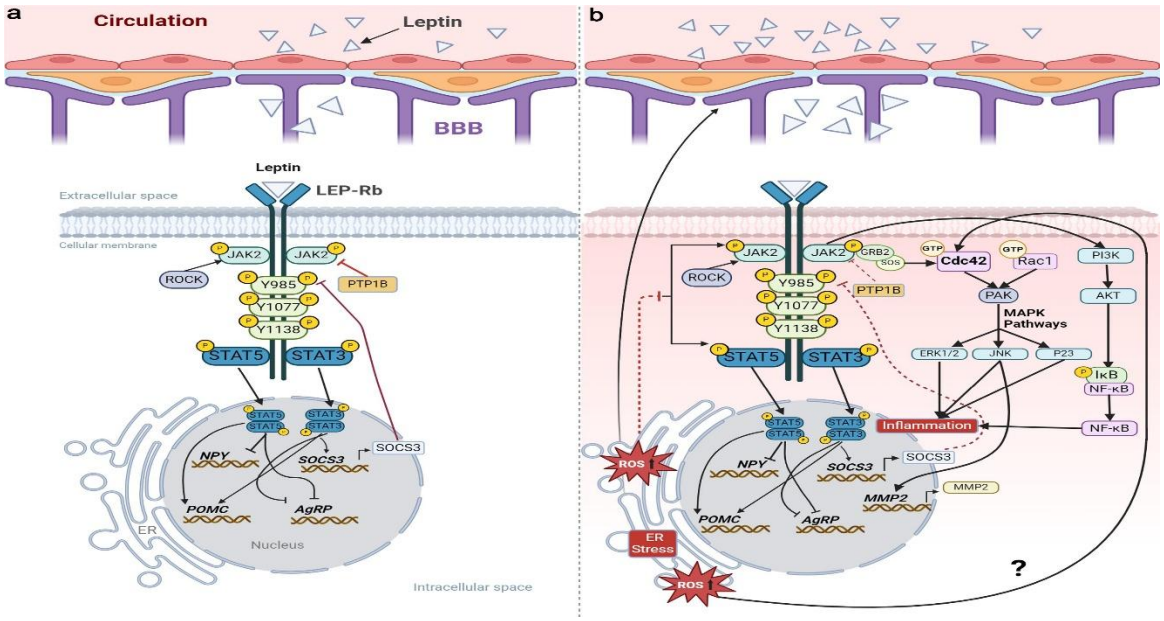

Fig:3a. Depicts the pathway of leptin entering and exerting its action

Fig 3b: Depicts the metabolism of leptin and its action inside the cell also with the use of other cellular organelles

Jak/STAT Pathway: Leptin-Mediated Signalling and Functional Implications

In the hypothalamus, leptin exerts its anorexigenic effects primarily through activation of the Janus kinase/signal transducer and activator of transcription (Jak/STAT) pathway, specifically leading to the phosphorylation of STAT3. This leptin-induced STAT3 activation is closely associated with reduced food intake and enhanced energy expenditure under physiological conditions. Upon receptor activation, phosphorylated STAT3 translocate to the nucleus, where it regulates the transcription of target genes, including suppressor of cytokine signalling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B). Both SOCS3 and PTP1B[42] serve as negative feedback regulators within the leptin signalling cascade, contributing to desensitization and attenuation of receptor activity to prevent overstimulation and maintain homeostasis.

Beyond the hypothalamic circuitry, leptin signalling via Jak/STAT and PI3K pathways exerts significant neuroprotective effects in the hippocampus—a region associated with learning and memory. Leptin enhances the expression of antioxidant enzymes like manganese superoxide dismutase (MnSOD) and anti-apoptotic molecules such as Bcl-xL,[43] thereby promoting neuronal survival. Moreover, leptin modulates synaptic activity by elevating intracellular Ca^{2+} levels in glutamatergic neurons, largely through facilitation of N-Methyl-D-aspartate (NMDA) receptor activity. This cascade influences the trafficking of AMPA receptors, resulting in long-lasting modifications in synaptic strength, a hallmark of synaptic plasticity. Animal models with disrupted leptin signalling—due to either leptin deficiency or receptor mutations—exhibit substantial impairments in spatial learning and memory, underscoring leptin's critical role in hippocampal function and cognitive processes.

