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Review

Brain Insulin Signaling Pathway Regulation of Hippocampal Neuroplasticity in Neurocognitive Disorders: Mechanisms and Therapeutic Implications

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Abstract

Neurocognitive disorders represent a significant global health challenge and are characterized by progressive cognitive decline across conditions including Alzheimer's disease, mild cognitive impairment, and diabetes-related cognitive impairment. The hippocampus is essential for learning and memory and requires intact neuroplasticity to maintain cognitive function. Recent evidence has identified the brain insulin signaling pathway as a key regulator of hippocampal neuroplasticity through multiple cellular processes including synaptic plasticity, neurotransmitter regulation, and neuronal survival. Dysregulation of this pathway contributes substantially to the pathophysiology of cognitive dysfunction in various disorders. Mechanistically, insulin modulates hippocampal neuroplasticity primarily through the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) cascades, both of which promote synaptic plasticity and support neurogenesis. Beyond its neuronal effects, insulin signaling also regulates glial and endothelial cell function, orchestrating a coordinated multicellular response that is critical for hippocampal integrity. Emerging therapeutic approaches that target this pathway include intranasal insulin administration, glucagon-like peptide-1 (GLP-1) receptor agonists, and peroxisome proliferator-activated receptor (PPAR) agonists. These have demonstrated promising efficacy in restoring hippocampal function and improving cognitive outcomes in both preclinical and clinical studies. This review synthesizes current knowledge on the relationship between brain insulin signaling and hippocampal neuroplasticity. In addition, we highlight the therapeutic potential of insulin-targeted interventions for neurocognitive disorders, including quantifiable outcomes and sex-specific considerations.

Keywords: cognitive dysfunction; Alzheimer disease; hippocampus; neuronal plasticity; insulin signaling; insulin resistance

1. Introduction

Neurocognitive disorders constitute a major global public health challenge. They affect millions of people worldwide and impose profound social, emotional, and economic burdens [1]. Alzheimer's disease (AD) and mild cognitive impairment (MCI) represent the most prevalent of these conditions, with AD affecting approximately 55 million people globally and with projections indicating this number could triple by 2050. The impact of these disorders extends far beyond the affected individuals, placing substantial strain on families, healthcare systems, and societal resources [2]. The clinical manifestations of neurocognitive disorders are characterized by progressive cognitive deterioration, loss of functional independence, and diminished quality of life. AD patients, for instance, typically present with progressive memory deficits, spatial disorientation, and impaired activities of daily living. This cognitive decline frequently co-occurs with neuropsychiatric symptoms and medical comorbidities, further complicating clinical management. Despite the increasing prevalence of neurocognitive disorders, current therapeutic approaches remain predominantly palliative rather than curative, focusing on symptom management rather than addressing the fundamental pathophysiological mechanisms. This gap in knowledge highlights the urgent need for innovative research aimed at understanding the underlying pathophysiology and identifying novel intervention targets.

The hippocampus is a critical brain structure for learning and memory processes and plays an essential role in cognitive function [3]. Its remarkable capacity for neuroplasticity enables the continuous formation and modification of neural connections in response to experiences and environmental stimuli. Elucidating the mechanisms that govern hippocampal neuroplasticity, particularly in the context of neurocognitive disorders, could facilitate the development of novel therapeutic strategies that enhance cog-

nitive function and improve outcomes for affected individuals [4]. Moreover, investigating the complex regulatory networks of hippocampal function and their relationship with insulin signaling pathways may reveal promising approaches for combating cognitive decline in these debilitating conditions [5].

The brain insulin signaling pathway has emerged as a critical modulator of hippocampal neuroplasticity. Beyond its well-established role in peripheral glucose homeostasis, insulin in the central nervous system influences a diverse array of neuronal processes, including synaptic plasticity, neurotransmitter dynamics, and neuronal survival [6]. Insulin receptors (IRs) are abundantly expressed throughout the hippocampus, where their activation initiates complex signaling cascades that regulate synaptic function and plasticity. Dysregulation of insulin signaling in the brain has been implicated in the pathophysiology of various neurocognitive disorders, suggesting that targeted modulation of this pathway could offer novel therapeutic avenues. Recent evidence indicates that insulin resistance in the brain is strongly correlated with cognitive decline and may contribute significantly to the development and progression of neurodegenerative diseases, particularly AD [7].

This review examines the intricate relationship between brain insulin signaling pathways and hippocampal neuroplasticity in neurocognitive disorders. We analyze the mechanisms through which insulin regulates neuroplasticity, incorporating recent advances in the understanding of synaptic function and neuronal network dynamics. Additionally, we explore the therapeutic potential of modulating insulin signaling in the brain to enhance hippocampal function and improve cognitive outcomes. By synthesizing current knowledge and recent discoveries, the present review provides a comprehensive overview of how targeting insulin signaling pathways in the brain could lead to innovative treatments for neurocognitive disorders. This approach holds promise for the development of novel therapeutic interventions for conditions characterized by impaired hippocampal function and progressive cognitive decline.

2. Brain Insulin Signaling: Origins, Distribution, and Molecular Pathways

2.1 Origin of Brain Insulin

The origin of brain insulin represents a complex and evolving area of neuroscience research. A significant source is peripheral insulin from pancreatic β-cells that is transported across the blood-brain barrier (BBB). However, the exact mechanisms and relative contributions remain under active investigation. This transport process is tightly regulated and maintains brain insulin levels that are related to, but not strictly proportional to, the peripheral insulin concentration. Under normal physiological conditions the cerebrospinal fluid (CSF) to plasma insulin ratio is approximately 1:4, demonstrating the precise regulation of insulin entry into the brain [8].

The relationship between peripheral and central insulin levels provides critical insights into how systemic metabolic disorders affect brain function. Recent research on insulin resistance in cognitive disorders has emphasized this peripheral-central connection. Mounting evidence also supports local insulin synthesis within the central nervous system (CNS), particularly in the hippocampus and hypothalamus regions [9]. This local production likely serves autocrine and paracrine functions, enabling rapid and region-specific insulin signaling. The detection of insulin mRNA and protein in various brain regions further supports the concept of central insulin production [10].

The contribution of locally produced insulin to overall brain insulin signaling continues to be explored, with recent research highlighting its neuroprotective properties, particularly in reducing neuroinflammation and supporting synaptic plasticity [11]. Interestingly, the origin and concentration of brain insulin show developmental variation, with higher proportions derived from local synthesis during fetal and early postnatal periods, and peripheral sources dominating in adulthood. A recent high-impact study found this developmental shift was linked to age-related metabolic and neurodegenerative conditions.

2.2 Insulin Transport Mechanisms Across the Blood-Brain Barrier

Insulin traverses the BBB primarily through a receptor-mediated transcytosis process involving insulin binding to receptors on the luminal surface of brain endothelial cells, followed by internalization, transport, and release into the brain interstitial fluid. This transport mechanism exhibits saturable kinetics and can be modulated by factors such as obesity, inflammation, and metabolic disorders, thus potentially contributing to central insulin resistance. Notable regional variations in insulin transport occur across the BBB, with higher transport rates observed in metabolically active areas like the hypothalamus. This is likely to reflect differences in capillary density, IR expression, or regional metabolic demands [12].

