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Review

The therapeutic effects and mechanisms of glucagon-like peptide-1 receptor agonists in neurocognitive disorders

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***Abstract*:** Chronic cerebral hypoperfusion (CCH) represents a key pathogenic contributor to neurocognitive disorders. It can lead to multifaceted pathological alterations including neuroinflammation, neuronal apoptosis, blood–brain barrier disruption, synaptic plasticity deficits, and mitochondrial dysfunction. The glucagon-like peptide-1 receptor (GLP-1R), ubiquitously expressed across multiple organ systems, exerts neuroprotective effects by maintaining intracellular homeostasis and mitigating neuronal damage triggered by oxidative stress, inflammatory cascades, apoptotic signaling, and ischemic insults. Furthermore, GLP-1R activity is modulated by gut microbiota composition and short-chain fatty acid abundance, implicating the gut–brain axis in its regulatory influence on neurological function. This review systematically examines the pathophysiological mechanisms underlying CCH and highlights the therapeutic potential of GLP-1R activation. Specifically, GLP-1R-targeted interventions attenuate hypoperfusion-induced damage through pleiotropic pathways and gut–brain crosstalk, thereby offering novel perspectives for advancing both fundamental research and clinical management of neurocognitive disorders.

Keywords: chronic cerebral hypoperfusion, glucagon-like peptide-1 (GLP-1), neurocognitive disorders, neuroinflammation, neuroprotective

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Introduction

Neurocognitive disorders comprise a spectrum of neurodegenerative conditions, including vascular dementia (VaD), Alzheimer's disease (AD), and Parkinson's disease (PD). Mounting evidence implicates chronic cerebral hypoperfusion (CCH) as a critical contributor to the pathophysiological mechanisms underlying these disorders.[1,2] CCH is widely acknowledged as a pivotal pathophysiological hallmark of VaD. Extensive research has demonstrated that CCH significantly contributes to the accumulation of β-amyloid protein (Aβ) and the elevation of phosphorylated tau protein levels. These pathological alterations are strongly correlated with the initiation and progression of AD.[3,4] In clinical investigations, magnetic resonance imaging studies of PD patients have consistently identified the presence of white matter hyperintensities and orthostatic hypotension. These findings indicates that recurrent hypotensive episodes may initiate cerebral hypoperfusion. Consequently, such hypoperfusion can lead to hypoxic injury in vulnerable brain regions, ultimately manifesting as cognitive dysfunction. Complementing clinical observations, preclinical studies using animal models have provided further validation of the adverse effects of cerebral hypoperfusion. Notably, experimental research has demonstrated that cerebral hypoperfusion exacerbates cognitive deficits in murine models of PD.[5]

CCH is strongly implicated in the pathogenesis of diverse neurocognitive impairments and has been causally linked to both the development and progression of neurodegenerative diseases.[6–8] Prolonged cerebral hypoperfusion drives characteristic pathological changes, including demyelination and axonal degeneration, which are hallmark features of white matter injury. These

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structural alterations contribute directly to cognitive deterioration and are associated with elevated risks of stroke, dementia, and functional disability.[6,9,10] Cumulatively, CCH precipitates a progressive decline in patients' quality of life, imposing substantial burdens on individual and public health systems.

CCH triggers a cascade of neuropathological events, including neuroinflammation,[11] metabolic dysregulation,[12] neuronal apoptosis,[6] oxidative stress,[7] blood–brain barrier (BBB) disruption,[13] synaptic plasticity impairment,[14] and mitochondrial dysfunction,[15] all of which are mechanistically implicated in the development and progression of CCH-associated neurocognitive disorders.[16] A critical mechanism involves CCH-induced microglial activation, in which activated microglia release pro-inflammatory mediators such as complement protein C1q, tumor necrosis factor-alpha (TNF-α), and interleukin-1 alpha (IL-1α). These cytokines propagate neuroinflammatory cascades within cerebral white matter, exacerbating structural damage and neuronal degeneration,[13] ultimately leading to learning and memory dysfunction.[17] Additionally, pro-inflammatory factors can shift astrocytes from their supportive and neuroprotective phenotype to an inflammatory phenotype that promotes neurodegeneration.[18] As mitochondrial function regulates cellular energy homeostasis and cell death signaling, it is critical for maintaining cellular health. CCH reduces mitochondrial ATP production; the subsequent loss of mitochondrial membrane potential and increased mitochondrial permeability elevate intracellular Ca^{2+} concentration, thereby activating intrinsic apoptotic pathways. Ca^{2+} influx-induced neuronal damage exacerbates reactive oxygen species (ROS) production, which triggers apoptosis via lipid peroxidation.[19] These processes collectively enhance apoptotic activity and aggravate neural functional impairment.