PI3K/Akt Pathway: Leptin Signalling and Synaptic Regulation

The phosphoinositide 3-kinase (PI3K)/Akt signalling pathway, which is shared by both leptin and insulin signalling cascades, plays a pivotal role in mediating several key cellular processes. Upon leptin binding to its receptor—primarily the long isoform ObRb—this pathway is initiated through the phosphorylation of insulin receptor substrates 1 and 2 (IRS-1/2). These phosphorylated adaptor proteins serve as docking sites for PI3K activation, which in turn catalyses the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3), leading to the recruitment and activation of protein kinase B (PKB/Akt). [44]

Activation of Akt orchestrates a wide array of downstream biological processes including glucose uptake and metabolism, cell survival and proliferation, transcriptional regulation, and cytoskeletal reorganization. Within the central nervous system, particularly in the hippocampus, the PI3K/Akt pathway is essential for proper neuronal functioning and plasticity. Experimental studies have demonstrated that Akt signalling is critical for synaptic modulation, notably in the regulation of long-term depression (LTD). In the CA1 region of the hippocampus, leptin-induced activation of the PI3K/Akt pathway has been shown to control LTD through enhanced synthesis and trafficking of N-Methyl-D-aspartate (NMDA) receptors.[45] These findings highlight the necessity of an intact and functional PI3K/Akt signalling axis for mediating the neuromodulatory and cognitive functions of leptin in hippocampal circuits. Disruption of this pathway impairs leptin-driven synaptic plasticity mechanisms, potentially contributing to cognitive deficits observed in leptin resistance or receptor dysfunction.

MAPK Pathway: Leptin-Induced Activation and Functional Interplay

The mitogen-activated protein kinase (MAPK) signalling cascade represents another key pathway activated by leptin through its membrane-bound receptors. Upon leptin binding, auto phosphorylation of specific tyrosine residues within the intracellular domain of the ObRb receptor occurs, notably at Tyr985. This phosphorylation site serves as a docking platform for adaptor proteins that facilitate the activation of the extracellular signal-regulated kinases 1 and 2 (ERK1/2), key components of the MAPK pathway.[46] Activation of ERK1/2 drives downstream signalling events that regulate transcription factors such as c-Fos and early growth response protein-1 (Erg-1), both of which are critical regulators of cell proliferation, differentiation, and plasticity. Within the central nervous system, particularly in the hippocampus, the MAPK pathway plays an important role in modulating synaptic plasticity and neuronal excitability. Electrophysiological data indicate that inhibition of MAPK signalling results in diminished neuronal excitability, underscoring its role in enhancing synaptic responsiveness. Moreover, studies reveal that the MAPK pathway functionally interacts with the PI3K/Akt pathway during leptin signalling. Rather than acting in isolation, these pathways exhibit complementary and sometimes opposing effects on synaptic activity. In vitro studies suggest that while PI3K/Akt supports NMDA receptor synthesis and long-term depression (LTD), MAPK activation may fine-tune these responses to maintain synaptic balance. Notably, the peak expression of Erg-1 coincides with heightened MAPK activity and reduced levels of phosphorylated Akt, suggesting a dynamic regulatory interplay crucial for maintaining hippocampal function, synaptic plasticity, and cognitive processes mediated by leptin.[47]

Physiological Effects of Leptin: Central and Peripheral Actions:

Leptin plays a crucial regulatory role in controlling food intake, energy homeostasis, and neuronal function through both central and peripheral mechanisms. Within the central nervous system, particularly the hypothalamus, leptin modulates the expression of several neuropeptides involved in energy balance. It suppresses the synthesis and release of orexigenic neuropeptides such as neuropeptide Y (NPY) and agouti-related peptide (AgRP), while simultaneously promoting the expression of anorexigenic peptides like pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). These neuropeptides act in hypothalamic nuclei to reduce appetite and increase energy expenditure. Additionally, leptin enhances the expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), particularly in the ventromedial hypothalamus, further influencing neural plasticity and metabolic homeostasis.[48]

Disruptions in these pathways—often resulting from chronic hyperleptinemia and central leptin resistance—have been implicated in pathological states such as obesity. These conditions impair neurogenesis, alter neuronal plasticity, and contribute to cognitive deficits. Moreover, leptin resistance reduces the hormone's ability to regulate hypothalamic circuits associated with body weight control, thus exacerbating metabolic dysregulation.