Various physiological and pathological conditions can modify the efficiency of insulin transport into the brain. Chronic hyperinsulinemia, which is characteristic of insulin resistance and type 2 diabetes, can downregulate BBB insulin transport mechanisms, potentially reducing brain insulin signaling and contributing to cognitive deficits. Additionally, BBB dysfunction associated with metabolic disorders can exacerbate central insulin resistance, further compromising cognitive and metabolic regulation [13].

Alternative transport mechanisms such as non-saturable diffusion across the BBB and transport via CSF at the choroid plexus have been proposed, but appear to be less important contributors to overall brain insulin levels. Understanding these complex transport mechanisms is essential for developing targeted therapeutic strategies to enhance central insulin action in neurodegenerative condi-

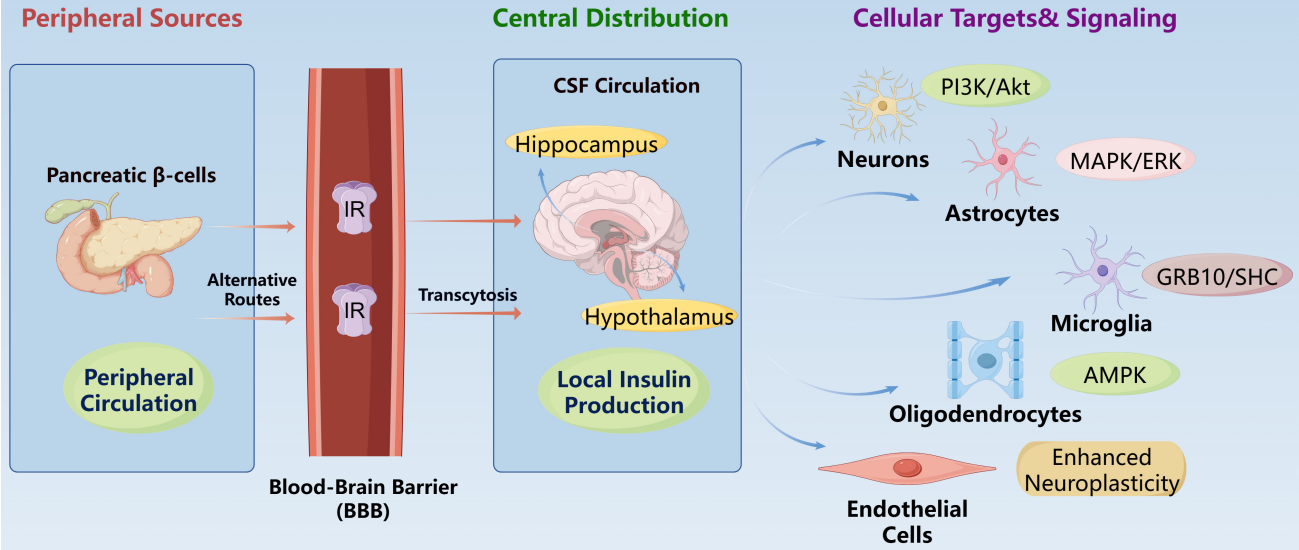

Fig. 1. Insulin signal transmission from the periphery to the central nervous system. This schematic illustrates the journey of insulin from the peripheral circulation to targets in the central nervous system. Peripherally-derived insulin (left) from pancreatic β-cells crosses the blood-brain barrier primarily through receptor-mediated transcytosis. Central insulin production (middle) occurs in select brain regions, including the hippocampus. Both sources contribute to the insulin pool that activates IRs on multiple neural cell types (right), initiating signaling cascades that regulate neuroplasticity, metabolism, and cognitive function. Dysfunction in this transmission pathway contributes to the pathophysiology of neurocognitive disorders. This figure was created using Figdraw (https://www.figdraw.com). Abbreviations: PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; GRB2, growth factor receptor-bound protein 2; SHC, src homology 2 domain-containing transforming protein; IRs, insulin receptors; AMPK, AMP-activated protein kinase.

tions such as AD, Parkinson's disease, and related disorders. These regional transport characteristics, together with the integration of peripheral insulin entry and central local production, form a complete insulin signaling transmission network in the brain, as visually summarized in Fig. 1.

2.3 Distribution of Insulin Receptors in the Brain

IRs are heterogeneously distribution throughout the brain, with particularly high concentrations in the hypothalamus, hippocampus, olfactory bulb, and cerebral cortex [14–16]. These regions govern critical functions including energy homeostasis, memory formation, and cognitive processing. The hypothalamus, especially the arcuate nucleus, has a very high IR density, reflecting the crucial role of insulin in regulating appetite and metabolism. This distribution pattern underscores the diverse functions of insulin within the CNS, beyond just its classical role in glucose homeostasis.

At the cellular level, IRs are expressed on both neurons and glial cells. In neurons, the receptors localize to cell bodies, dendrites, and axon terminals, where they modulate synaptic plasticity and neurotransmitter release [17]. Astrocytes also express IRs, enabling insulin to influence glucose metabolism and provide metabolic support to neurons. Similarly, oligodendrocytes express IRs, suggesting insulin's involvement in myelination processes. The subcellular distribution of IRs spans multiple compartments including the plasma membrane, endosomes, and nucleus. This allows insulin to exert rapid non-genomic effects, as well as longer-term transcriptional regulation [18]. Nuclear IRs in particular may influence gene expression, although their precise functions are still being investigated.

2.4 Key Insulin Signaling Pathways and Their Neuromodulatory Effects

Brain insulin signaling operates through several interconnected molecular cascades, with the predominant pathways being phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) [19]. The Akt pathway regulates multiple cellular processes including glucose metabolism, cell survival, and synaptic plasticity. Upon activation, this pathway phosphorylates downstream targets such as glycogen synthase kinase 3 beta (GSK-3β) and mechanistic target of rapamycin (mTOR). The inhibition of GSK-3β promotes neuroprotection, while mTOR activation enhances protein synthesis that is essential for synaptic function [20]. The MAPK/ERK pathway has complementary and critical roles in synaptic plasticity and memory formation, particularly within the hippocampus, by regulating gene expression and protein synthesis necessary for long-term potentiation and memory consolidation.