Glucagon-like peptide-1 (GLP-1), an intestinal hormone secreted by enteroendocrine L cells, functions by enhancing glucose-dependent insulin secretion from pancreatic β-cells.[20] This peptide regulates blood glucose through three synergistic mechanisms: stimulating insulin secretion, delaying gastric emptying, and suppressing appetite, thus demonstrating therapeutic potential for glycemic control and weight management.[21,22] The physiological actions of GLP-1 are mediated via binding to the glucagon-like peptide-1 receptor (GLP-1R). Newly emerged evidence suggests that GLP-1R activation not only regulates glucose homeostasis but also exerts multiple effects to directly alleviate the progression of atherosclerosis, providing a reduction in cardiovascular risk.[23] Furthermore, GLP-1R agonists (GLP-1RA) exhibit protective roles in cerebrovascular contexts by mitigating cerebrovascular disease incidence and alleviating neurocognitive deficits associated with ischemic cerebrovascular events. Substantial preclinical studies highlight the involvement of GLP-1 signaling in modulating central nervous system (CNS) functions, particularly through neurotrophic support and neuroprotective mechanisms that ameliorate cognitive impairments.[22,24,25] Animal models of cerebral hypoperfusion further reveal that both GLP-1 and its analogs confer ischemic neuroprotection through GLP-1R activation-mediated suppression of oxidative stress and neuroinflammation, alongside reductions in neuronal apoptosis and infarct volume.[26] This review synthesizes current knowledge on the GLP-1/GLP-1R axis in CCH-induced neurocognitive disorders, thereby providing perspectives for translational research and clinical applications.

GLP-1 analogs and their receptor (GLP-1R)

The GLP-1R, a prototypical G protein-coupled receptor (GPCR) of the glucagon receptor family, exhibits broad tissue distribution including the pancreas, gastrointestinal tract, heart, lungs, kidneys, lymphatic system, and CNS.[27,28] Activation of GLP-1R by its ligand mediates intracellular homeostasis maintenance and confers neuroprotection against oxidative stress, neuroinflammation, apoptosis, and ischemic injury.[26] However, endogenous GLP-1 undergoes rapid enzymatic degradation in circulation (half-life: 2–3 min), substantially limiting its therapeutic potential. This pharmacokinetic limitation has driven the development of engineered GLP-1RAs with enhanced metabolic stability.

GLP-1 and its analogs exhibit class-wide pharmacological effects and demonstrate therapeutic benefits in preclinical models of neurodegenerative diseases. These effects encompass memory enhancement, synaptic integrity preservation, neurogenesis promotion, apoptosis suppression, neuronal oxidative stress mitigation, atherosclerotic plaque reduction, and chronic neuroinflammation

Table 1. Common types of GLP-1R used in the research of degenerative diseases and their pharmacokinetics.

GLP-1RA	Half-life	Frequency	Administration	Cognitive dysfunction diseases
Exenatide	2.4 h	Twice daily	Subcutaneous injection	AD, PD, VaD
Liraglutide	10–14 h	Once daily	Subcutaneous injection	AD, PD, VaD
Lixisenatide	2–4 h	Once daily	Subcutaneous injection	Early PD
Semaglutide	5.7–6.7 d	Once weekly	Subcutaneous injection/ oral administration	AD, PD, VaD
NLY01	12.5 d	–	Subcutaneous injection	AD, PD

AD, Alzheimer's disease; GLP-1R, glucagon-like peptide-1 receptor; PD, Parkinson's disease; VaD, vascular dementia.