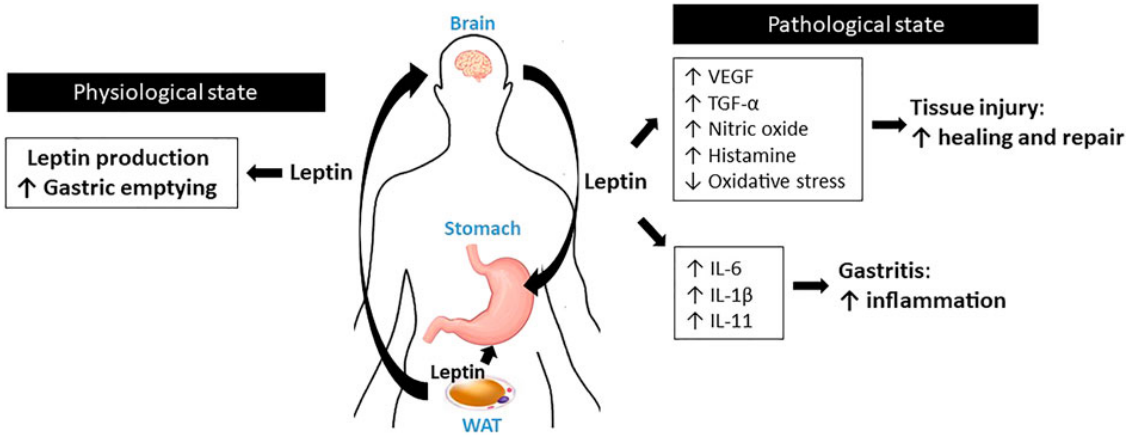

Fig:4 Image depicting the physiological role and the alteration of the leptin action in pathological states

Peripherally, leptin exerts significant metabolic effects in tissues such as the liver, adipose tissue, skeletal muscle, and heart. In hepatocytes, leptin enhances energy expenditure primarily through stimulation of fatty acid β-oxidation. In adipose tissue, leptin induces lipolysis; however, this effect is absent in leptin receptor-deficient (db/db) mice, underscoring the necessity of functional receptor signalling. In skeletal muscle, leptin activates AMP-activated protein kinase (AMPK), thereby promoting β-oxidation and reducing intramyocellular triglyceride accumulation.[49] This contributes to improved insulin sensitivity and overall metabolic efficiency. In cardiac tissue, leptin supports β-oxidation and additionally acts as a cardiotrophic factor, promoting cardiomyocyte growth independent of AMPK signalling.[50]

Beyond its well-established role in energy regulation, leptin has attracted substantial interest for its modulatory effects on synaptic plasticity and cognitive function, particularly within the hippocampus. Leptin influences excitatory neurotransmission and synaptic remodelling, as demonstrated by its capacity to enhance long-term potentiation (LTP) and spatial memory when administered directly into the dentate gyrus or the CA1 region of the hippocampus. Leptin also enhances the induction of LTP and facilitates NMDA receptor-dependent synaptic plasticity by enabling the transition from short-term potentiation to sustained LTP. Furthermore, leptin induces a form of synaptic weakening known as depotentiation, a variant of long-term depression (LTD) that is NMDA receptor-dependent.[51] This action serves as a protective mechanism against neuronal hyperexcitability and maintains synaptic homeostasis. Leptin also promotes structural synaptic changes by increasing dendritic spine density and mobility, thereby reinforcing excitatory synaptic efficacy.

Dysfunction of leptin signalling is increasingly recognized as a key contributor to cognitive and synaptic abnormalities in various disease models. Mice with genetic defects in leptin or its receptor exhibit substantial deficits in hippocampal plasticity, including impairments in both LTP and LTD, which correlate with compromised spatial learning and memory.[52] Similarly, in models of diet-induced obesity (DIO), impaired hippocampal leptin signalling results in altered glutamate metabolism, reduced synaptic integrity, and impaired memory performance. These changes are accompanied by aberrant LTD mechanisms, reduced dendritic spine density, and altered neuronal morphology. Notably, findings from animal studies are consistent with human data, confirming that the adverse impact of leptin resistance—often driven by excessive dietary fat intake—extends to cognitive function and brain structural integrity across the lifespan.

Leptin Resistance and Its Impact on Hippocampal Function and Cognition

Leptin resistance is a critical pathophysiological consequence of obesity, typified by the reduced ability of central nervous system (CNS) structures, particularly the hypothalamus and hippocampus, to respond to circulating leptin despite its elevated plasma concentrations. Under physiological conditions, leptin functions as a key regulatory hormone, inhibiting appetite and stimulating energy expenditure to maintain energy homeostasis and body weight. However, in the leptin-resistant state, these homeostatic mechanisms are disrupted, resulting in persistent hyperphagia, decreased energy output, and continued weight gain.

In obesity, excessive caloric intake promotes adipocyte hypertrophy and hyperplasia, leading to adipose tissue dysfunction characterized by chronic low-grade inflammation. This pro-inflammatory environment is driven by immune cell infiltration and is associated with altered secretion of adipokines, including increased leptin and decreased adiponectin levels.[53] Although circulating leptin concentrations are markedly elevated in obese individuals, its central anorexigenic and neurotrophic actions are diminished due to impaired signalling mechanisms—collectively termed leptin resistance[54].