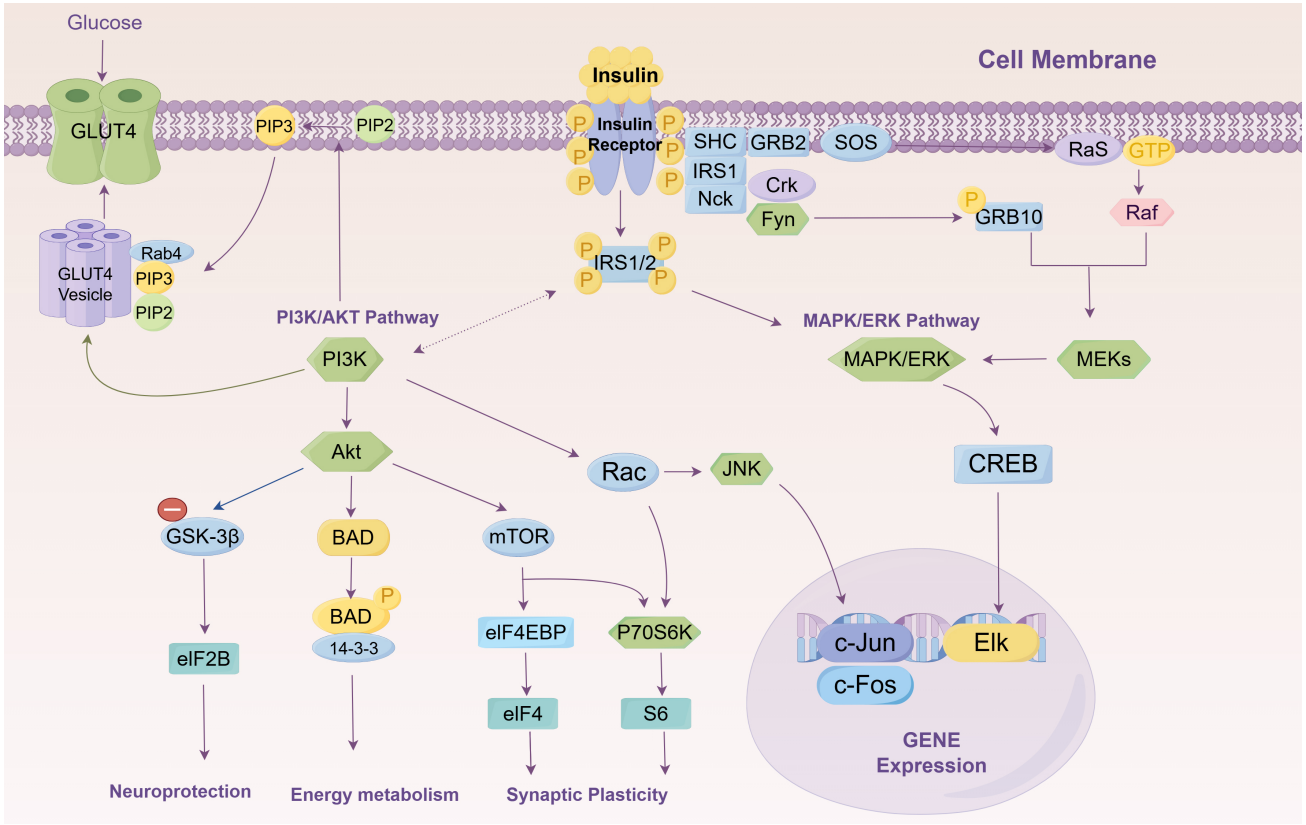

Fig. 2. Brain insulin signaling pathways and their functions in neurons. This schematic shows how insulin activates two major pathways in neurons: PI3K/Akt and MAPK/ERK. The binding of insulin to its receptor triggers phosphorylation cascades. The PI3K/Akt pathway branches into three functions: neuroprotection (via GSK-3β inhibition), regulation of energy metabolism (via BAD phosphorylation), and synaptic plasticity (via mTOR activation). The MAPK/ERK pathway acts through adaptor proteins to activate transcription factors that control gene expression. Insulin also promotes the movement of GLUT4 to the cell membrane for glucose uptake. This network explains the diverse roles of insulin in brain function. This figure was created using Figdraw (https://www.figdraw.com). Abbreviations: GSK-3β, glycogen synthase kinase 3 beta; BAD, Bcl-2-associated death promoter; mTOR, mammalian target of rapamycin; GLUT4, glucose transporter type 4; SOS, son of sevenless; CREB, cAMP response element-binding protein; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; Rab4, ras-related protein rab-4; eIF2B, eukaryotic translation initiation factor 2b; eIF4EBP, eukaryotic translation initiation factor 4e-binding protein; eIF4, eukaryotic translation initiation factor 4; Rac, ras-related c3 botulinum toxin substrate; JNK, c-jun n-terminal kinase; Elk, ets-like transcription factor; c-Jun, jun proto-oncogene; c-Fos, fos proto-oncogene; IRS1/2, insulin receptor substrate 1/2; IRS1, insulin receptor substrate 1; Nck, non-catalytic region of tyrosine kinase adaptor protein; Crk, ct10 regulator of kinase; Fyn, fyn proto-oncogene, src family tyrosine kinase; Ras, rat sarcoma viral oncogene; Raf, raf proto-oncogene serine/threonine-protein kinase.

Beyond metabolism and synaptic plasticity, insulin signaling exerts profound neuroprotective effects and modulates neurotransmitter systems. Activation of the PI3K/Akt pathway leads to phosphorylation and inhibition of GSK-3β, potentially mitigating tau hyperphosphorylation. This is a key pathological feature in neurodegenerative disorders such as AD [21]. Recent research has illuminated the role of insulin in maintaining mitochondrial function through increased expression of proteins involved in the electron transport chain and mitochondrial biogenesis. This action improves energy production and reduces oxidative stress, ultimately protecting neurons from damage [22].

In addition to these canonical pathways, insulin signaling in the brain also operates through other significant cascades. The growth factor receptor-bound protein 10/Src homology 2 domain-containing (GRB10/SHC) pathway is an important regulatory mechanism in neuronal insulin signaling [23]. Following IR activation, SHC adaptor proteins are recruited and phosphorylated, initiating a signaling cascade that is distinct from PI3K/Akt. While the SHC branch primarily activates the Ras-MAPK pathway, GRB10 functions as a negative regulator of insulin signaling through direct interaction with the IR, providing crucial feedback inhibition that prevents excessive pathway activation [24]. This regulatory function is particularly important in the hip-

pocampus, where precise control of insulin signaling is essential for optimal neuroplasticity and cognitive function.

The AMP-activated protein kinase (AMPK) pathway is another critical component of brain insulin signaling with significant implications for neuronal metabolism and neuroprotection. AMPK, a cellular energy sensor activated during metabolic stress, intersects with insulin signaling through multiple mechanisms. Insulin typically suppresses AMPK activity by promoting energy abundance, while AMPK can reciprocally inhibit insulin signaling through serine phosphorylation of IR substrate proteins [25]. In the hippocampus, this crosstalk maintains metabolic homeostasis during fluctuating energy demands associated with synaptic activity and memory formation. Furthermore, AMPK activation enhances mitochondrial biogenesis and autophagy, potentially protecting neurons from metabolic and oxidative stress associated with neurodegenerative conditions [26]. Dysregulation of this pathway has been implicated in insulin resistance and cognitive impairment, suggesting its importance in maintaining neural health and function.

Insulin signaling also influences the release and reuptake of neurotransmitters such as dopamine and serotonin, thereby affecting mood, cognition, and reward-related behaviors [27]. In brain energy metabolism, insulin promotes glucose transporter 4 (GLUT4) translocation to neuronal membranes and regulates glucose transporter 1 (GLUT1) expression in astrocytes, thereby facilitating glucose uptake and utilization. Emerging research has also revealed complex interactions between insulin signaling and neuroinflammatory processes, with significant implications for neurodegenerative and psychiatric disorders [7]. This multifaceted role highlights the importance of insulin signaling in maintaining cognitive function, neuroprotection, and overall brain health. Recent advances in the understanding of these molecular mechanisms have opened promising avenues for therapeutic interventions in various neurological and psychiatric conditions. Insulin signaling in the brain operates through several interconnected molecular cascades, with the predominant pathways being PI3K/Akt and MAPK/ERK (Fig. 2). Collectively, these pathways contribute to enhanced cognitive function and neuroprotection through multiple cellular mechanisms.