At the molecular level, leptin resistance involves multiple disruptions in leptin receptor-mediated signalling. Central to this impairment are alterations in the Janus kinase/signal transducer and activator of transcription (Jak/STAT) signalling cascade, including reduced phosphorylation of STAT3. Additionally, upregulation of negative feedback regulators such as suppressor of cytokine signalling (SOCS3) and protein tyrosine phosphatase 1B (PTP1B) further attenuates effective leptin signalling.

Modifications or downregulation of leptin receptor isoforms, particularly ObRb, also contribute to diminished receptor functionality. These molecular alterations result in the attenuation or complete loss of leptin's central actions despite hormone excess, thereby exacerbating metabolic dysfunction.

Beyond its metabolic effects, leptin resistance has significant implications for hippocampal function and cognitive health. Under normal physiological conditions, leptin acts as a neuromodulator in the hippocampus, enhancing synaptic plasticity through facilitation of long-term potentiation (LTP), modulation of glutamatergic transmission, and regulation of dendritic spine density and dynamics. These processes are fundamental for learning and memory formation. Leptin achieves these effects through the activation of signalling pathways such as MAPK, PI3K/Akt, and Jak/STAT, which converge on NMDA receptor function and synaptic remodelling.

However, in the leptin-resistant state, as induced by chronic high-fat diets (HFDs) or aging, these neuroplastic actions are significantly compromised. Animal models of diet-induced obesity (DIO) and aged rodents exhibit marked resistance to hippocampal leptin signalling. In such models, the ability of leptin to induce LTP or facilitate NMDA receptor-dependent long-term depression (LTD) in the CA1 region is significantly blunted or absent. These synaptic impairments are accompanied by changes in glutamate neurotransmission, reduced dendritic spine density, and altered neuronal morphology, all of which contribute to dysfunctional plasticity.

Behaviourally, leptin resistance is associated with impairments in hippocampal-dependent cognitive tasks. Rodents with leptin resistance demonstrate poor performance in the Morris water maze and other spatial learning paradigms, despite intact motor capabilities. For example, Zucker rats—genetically predisposed to leptin receptor dysfunction—exhibit deficits in memory retention, particularly under task conditions that demand robust hippocampal engagement such as long delays between trials. These observations underscore the impact of leptin resistance on hippocampal integrity and cognitive processing.

Moreover, leptin resistance often coexists with other metabolic disturbances, including insulin resistance, dyslipidemia, and systemic inflammation, all of which may compound neuronal dysfunction. The convergence of these factors further accentuates hippocampal vulnerability, particularly in the context of aging and neurodegenerative conditions.

Cognitive Implications of Hippocampal Leptin Resistance in Obesity

Hippocampal leptin resistance, a condition commonly associated with obesity, exerts wide-ranging consequences that extend beyond the regulation of metabolism. Accumulating evidence suggests that impaired leptin signalling in the hippocampus significantly affects cognitive domains, including learning, memory, and reward processing. These cognitive disturbances, in turn, exacerbate maladaptive behaviors such as impulsive decision-making and compulsive eating, which contribute to the maintenance and progression of obesity in both rodent models and humans.

Traditionally recognized as a key region for spatial learning and memory, the hippocampus is now increasingly acknowledged for its role in the neurocognitive regulation of feeding behavior. Specifically, it contributes to higher-order cognitive functions that influence food-related decision-making, impulse control, and the integration of environmental cues with satiety signals. Disruption of leptin signalling in hippocampal circuits undermines these processes, resulting in dysregulated eating behaviors that resemble those observed in addiction. The consumption of high-fat, energy-dense, and highly palatable foods—often observed in diet-induced obesity (DIO)[55]—has been shown to impair hippocampal function, interfering with memory and learning mechanisms critical for the appropriate regulation of food intake.

Numerous studies demonstrate that diets rich in saturated fats have a detrimental impact on hippocampal structure and function, impairing synaptic plasticity and adult neurogenesis—both of which are essential for cognitive performance. These adverse effects are particularly pronounced during sensitive developmental windows, such as adolescence, a period characterized by dynamic neural remodelling, including extensive synaptic pruning and significant changes in glutamatergic neurotransmission. During this critical phase, the hippocampus is especially susceptible to dietary insults, including excessive saturated fat intake, which can disrupt neural circuits responsible for cognitive control over feeding.