2.5 Experimental Evidence of Dysregulated Insulin Signaling in Cognitive Decline

Dysregulation of brain insulin signaling has been extensively studied in various experimental models ranging from cellular systems to animal models and human studies. These investigations have provided compelling evidence for a causal relationship between impaired insulin signaling and cognitive dysfunction. Table 1 (Ref. [28–36]) summarizes the key experimental studies demonstrating this relationship across different research paradigms.

Collectively, these studies have established a strong mechanistic link between dysregulation of insulin signaling and cognitive decline across multiple experimental paradigms. *In vitro* studies have elucidated cellular mechanisms that show how insulin resistance affects synaptic function, protein phosphorylation, and cellular metabolism [28,29,37]. These findings were extended by animal models that established causal relationships between impaired insulin signaling and cognitive deficits, while allowing detailed investigation of the temporal progression of pathophysiological changes [30–32].

Human studies have provided critical translational evidence that the mechanisms identified in preclinical models are relevant to human cognition and disease [33–35]. Postmortem analyses have demonstrated altered insulin signaling components in the brain tissues of patients with AD and other neurocognitive disorders. These alterations correlate with disease severity and neuropathological markers, supporting a pathogenic role for insulin resistance in disease progression. Additionally, neuroimaging studies have revealed associations between insulin signaling, cerebral metabolism, and cognitive function in living patients, providing further evidence for the clinical relevance of these pathways.

This accumulated experimental evidence has established brain insulin resistance as a fundamental pathophysiological mechanism in neurocognitive disorders, thus linking correlative observations to a causal factor with therapeutic implications. The convergence of findings from diverse experimental approaches highlights the robustness of this relationship and provides a strong scientific foundation for the targeting of brain insulin signaling as a therapeutic strategy.

3. Insulin Regulation of Hippocampal Neuroplasticity in Cognitive Function

3.1 Insulin Effects on Neuronal Excitability and Synaptic Plasticity

Insulin signaling orchestrates a complex symphony of molecular mechanisms that govern hippocampal neuroplasticity, a fundamental process that underlies learning and memory formation. At the forefront of these mechanisms is insulin's modulation of glutamatergic neurotransmission through precise regulation of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor function [36]. Upon binding to neuronal IRs, insulin activates the PI3K/Akt signaling cascade, which then phosphorylates specific subunits of these receptors. This phosphorylation enhances receptor conductance and facilitates their insertion into synaptic membranes, ultimately strengthening excitatory transmission and promoting both long-term potentiation (LTP) and long-term depression (LTD). These bidirectional forms of synaptic plasticity are essential for memory formation [38].

Table 1. Experimental studies on dysregulated insulin signaling in cognitive decline.

Study Type	Model/Subjects	Key findings	Reference
		In Vitro studies	
Primary neuronal culture	Rat hippocampal neurons	Insulin resistance induced by palmitate treatment reduced dendritic spine density and AMPA receptor trafficking	[28]
Cell line	SH-SY5Y neuroblastoma cells	Insulin signaling blockade increased tau phosphorylation via GSK-3β activation	[29]
Brain organoids	Human iPSC - derived brain organoids	Insulin resistance impaired synaptic development and accelerated amyloid-β accumulation	[30]
		In Vivo studies	
Animal studies			
Transgenic model	IR knockout mice (neuron-specific)	Progressive cognitive decline with impaired spatial memory and hippocampal LTP deficits	[31]
Diet-induced model	High-fat diet fed rats	Hippocampal insulin resistance preceded cognitive impairment and was associated with reduced BDNF expression	[32]
Pharmacological model	Streptozotocin-ICV injected mice	Impaired hippocampal insulin signaling with accelerated amyloid pathology and memory deficits	[33]
Human studies			
Post-mortem analysis	AD patients vs. controls	Decreased IR expression and IRS - 1/PI3K signaling in hippocampus correlated with Braak stage	[34]
Neuroimaging	MCI patients	Reduced cerebral glucose metabolism correlated with CSF insulin levels and cognitive scores	[35]
Clinical trial	Early AD patients	Intranasal insulin improved delayed memory and preserved cerebral glucose metabolism	[36]

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; SH-SY5Y, human neuroblastoma cell line; iPSC, induced pluripotent stem cell; LTP, long-term potentiation; BDNF, brain-derived neurotrophic factor; ICV, intracerebroventricular; IRS, IR substrate; AD, Alzheimer's disease; MCI, mild cognitive impairment; CSF, cerebrospinal fluid.

Insulin further reinforces the structural foundation of synaptic plasticity through its effects on dendritic spine morphology and cytoskeletal architecture. It promotes the formation, maturation, and stabilization of dendritic spines by regulating actin polymerization dynamics and the expression of key synaptic scaffold proteins, particularly post-synaptic density protein 95 (PSD-95) and synaptophysin [39]. These specialized protrusions serve as primary sites for excitatory synaptic transmission, with their density being directly correlated with cognitive performance. Complementing these structural effects, insulin also modulates the functional properties of voltage-gated ion channels, particularly potassium and calcium channels, thereby fine-tuning membrane excitability and the generation of action potential. The resulting calcium influx triggers downstream signaling cascades that regulate gene expression patterns essential for long-term synaptic modifications and memory consolidation.

The metabolic dimension of insulin action represents another critical facet of its influence on hippocampal function. Neurons are highly energy-dependent cells, with synaptic transmission consuming a substantial portion of their ATP reserves. Insulin enhances neuronal energy metabolism by promoting the translocation of GLUT4 to the cell membrane, thereby facilitating glucose uptake and subsequent ATP production. This metabolic support is especially crucial in the hippocampus, where the high density of synaptic connections necessitates substantial energy reserves to sustain activity-dependent plasticity [38]. Interestingly, the metabolic effects of insulin extend beyond glucose metabolism to include lipid regulation, in particular cholesterol biosynthesis and turnover. Cholesterol is a major component of neuronal membranes and myelin sheaths. It plays a pivotal role in maintaining membrane fluidity, receptor trafficking, and axonal conduction, all of which are essential for optimal hippocampal function [40].

Mitochondrial dynamics form a convergence point where the metabolic and neuroprotective effects of insulin intersect. Insulin enhances mitochondrial biogenesis, respiratory capacity, and antioxidant defense mechanisms through its activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and related transcription factors [41]. This mitochondrial optimization serves dual purposes: meeting the elevated energy demands of synaptic activity, while simultaneously reducing oxidative stress that can impair neuronal function. Recent evidence suggests that impaired insulin-mediated mitochondrial regulation in the hippocampus may represent an early pathogenic mechanism in various neurocognitive disorders, highlighting the therapeutic potential of targeting this pathway [42].

3.2 Insulin-Mediated Modulation of Hippocampal Neurotransmitter Systems

Beyond its direct effects on neuronal excitability and metabolism, insulin exerts profound influences on multiple neurotransmitter systems within the hippocampus, creating an integrated network of communication essential for cognitive processing. Within the glutamatergic system, insulin not only modulates receptor function as previously described, but also regulates the expression and activity of glutamate transporters in both neurons and surrounding glial cells [43]. By enhancing glutamate clearance from the synaptic cleft, insulin prevents excitotoxicity while maintaining the temporal precision of synaptic signaling necessary for information processing. This meticulous control of the extracellular glutamate concentration is a crucial neuroprotective mechanism, particularly in pathological conditions characterized by excessive glutamatergic transmission.

Complementary to its actions on excitatory transmission, insulin also fine-tunes inhibitory neurotransmission through interactions with the GABAergic system. IR activation modulates GABA receptor phosphorylation, surface expression, and channel kinetics, thereby adjusting the strength of inhibitory inputs to hippocampal circuits [44]. Additionally, insulin influences the presynaptic GABA release machinery, thereby affecting the probability and magnitude of inhibitory transmission. This bidirectional regulation of excitatory and inhibitory systems establishes the precise excitation-inhibition balance that is critical for network stability, spike timing-dependent plasticity, and information processing within hippocampal circuits. Disruption of this delicate balance, often observed in conditions of insulin resistance, contributes significantly to cognitive deficits and increased susceptibility to hyperexcitability disorders [45].

The modulatory influence of insulin extends to additional neurotransmitter systems that play essential roles in cognitive function. Within the dopaminergic system, insulin regulates dopamine synthesis, vesicular packaging, release probability, and receptor sensitivity through direct actions on dopaminergic neurons and also indirect effects via striatal-hippocampal circuits. These interactions significantly impact reward-based learning, motivation, and goal-directed behaviors that rely on hippocampal-striatal connectivity [46]. Similarly, insulin modulates serotonergic transmission by influencing tryptophan hydroxylase activity, serotonin re-uptake mechanisms, and receptor expression patterns, thereby affecting mood, anxiety, and cognitive flexibility. These emotional aspects of cognition are intimately linked to hippocampal function [47].

Of particular relevance to hippocampal-dependent memory is insulin's enhancement of cholinergic transmission. By increasing the expression of choline acetyltransferase, facilitating acetylcholine release, and modulating nicotinic and muscarinic receptor sensitivity, insulin amplifies cholinergic signaling that is critical for attention, encoding of new information, and memory consolidation. This cholinergic modulation represents a pivotal mechanism through which insulin influences cognitive performance, with evidence suggesting that disrupted insulin-cholinergic interactions may contribute to the cognitive deficits observed in both AD and diabetes-related cognitive impairment [48].

The remarkable breadth of insulin's neurotransmitter modulation underscores its position as a master regulator of hippocampal function. Through coordinated effects across multiple neurotransmitter systems, insulin orchestrates a harmonious balance of signaling that is essential for cognitive processes ranging from attention and perception to learning and memory consolidation. Recent advances in neuropharmacology have begun to leverage this understanding by developing targeted approaches to enhance insulin signaling within specific neurotransmitter systems. This offers promising new therapeutic avenues for conditions characterized by hippocampal dysfunction and cognitive decline.

4. Insulin Signaling Effects on Non-Neuronal Cells in the Central Nervous System

The brain insulin signaling pathway exerts pleiotropic effects beyond neurons, orchestrating coordinated responses across multiple glial and vascular cell populations. This multicellular regulation creates an integrated functional network that is critical for hippocampal homeostasis and cognitive processing. The following subsections describe cell-specific insulin actions and their pathophysiological implications in neurocognitive disorders.

4.1 Astrocytic Insulin Signaling: Metabolic Coupling and Neurotrophic Support

Astrocytes express abundant IRs that, upon binding to insulin, initiate the phosphorylation of IR substrate (IRS) and subsequent activation of the PI3K/Akt pathway. This signaling cascade culminates in GLUT1 translocation to the plasmalemma, thereby increasing the glucose uptake capacity [49,50]. Insulin-mediated enhancement of astrocytic glucose metabolism is a fundamental component of the astrocyte-neuron lactate shuttle, whereby astrocytes metabolize glucose via aerobic glycolysis to generate lactate. This is subsequently transported to neurons via monocarboxylate transporters (MCTs) as an energetic substrate during periods of synaptic activity.

Insulin signaling in astrocytes modulates glutamatergic neurotransmission through transcriptional upregulation of excitatory amino acid transporters, primarily glutamate transporter-1 (GLT-1/EAAT2) and glutamate-aspartate transporter (GLAST/EAAT1) [51]. The enhanced glutamate clearance capacity maintains extracellular glutamate at physiological concentrations, thereby preventing excitotoxicity while preserving synaptic efficacy. Con-

comitantly, insulin promotes the secretion of neurotrophic factors by astrocytes, including brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1), while attenuating nuclear factor kappa B (NF-κB)-mediated production of proinflammatory cytokines [52].

In pathological states characterized by central insulin resistance, astrocytic dysfunction manifests as impaired metabolic coupling, reduced glutamate uptake capacity, and aberrant inflammatory activation. These alterations contribute to excitotoxicity, bioenergetic compromise, and synaptic dysfunction observed in the various neurodegenerative and metabolic disorders affecting cognition.

4.2 Insulin Regulation of Microglial Polarization and Neuroinflammatory Responses

Microglia are the resident macrophages of the central nervous system and express both IRs and insulin-like growth factor 1 receptors (IGF-1R), making them critical mediators of neuroinflammatory homeostasis [53]. Under physiological conditions, microglial IR activation promotes anti-inflammatory phenotypic polarization (historically termed "M2-like") characterized by enhanced phagocytic capacity and secretion of anti-inflammatory cytokines, particularly interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). This immunomodulatory effect creates a neuroprotective microenvironment that is conducive to synaptic plasticity and neuronal viability.

Insulin enhances microglial bioenergetics via GLUT4 translocation, facilitating glucose uptake necessary for sustaining the highly energy-dependent surveillance functions of these cells. Conversely, in insulin-resistant states, microglia frequently demonstrate proinflammatory activation patterns with increased secretion of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and reactive oxygen species (ROS), thus contributing to neuroinflammatory cascades implicated in neurodegenerative pathogenesis [54,55].

Recent investigations have elucidated the modulatory effects of insulin on microglial autophagy through mechanistic target of rapamycin (mTOR) signaling to enhance phagocytic clearance of protein aggregates and cellular debris [56]. These autophagy-enhancing properties may be particularly relevant for proteinopathies characterized by the accumulation of misfolded proteins, including AD and related neurodegenerative disorders.

4.3 Insulin Influence on Oligodendrocyte Maturation and Myelin Maintenance

Oligodendrocytes and their precursor cells (OPCs) express IRs throughout the progression of their developmental lineage. Insulin promotes OPC proliferation and survival via the concurrent activation of PI3K/Akt and MAPK/ERK cascades, establishing an adequate progenitor pool for subsequent differentiation. During oligodendrocyte maturation, insulin enhances differentiation and myelinogenesis through transcriptional upregulation of myelin structural proteins, including myelin basic protein (MBP), proteolipid protein (PLP), and myelin-associated glycoprotein (MAG) [57].