Diet-induced modifications in glutamatergic signalling, particularly through NMDA (N-Methyl-D-aspartate) receptors, are especially concerning. NMDA receptor function is essential for synaptic plasticity, learning, and memory. Diets high in fat have been shown to impair NMDA receptor-mediated signalling, with repercussions for long-term potentiation (LTP) and other plasticity-related processes. During neurodevelopment, the subunit composition of NMDA receptors undergoes a shift from NR2B-dominant to NR2A-dominant expression, a process that is critical for synaptogenesis and neuronal maturation. However, the impact of high-fat diets on this developmental transition, particularly in adolescent versus adult brains, remains poorly understood. Disruption of NMDA receptor maturation during adolescence could have enduring consequences, setting the stage for lifelong cognitive vulnerabilities and impairments in top-down control of feeding behavior.[56]

Moreover, hippocampal leptin resistance influences reward-based learning and the hedonic aspects of food intake. Leptin normally acts within hippocampal circuits to facilitate learning about food-related cues and to suppress overconsumption. In leptin-resistant states, however, these suppressive effects are diminished, and the enhanced saliency of palatable foods promotes compulsive intake. This process mimics the neurobiological mechanisms of addiction, where reward pathways are

over activated, and inhibitory control is compromised. The result is a feedback loop in which excessive energy intake further enhances leptin resistance, amplifying both metabolic dysfunction and cognitive decline.

The cumulative effect of cognitive impairments caused by hippocampal leptin resistance is especially alarming given the potential irreversibility of obesity-induced neural damage. Several studies indicate that early exposure to high-fat diets can induce long-term or even permanent changes in hippocampal architecture and function, diminishing neural plasticity and increasing susceptibility to neurodegenerative diseases in later life. These findings underscore the urgent need for early intervention strategies aimed at preventing diet-induced cognitive dysfunction. Moreover, the identification of specific molecular targets, such as components of the NMDA receptor complex, may offer future therapeutic avenues for mitigating cognitive impairments and maladaptive eating behaviors associated with obesity.

In conclusion, hippocampal leptin resistance emerges as a critical mediator linking metabolic dysfunction with cognitive deficits. The bidirectional relationship between neurocognitive health and dietary behavior highlights the indispensable role of the hippocampus in integrating homeostatic and hedonic factors governing food intake. Preventing or reversing hippocampal leptin resistance could not only improve cognitive outcomes but also represent a vital strategy in the battle against obesity and its long-term neurological consequences.

Table 1. Ongoing Clinical Trials (upto October 2024) Investigating Amylin Analogs and Celastrol in Obesity/Overweight

NCT Number	Phase/Design	Intervention	Condition(s)	Primary Outcome(s)	Sponsor	Status
Pramlintide						
NCT03560960	Early Phase I/Diagnostic	Pramlintide (monotherapy)	Alzheimer's, MCI	Plasma Aβ/t-tau, inflammation, metabolic changes post-dose	Boston University	Recruiting
NCT00691158	N/A/RTBPC	Pramlintide ± Metreleptin vs. placebo	Obesity	fMRI brain response	OHSU	Active, not recruiting
NCT00690235	IV/RDBPC	Pramlintide vs. placebo	Schizophrenia, weight gain	Weight loss (antipsychotic-induced)	UT Southwestern	Completed (2018)
NCT00189514	II/RDBPC	Pramlintide acetate vs. placebo	Obesity	Long-term weight effects, safety	AstraZeneca	Completed (2015)
Cagrilintide						
NCT06131372	II/RQBPC	CagriSema vs. Cagrilintide/Semaglutide	CKD, T2D, Obesity	UACR change (baseline to week 26)	Novo Nordisk	Recruiting

NCT Number	Phase/Design	Intervention	Condition(s)	Primary Outcome(s)	Sponsor	Status
NCT06388187	III/RQBPC	CagriSema (2 doses) vs. placebo	Obesity	Weight change (week 68); ≥5% weight loss	Novo Nordisk	Recruiting
NCT06131437	III/ROL	CagriSema vs. Tirzepatide	Obesity	Weight change (week 72)	Novo Nordisk	Active, not recruiting
Celastrol						
NCT05494112	N/A/Safety OL	Celastrol (supplement)	Healthy volunteers	Liver function	Legend Labz	Unknown (2022)

Abbreviations:

RDBPC: Randomized double-blind placebo-controlled

ROL: Randomized open-label

RQBPC: Randomized quadruple-blind placebo-controlled

RTBPC: Randomized triple-blind placebo-controlled

MCI: Mild cognitive impairment; CKD: Chronic kidney disease; T2D: Type 2 diabetes

Key Improvements:

Grouped by Drug: Pramlintide, Cagrilintide (including CagriSema), and Celastrol trials are separated for clarity.