Insulin optimizes oligodendrocyte bioenergetics by enhancing glucose uptake via increased GLUT1 and GLUT3 expression, providing the substantial energy required for lipid synthesis and myelin elaboration [58]. Additionally, insulin confers oligodendrocytes with protection against oxidative stress through upregulation of antioxidant defense systems and the promotion of peroxisome PGC-1α-mediated mitochondrial biogenesis [59].

Insulin signaling also facilitates oligodendrocyte-mediated axonal trophic support through increased expression of monocarboxylate transporters (MCTs) and neurotrophic factors. This metabolic and trophic coupling between oligodendrocytes and axons is essential for maintaining axonal integrity and impulse propagation, particularly during periods of high neuronal activity or metabolic challenge.

4.4 Insulin Signaling in Endothelial Cells: Blood-Brain Barrier Integrity and Function

Cerebrovascular endothelial cells that form the BBB express abundant IRs and show dynamic responsiveness to systemic and central insulin. Endothelial IR activation enhances BBB integrity through PI3K/Akt-mediated upregulation of tight junction proteins, particularly claudin-5, occludin, and zonula occludens-1 (ZO-1) [60,61]. This molecular reinforcement of paracellular barriers maintains selective permeability essential for neural homeostasis. Concurrently, insulin modulates transendothelial transport systems, including facilitative enhancement of GLUT1-mediated glucose transport and receptor-mediated transcytosis of essential nutrients.

Insulin influences cerebrovascular hemodynamics through activation of endothelial nitric oxide synthase (eNOS) via the PI3K/Akt pathway. This increases nitric oxide (NO) production, which enhances vasodilation and regional cerebral blood flow. The above mechanism is integral to neurovascular coupling, which is the precise matching of local perfusion to neuronal metabolic demands [62]. Disruption of insulin-mediated neurovascular regulation may contribute to the cerebrovascular dysfunction and cognitive deficits observed in insulin-resistant conditions. These findings demonstrate how insulin coordinates multicellular responses in the hippocampus, with different cell types exhibiting unique but complementary responses to insulin signaling (Fig. 3).

4.5 Intercellular Coordination of Insulin Signaling: Neuron-Glia Metabolic Coupling

The functional integrity of the brain relies not only on cell-specific insulin responses, but also on sophisticated intercellular coordination across the neurovascular unit to

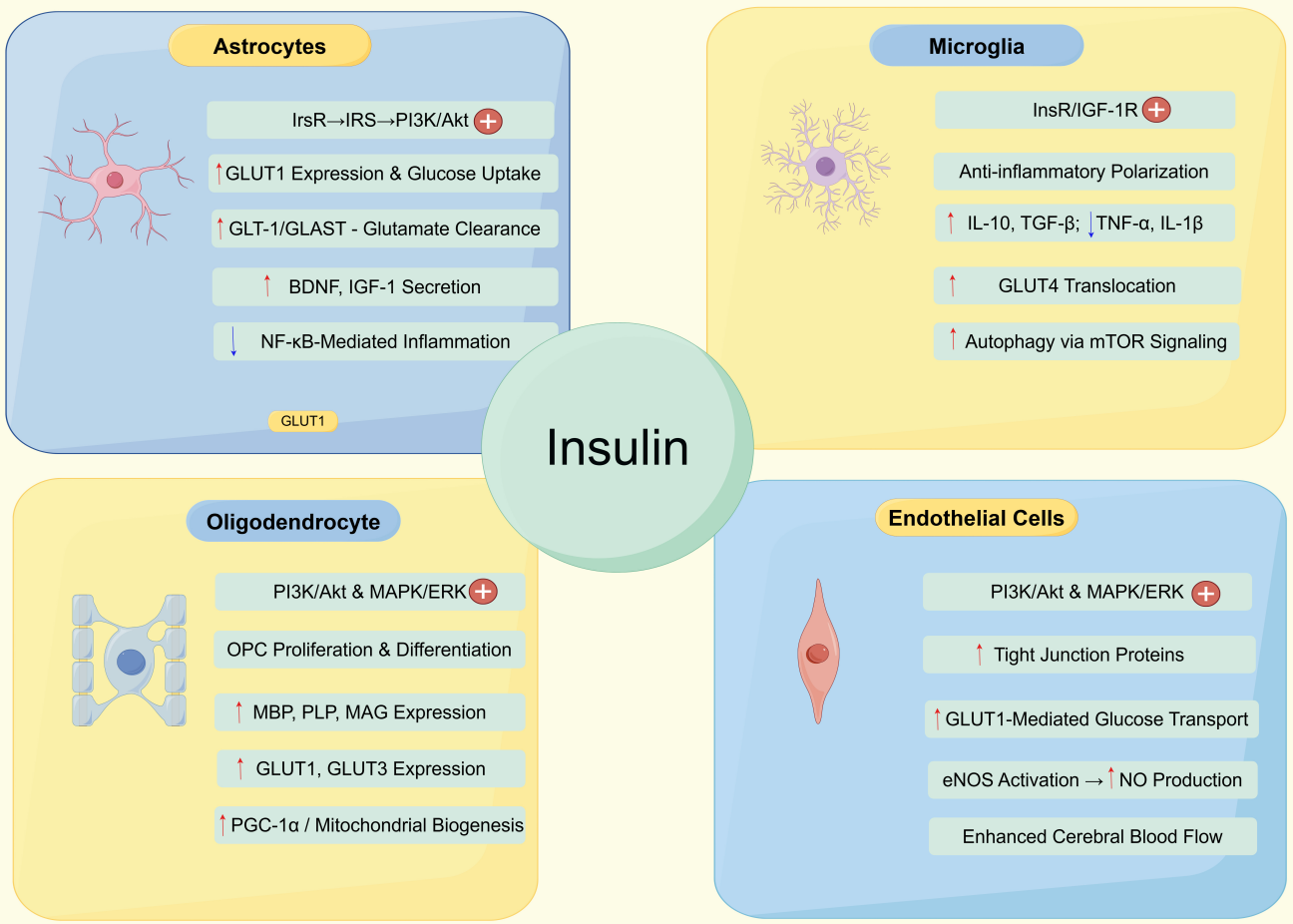

Fig. 3. Insulin effects on different neural cell types in the hippocampus. This figure illustrates the cell-specific actions of insulin on astrocytes, microglia, oligodendrocytes, and endothelial cells. Each quadrant shows characteristic cell responses, including signaling pathway activation, metabolic effects, and functional changes that collectively support hippocampal function and cognitive performance through coordinated multicellular regulation. Red arrows represent positive regulation/activation: indicating that insulin enhances, promotes, or upregulates these cellular processes; blue arrows represent negative regulation/inhibition: indicating that insulin suppresses, reduces, or downregulates these processes (particularly inflammatory responses). This figure was created using Figdraw (https://www.figdraw.com). GLUT1, glucose transporter 1; GLT-1, glutamate transporter 1; GLAST, glutamate aspartate transporter; OPC, oligodendrocyte precursor cell; MBP, myelin basic protein; PLP, proteolipid protein; MAG, myelin-associated glycoprotein; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; NO, nitric oxide; eNOS, endothelial nitric oxide synthase.