Simplified Outcomes: Focused on primary endpoints (e.g., weight change, safety).

Status Highlight: Added completion years for older trials.

Consistent Format: Uniform abbreviations and outcome phrasing.

Therapeutic Interventions and Future Directions to Counter Hippocampal Leptin Resistance

Mounting evidence suggests that modulating leptin signalling holds therapeutic potential in mitigating the cognitive impairments associated with hippocampal leptin resistance. In particular, strategies aimed at enhancing leptin sensitivity or restoring leptin signalling in the central nervous system (CNS) have emerged as a promising avenue for addressing neurocognitive dysfunction, particularly in the context of metabolic disorders such as obesity.

Preclinical and clinical studies have demonstrated the beneficial effects of leptin administration in leptin-deficient models. Leptin supplementation not only corrects metabolic abnormalities, such as hyperphagia and insulin resistance, but also improves cognitive performance and promotes neuroplasticity in key brain regions including the hippocampus, cerebellum, and anterior cingulate cortex. These neurotrophic effects highlight leptin's broader role beyond energy homeostasis, implicating it as an important modulator of neuronal development and function. In leptin-deficient individuals, leptin therapy has been shown to normalize hippocampal structure and function, enhancing neurogenesis, axonal outgrowth, synaptogenesis, long-term potentiation (LTP), and memory consolidation. As such, targeting impaired leptin signalling in the brain represents a viable strategy to counteract hippocampal atrophy and cognitive decline observed in metabolic disorders.

Despite this therapeutic promise, the clinical translation of leptin-based treatments faces significant challenges—foremost among them being leptin resistance, particularly in the context of obesity. Analogous to insulin resistance in type 2 diabetes mellitus, individuals with leptin resistance often present with elevated leptin levels yet fail to exhibit the expected physiological or cognitive responses. This diminished sensitivity to endogenous or exogenous leptin severely compromises the efficacy of leptin supplementation. Therefore, enhancing leptin sensitivity through pharmaceutical or lifestyle interventions has become a central objective in the development of effective therapies for metabolic and neurodegenerative

diseases. One promising class of therapeutic agents includes leptin sensitizers, particularly amylin analogs and small molecules such as Celastrol. Amylin is a pancreatic hormone co-secreted with insulin, which has been shown to enhance the CNS's response to leptin. Several synthetic amylin analogs—such as pramlintide, cagrilintide, davalintide (AC2307), and GUBamy (GUB014295)[58-59]—have demonstrated efficacy in reducing body weight and improving metabolic outcomes, primarily by acting synergistically with leptin to restore its signalling efficacy—thereby offering a potential solution to overcome leptin resistance. Clinical studies have explored the potential cognitive and metabolic benefits of amylin analogs. For example, pramlintide has not only demonstrated success in glycaemic control and appetite suppression but has also shown promise in improving cognitive deficits, particularly those associated with metabolic dysfunction. Similarly, cagrilintide, a long-acting amylin analog currently in phase III clinical trials, has demonstrated substantial efficacy in promoting weight loss, enhancing insulin sensitivity, and improving metabolic biomarkers such as triglyceride levels and cardiovascular risk factors. These physiological effects could indirectly support cognitive function by ameliorating the metabolic impairments that contribute to hippocampal dysfunction. Notably, trials such as NCT00690235 (focused on schizophrenia-associated weight gain) and NCT03560960 (targeting mild cognitive impairment and Alzheimer's disease) seek to explore the broader implications of leveraging leptin sensitizers in neurological and psychiatric conditions characterized by metabolic disturbances.

In addition to amylin analogues, Celastrol—a triterpenoid compound[60] derived from the Tripterygium wilfordii plant—has emerged as a promising leptin sensitizer. Preclinical findings indicate that Celastrol may enhance leptin receptor signalling pathways, restore leptin sensitivity, promote weight loss, and improve neurobehavioral outcomes in leptin-resistant models. A clinical trial (NCT05494112) is currently underway to assess its effectiveness in treating obesity by reactivating leptin signalling pathways. Given the known association between metabolic impairment and neurodegenerative disease, such pharmacological re-sensitization to leptin may hold future therapeutic implications in brain pathologies such as Alzheimer's disease and obesity-related cognitive impairment.[61]

Despite encouraging findings, it is important to acknowledge that leptin's diverse physiological roles, particularly its interactions with insulin, inflammatory pathways, and sex hormones, can confound the interpretation of its isolated effects on hippocampal structure and function. Therefore, future investigations should focus on disentangling these interconnected signalling cascades to clarify the specific contributions of leptin to neuronal plasticity and cognitive function. This will enable the development of precisely targeted interventions that selectively enhance leptin's neurotrophic effects without exacerbating peripheral resistance or promoting unwanted metabolic side effects.[62]

In parallel with pharmacological strategies, lifestyle-based interventions such as caloric restriction and physical exercise have been shown to effectively modulate leptin sensitivity and improve both metabolic and cognitive health. Caloric restriction enhances leptin signalling by improving leptin receptor responsiveness and reducing systemic inflammation—both of which contribute to central leptin resistance. Physical activity similarly promotes hippocampal neurogenesis and synaptic plasticity, while also enhancing peripheral insulin and leptin sensitivity.[63] These non-pharmacologic approaches, either independently or as adjuncts to leptin sensitizer therapy, warrant further exploration as cost-effective and accessible means of managing leptin resistance and its neurological consequences. Moreover, given the critical periods of brain development during which the hippocampus is particularly sensitive to metabolic insults, early intervention is vital. Adolescence, characterized by rapid synaptic pruning and maturation of glutamatergic systems—particularly N-Methyl-D-aspartate (NMDA) receptor subunits such as NR2B and NR2A—is a window of heightened vulnerability to the detrimental effects of high-fat diets.[64] Alterations to NMDA receptor function in this context can lead to long-term impairments in synaptic plasticity and memory consolidation. Thus, therapeutic strategies aimed at modulating NMDA receptor function or supporting its development should be considered in the broader context of leptin-based interventions. Continued research is also needed to delineate the long-term outcomes of enhancing leptin signalling through pharmacological interventions and to determine the permanence of cognitive recovery once hippocampal leptin function is restored. Importantly, translating preclinical findings to clinical applications will require multidisciplinary collaboration, robust clinical trial design, and the development of biomarkers to monitor leptin responsiveness in the brain.[64] In conclusion, therapeutic strategies aiming to restore leptin sensitivity, particularly in the hippocampus, hold significant promise for treating cognitive dysfunctions associated with obesity and metabolic disorders.[65] The use of leptin sensitizers such as amylin analogues (e.g., pramlintide and cagrilintide) and Celastrol represents an innovative approach to overcome the limitations of leptin therapy in resistant individuals. Clinical trials assessing these agents are expanding our understanding of how metabolic and cognitive processes intersect, opening new avenues for targeted therapies in neurodegenerative conditions. Furthermore, integrating pharmacological approaches with lifestyle modifications may yield synergistic benefits, enhancing the efficacy of interventions aimed at preserving cognitive health.[66] As our understanding of leptin's neuromodulatory roles deepens, efforts must be directed toward refining and personalizing therapeutic strategies that restore leptin-dependent hippocampal function while addressing systemic metabolic dysregulation. Such integrative approaches will be indispensable in tackling the dual challenge of cognitive impairment and obesity, ultimately improving quality of life and long-term health outcomes.

Clinical Implications and Future Outlook of Hippocampal Leptin Resistance

Hippocampal leptin resistance has emerged as a critical pathophysiological mechanism linking obesity and metabolic

dysfunction to cognitive decline. Clinically, the disruption of leptin signalling within the hippocampus is associated with impairments in neurogenesis, synaptic plasticity, and overall hippocampal function—processes that are integral to learning, memory formation, and decision-making. These cognitive domains are frequently compromised in individuals with obesity-related metabolic disorders, in which leptin resistance is a common feature. The inability of the hippocampus to respond effectively to leptin, despite elevated circulating levels, results in deficits in spatial memory, working memory, and executive function.[67]

In addition to impairing cognitive processes, hippocampal leptin resistance contributes to the dysregulation of reward signalling pathways. This reinforces maladaptive behaviors, such as compulsive eating and impaired inhibitory control, creating a feed-forward cycle wherein excessive consumption of highly palatable, energy-dense foods further exacerbates obesity and leptin resistance. These behavioral changes have been likened to addiction-related neuroadaptations, further implicating the hippocampus in the overlapping domains of cognition and emotional regulation in the context of metabolic disease.