create synergistic effects that exceed the sum of individual cellular actions. Insulin orchestrates this multicellular symphony through several parallel and complementary mechanisms. First, it simultaneously enhances astrocytic glucose uptake via GLUT1 while increasing neuronal MCT2 expression to optimize the astrocyte-neuron lactate shuttle [63]. Second, it coordinates glutamatergic transmission by upregulating both neuronal NMDA receptor function and astrocytic glutamate transporters [64]. Third, it promotes oligodendroglial production of BDNF and metabolic substrates that enhance neuronal insulin sensitivity, while stimulating neuronal production of neuregulins that support myelination [65]. Fourth, it directs microglia toward anti-inflammatory phenotypes that secrete factors which enhance neuronal plasticity, while modulating neuronal release of fractalkine that regulates microglial insulin sensitivity [66]. Finally, it synchronizes endothelial glucose transport with neuronal and astrocytic production of vasoactive substances to ensure precise neurovascular coupling. In insulin-resistant states, this coordination deteriorates across multiple cell types, disrupting not only individual cellular functions but also their synchronized temporal response pattern, thus contributing significantly to cognitive dysfunction. These intercellular dynamics suggest that effective therapeutic strategies must target multiple components of the neurovascular unit simultaneously rather than focusing on isolated cellular effects. This could potentially explain why combinatorial approaches to insulin resistance demonstrate superior efficacy in improving cognitive outcomes compared to single-target interventions.

Table 2. Therapeutic approaches targeting brain insulin signaling pathways.

Therapeutic Approach	Mechanism of Action	Clinical Evidence and Applications	References
Intranasal Insulin Administration	(1) Bypasses the blood-brain barrier (2) Enhances PI3K/Akt signaling (3) Reduces neuroinflammation	(1) Cognitive improvements in AD and MCI (2) Increased cerebral glucose metabolism (3) Improved insulin sensitivity in T2D	[67–75]
GLP-1 Receptor Agonists	(1) Binds to CNS GLP-1 receptors (2) Promotes neuronal survival (3) Reduces β-amyloid and tau phosphorylation	(1) Enhanced learning and memory in T2D (2) Improved hippocampal function (3) Preserved synaptic density in preclinical models	[76–78]
PPAR Agonists	(1) Modulates glucose/lipid metabolism genes (2) Upregulates insulin sensitivity (3) Inhibits NF-κB signaling	(1) Improved executive function in metabolic disorders (2) Enhanced mitochondrial function (3) Preserved long-term potentiation	[79–82]
Metformin	(1) Activates AMPK pathway (2) Enhances GLUT4 translocation (3) Suppresses neuroinflammation	(1) Reduced dementia risk in long-term diabetic users (2) Improved executive function in MCI (3) Enhanced functional connectivity in cognitive networks	[83,84]
Cholinesterase Inhibitors	(1) Restores IR expression (2) Enhances IRS - 1 phosphorylation (3) Reduces neuroinflammation-induced insulin resistance	(1) Improved cognitive performance beyond cholinergic effects (2) Modest improvements in glycemic control in AD patients (3) Synergistic effects with insulin- sensitizing agents	[85]
Memantine	(1) Prevents excitotoxicity-induced insulin resistance (2) Maintains IR expression (3) Enhances insulin-stimulated Akt phosphorylation	(1) Preserved insulin signaling in Aβ- exposed neurons (2) Reduced oxidative stress impacting insulin pathway (3) Potential benefits in patients with comorbid metabolic disorders	[86,87]

CNS, central nervous system; T2D, Type 2 Diabetes; PPAR, peroxisome proliferator-activated receptor; GLUT4, glucose transporter 4.

5. Therapeutic Approaches Targeting Brain Insulin Signaling Pathways

The critical role of brain insulin signaling in cognitive function has catalyzed the development of novel therapeutic strategies for neurocognitive disorders that target this pathway. These approaches aim to enhance central insulin action, improve neuroplasticity, and mitigate cognitive decline in conditions ranging from AD to diabetes-related cognitive impairment (Table 2, Ref. [67–87]).

5.1 Intranasal Insulin Administration: Mechanisms and Clinical Applications

Intranasal delivery of insulin is a promising therapeutic strategy for enhancing insulin signaling in the brain while minimizing systemic effects. This approach leverages the anatomical connection between the nasal cavity and the central nervous system, allowing insulin to bypass the BBB and directly access brain regions that are critical for cognitive function [67].

A significant consideration in intranasal insulin therapy is its non-uniform brain distribution, with preferential targeting to regions with high IR density: the olfactory bulb, hypothalamus, hippocampus, and prefrontal cortex [68]. This regional selectivity explains the specificity of cognitive improvements, which are observed primarily in hippocampal-dependent memory and prefrontal-mediated executive functions. The CSF glucose concentration serves as both a mediator of insulin's cognitive effects and a potential biomarker in neurocognitive disorders. In AD and related conditions, the normal CSF-to-plasma glucose ratio becomes dysregulated, correlating with cognitive decline. Intranasal insulin influences this relationship by enhancing glucose transport across the blood-CSF barrier and modulating astrocyte glucose metabolism [69]. Importantly, therapeutic responses correlate with the normalization of CSF glucose dynamics, suggesting that CSF glucose may predict treatment efficacy and represent a therapeutic target itself.

Clinical studies with AD patients have demonstrated modest improvements in cognitive function following intranasal insulin treatment, with reduced phosphorylated tau protein levels suggesting potential disease-modifying effects. In patients with MCI, intranasal insulin has resulted in significant improvements in memory and attention, correlating with increased cerebral glucose metabolism as visualized by positron emission tomography (PET) imaging [70,71]. These findings support the hypothesis that intranasal insulin may delay the progression of MCI to more severe neurodegenerative states.

In type 2 diabetes patients with cognitive impairment, intranasal insulin has demonstrated dual benefits: enhanced cognitive performance and improved peripheral insulin sensitivity. Preclinical research has identified multiple neuroprotective mechanisms, including enhanced PI3K/Akt signaling, increased expression of synaptic proteins, and mitigation of ferroptosis and neuroinflammation [72].

Sun *et al.* [73] reported that intranasal delivery of insulin-like peptides showed efficacy in animal models of ischemic stroke, suggesting broader applications for neurovascular disorders. Despite these promising findings, challenges remain in optimizing intranasal delivery systems for insulin. Factors such as dosing regimen, formulation stability, and individual variability in nasal absorption must be addressed to maximize efficacy and minimize risks [74]. Ongoing advances in intranasal drug delivery technologies, including the use of nanocarriers and bio-adhesive formulations, hold promise for overcoming these hurdles [75]. Further large-scale clinical trials are needed to establish the long-term safety and efficacy of intranasal insulin as a therapeutic intervention for CNS disorders.