These insights underscore a critical and currently unmet clinical need for early and targeted interventions that address hippocampal leptin resistance. Pharmacological strategies that aim to restore or enhance leptin sensitivity within the central nervous system represent one promising avenue. Amylin analogues, including pramlintide and cagrilintide, have demonstrated the capacity to potentiate leptin signalling, resulting in reduced food intake, body weight, and improvements in metabolic outcomes. These agents may also confer neuroprotective benefits indirectly through the resolution of systemic inflammation and the restoration of metabolic balance, thereby alleviating some of the cognitive deficits associated with leptin resistance. Another candidate is Celastrol[68], a plant-derived triterpenoid that has garnered attention for its leptin-sensitizing properties. Preliminary findings suggest that Celastrol enhances central leptin signalling in preclinical models of diet-induced obesity, promoting weight loss and potentially improving cognitive outcomes. Both classes of agents are currently under investigation in clinical trials that also assess parameters of cognitive and neuropsychiatric function, reflecting the growing recognition of the interplay between metabolic and cognitive health. In parallel, lifestyle interventions such as caloric restriction and regular physical exercise have shown efficacy in enhancing central leptin sensitivity. These non-pharmacological strategies are known to improve hippocampal plasticity, reduce neuroinflammation, promote neurogenesis, and normalize leptin receptor function within the brain. When combined with pharmacotherapy,[69] such interventions may produce synergistic effects, paving the way for comprehensive approaches to prevent or mitigate cognitive impairment in individuals at high risk due to obesity or metabolic syndrome. Nevertheless, the pleiotropic nature of leptin's actions within the central nervous system introduces significant complexity. Leptin interacts with a wide array of signalling pathways and physiological systems, including those involving insulin, inflammatory mediators, and sex hormones. Therefore, developing targeted therapeutic strategies that enhance leptin signalling specifically within the brain—without concurrently exacerbating peripheral leptin resistance—represents a significant challenge.

2. CONCLUSIONS

Recent advances in neuroscience and neuroendocrinology have significantly advanced our understanding of hippocampal leptin resistance and its critical role in cognitive dysfunction. Specifically, impaired leptin signalling within the hippocampus has been closely associated with deficits in executive functions, including impaired decision-making, reduced impulse control, and memory disturbances. These cognitive alterations, commonly observed in individuals with obesity, highlight the broader neurobehavioral consequences of metabolic dysregulation. Furthermore, hippocampal leptin resistance has been increasingly implicated in the pathogenesis of neurodegenerative disorders, such as Alzheimer's disease, reinforcing the link between metabolic dysfunction and progressive cognitive decline.

Leptin, traditionally regarded as a metabolic hormone, also exerts significant neuromodulatory effects, particularly within brain regions responsible for learning, memory, and executive control. In states of obesity or chronic high-fat diet exposure, leptin receptors[70] in the hippocampus may become desensitized, leading to an attenuation of the hormone's neuroprotective and neurogenic functions. This diminished responsiveness contributes to reduced synaptic plasticity, impaired neurogenesis, and heightened vulnerability to cognitive deterioration.

Consequently, addressing hippocampal leptin resistance represents a compelling therapeutic target. Emerging interventions aim to restore leptin sensitivity either through pharmacological agents—such as leptin sensitizers like amylin analogues and the phytochemical Celastrol—or through lifestyle-based strategies including caloric restriction and physical activity. These approaches have demonstrated promise not only in enhancing leptin signalling and modulating food intake but also in improving hippocampal function, promoting synaptic remodelling, and reversing memory deficits in preclinical models. Furthermore, clinical trials assessing amylin analogues (e.g., cagrilintide and pramlintide) for obesity and cognitive impairments highlight the therapeutic potential of integrated interventions to support both metabolic and cognitive outcomes.

Nevertheless, the multifaceted nature of leptin's actions within the central nervous system necessitates further investigation. Leptin interacts with other neuroendocrine systems, including insulin signalling and inflammatory pathways, complicating direct assessments of its isolated role in brain function. Deciphering the cellular and molecular mechanisms that underlie leptin's effects on hippocampal circuits will be essential to designing brain-targeted therapies that selectively enhance leptin

activity without worsening peripheral leptin resistance—an important consideration, particularly in obese individuals where leptin levels are already elevated. Given the increasing global burden of obesity and the parallel rise in obesity-associated cognitive impairments, early interventions targeting leptin resistance may represent a preventive strategy to offset long-term neurological consequences.[71] Promoting a deeper understanding of the bidirectional relationship between metabolic health and cognitive function is essential for the development of personalized and effective interventions. In summary, hippocampal leptin resistance constitutes a central link between obesity and cognitive decline. The development of multifaceted therapeutic strategies—potentially combining pharmacological agents, behavioral modifications, and preventive approaches—offers significant promise in enhancing cognitive resilience, mitigating neurodegenerative risk, and addressing the intertwined challenges of metabolic and neurological health. An integrated research and clinical agenda is now paramount to effectively translate these insights into meaningful interventions that improve both brain function and quality of life.

Funding: Self-Funding

Conflict of Interest: The author declares no conflict of interest with any person or organisation

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