5.2 GLP-1 Receptor Agonists: Indirect Enhancers of Central Insulin Signaling

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), initially developed for the management of type 2 diabetes, have been shown to enhance central insulin signaling pathways by binding to GLP-1 receptors expressed throughout the CNS [76]. Their neuroprotective mechanisms extend beyond enhancing insulin sensitivity and include the promotion of neuronal survival, stimulation of neural progenitor cell proliferation, and reduction of β-amyloid accumulation and tau phosphorylation.

Clinical evidence obtained in type 2 diabetes patients shows improvements in learning, memory, and executive function beyond what would be expected from glycemic control alone [77]. Imaging studies have demonstrated enhanced hippocampal function and connectivity following GLP-1RA treatment. Moreover, preclinical studies have consistently shown increased neuronal survival, reduced oxidative stress, decreased β-amyloid deposition, and preserved synaptic density in neurodegenerative disease models [78].

Current research priorities include determining the optimal dosing regimens for neuroprotection, assessing long-term safety in non-diabetic populations, and enhancing BBB penetration to maximize central effects.

5.3 PPAR Agonists: Targeting Insulin Resistance and Neuroinflammation

Peroxisome proliferator-activated receptor (PPAR) agonists address brain insulin resistance and cognitive dysfunction by modulating genes involved in glucose and lipid metabolism, insulin sensitivity, and inflammatory responses. These compounds upregulate insulin sensitivity-related genes and glucose transporters, while reducing inflammatory mediators through inhibition of NF-κB signaling [79,80].

Clinical studies in populations with metabolic disorder show improved cognitive performance following treat-

ment with PPAR-γ agonists, particularly in terms of executive function, attention, and working memory. These improvements correlate with enhanced peripheral insulin sensitivity. Evidence from preclinical studies has shown that PPAR agonists protect hippocampal neurons, reduce oxidative damage, enhance mitochondrial function, and preserve long-term potentiation in models of neurodegeneration [81].

Limitations of PPAR agonists include the potential for systemic side effects, and the relatively low specificity for CNS targets. The development of brain-penetrant PPAR modulators with enhanced selectivity represents an active area of research [82].

Future directions for these therapeutic approaches include developing combination strategies that leverage complementary mechanisms, identifying predictive biomarkers of treatment response, and establishing personalized dosing protocols based on individual metabolic and cognitive profiles.

5.4 Metformin: Modulation of Brain Insulin Signaling via AMPK Activation

Metformin, the first-line treatment for type 2 diabetes, exerts significant effects on brain insulin signaling by crossing the BBB and activating AMP-activated protein kinase (AMPK). This activation enhances neuronal insulin sensitivity through multiple mechanisms, including the promotion of insulin-independent GLUT4 translocation to facilitate glucose uptake in hippocampal neurons, inhibiting NF-κB signaling to suppress neuroinflammation in glial cells, and increasing mitochondrial biogenesis to improve bioenergetic function in neural cells. These complementary actions create a coordinated response across the neurovascular unit that addresses both the metabolic and inflammatory components of brain insulin resistance.

Clinical evidence suggests that metformin offers cognitive benefits in specific populations. Long-term use in diabetic patients correlates with a reduced incidence of dementia compared to other anti-diabetic medications, while trials in non-diabetic patients with MCI have shown improvements in executive function and attention, accompanied by enhanced functional connectivity in cognitive networks [83]. However, the response heterogeneity across studies indicates the cognitive benefits of metformin may be influenced by factors such as disease stage, metabolic status, and genetic background, thus necessitating personalized therapeutic approaches.

Metformin shows particular promise in combination therapeutic strategies. Preclinical models have demonstrated synergistic effects when metformin is combined with intranasal insulin or GLP-1 receptor agonists, achieving superior neuroprotective outcomes compared to monotherapy [84]. This synergism likely results from targeting complementary aspects of the insulin signaling network, with metformin primarily enhancing insulin sensitivity through AMPK activation, while other agents directly stimulate IR signaling. Future research should be aimed at optimizing these combination approaches, establishing appropriate dosing regimens for CNS effects, and identifying reliable biomarkers to predict treatment response in neurocognitive disorders associated with brain insulin resistance.

5.5 Conventional Alzheimer's Disease Therapeutics: Intersections with Insulin Signaling

The conventional therapies for AD, cholinesterase inhibitors (ChEIs) and memantine, exhibit significant interactions with brain insulin signaling that are likely to contribute to their therapeutic efficacy. The ChEIs donepezil, rivastigmine, and galantamine not only enhance cholinergic transmission, but also improve insulin signaling through distinct mechanisms. Donepezil restores hippocampal IR expression and enhances IRS-1 phosphorylation, rivastigmine attenuates neuroinflammation-induced insulin resistance, and galantamine activates α7 nicotinic receptors, thereby reducing the inhibitory serine phosphorylation of IRS-1 and promoting GLUT4 translocation [85]. These insulin-sensitizing effects occur in parallel to improvements in cognitive performance and synaptic plasticity, suggesting that cholinergic and insulin pathways engage in significant cross-talk.

Memantine, an NMDA receptor antagonist, also influences insulin signaling through multiple mechanisms. By blocking excessive calcium influx, memantine prevents excitotoxicity-induced serine phosphorylation of insulin signaling components that would otherwise promote insulin resistance [86]. In addition, it preserves IR expression in hippocampal neurons exposed to amyloid-β, reduces oxidative stress that impairs insulin signaling, and enhances insulin-stimulated Akt phosphorylation by inhibiting stress kinases [87]. These actions create a more favorable cellular environment for insulin signaling, potentially explaining the neuroprotective effects of memantine beyond the simple regulation of glutamate.

While the clinical evidence is still limited, the findings to date support these mechanistic findings. AD patients treated with ChEIs show modest improvements in glycemic control independently of other factors, while preliminary studies indicate that combination therapies with ChEIs and insulin-sensitizing agents provide synergistic cognitive benefits [88,89]. These observations highlight the complex interplay between neurotransmitter systems and metabolic signaling in the pathophysiology of AD, suggesting that conventional therapeutics can partially address metabolic dysfunction. Future strategies should leverage these interactions through dual-action compounds or optimized combination therapies, while recognizing that patient-specific variations in insulin sensitivity may influence treatment responses that could potentially explain the heterogeneity in clinical outcomes with these agents.

6. Conclusion

In summary, this review highlights brain insulin signaling as a crucial regulator of hippocampal neuroplasticity, with effects on neuronal function, neurotransmitter systems, and multicellular networks. Dysregulation of this signaling pathway is a significant contributor to neurocognitive disorders, thus offering a promising therapeutic target. Current approaches, including intranasal insulin, GLP-1 receptor agonists, PPAR agonists, and metformin have shown encouraging results in both preclinical and clinical studies, particularly at the metabolism-cognition intersection. Future investigations should aim to optimize treatment protocols, identify response biomarkers, and develop selective agents for specific cell populations. Continued research into this intricate relationship will advance our ability to more effectively combat the growing burden of neurocognitive disorders.

Author Contributions

YM and WM designed the review. YH and MS (co-first authors) conducted literature search, data collection, and wrote the manuscript. MQ and YXL contributed to data collection and reference organization. HY assisted with figure designing and preparation. RW, YFL, and PL contributed to designing and drawing the figures and tables and manuscript revision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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