attenuation.[29] A meta-analysis evaluating GLP-1RAs in diabetic populations confirmed their consistent efficacy for primary and secondary prevention of cerebro-cardiovascular events, including high-risk individuals with prior myocardial infarction or stroke history.[30] Complementing these findings, another meta-analysis revealed substantial neuroprotective effects of GLP-1R activation in nondiabetic ischemic stroke patients.[31] Current research on GLP-1RAs in neurological disorders encompasses five agents (Table 1). Lixisenatide shows clinical promise for early-stage PD management,[32] while NLY01, a BBB-penetrant novel agonist, ameliorates neurodegeneration and symptoms in murine models of PD and AD.[27] The remaining three agonists have been systematically investigated in AD, PD, and VaD studies. Emerging evidence suggests additional neuroprotective mechanisms beyond direct receptor agonism; Semaglutide, for instance, modulates gut microbiota (GM) composition to alleviate neuroinflammation and cognitive deficits.[33] Collectively, these findings position the GLP-1/GLP-1R axis as a mechanistic regulator of ischemic neuropathology and a novel therapeutic target for cerebral hypoperfusion-induced neurocognitive disorders.

GLP-1/GLP-1R axis signaling pathways

GLP-1 and its mimetics bind to GLP-1R, inducing conformational changes in this GPCR. Following α subunit activation, adenylate cyclase is stimulated to elevate intracellular cyclic adenosine monophosphate (cAMP) levels, thereby initiating phosphorylation cascades through three principal signaling branches: (1) the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK; Ras-Raf-MEK-ERK) pathway; (2) the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) axis; and (3) the cAMP/protein kinase A/cAMP response element-binding protein (cAMP/PKA/CREB) cascade.[34–36] Specifically, the MAPK/ERK pathway mediates cellular proliferation, differentiation, migratory dynamics, senescence, and apoptotic regulation.[37] Experimental evidence indicates that GLP-1R activation exerts neuroprotective effects on dopaminergic and primary cortical neurons in PD models, with mechanistic reliance on both MAPK and PI3K signaling.[38] These pathways converge on mechanistic target of rapamycin (mTOR) activation, critically regulating autophagic flux and inflammatory responses.[39] Notably, mTOR dysfunction is implicated in neurodegenerative pathogenesis, including AD and PD. mTOR further modulates microglial and astrocytic anti-inflammatory functions, thereby influencing neuronal survival, metabolic homeostasis, autophagy, and apoptosis.[40]

The cAMP/PKA/CREB signaling pathway serves critical functions in regulating neuronal growth, proliferation, differentiation, synaptic plasticity, neurogenesis, and memory formation.[36] Specifically, CREB modulates transcriptional activation of genes encoding anti-apoptotic proteins, including B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra large (Bcl-xL), to mitigate cellular apoptosis.[41] Experimental evidence indicates that lixisenatide suppresses neuroinflammatory responses in AD mouse models and ameliorates PD-associated motor deficits by attenuating p38/MAPK signaling via cAMP/PKA/CREB-dependent mechanisms.[42,43] Importantly, these pathways do not operate independently; rather, they function through complex cross-regulation mediated by shared molecular

components, thereby working synergistically to promote neurotrophic effects, inhibit apoptotic cascades, and safeguard cellular homeostasis.

GLP-1R's role in inhibiting neuroinflammation

GLP-1 and its mimetics activate the GLP-1R, downregulating pro-inflammatory mediators such as TNF-α, IL-6, IL-10, and C1q in microglia while suppressing reactive astrogliogenesis.[18,44] Studies have demonstrated that GLP-1 analogs attenuate microglial inflammatory activation, promote their protective phenotype, and inhibit M1 microglial polarization, collectively counteracting neuroinflammatory processes.[43] In PD models, the GLP-1 analog NLY01 directly antagonizes microglia-mediated astrocyte conversion to the A1 neurotoxic phenotype, reduces cerebral inflammatory factor levels, and confers neuroprotection.[45] Mao et al.[46] reported that dioscin upregulates GLP-1 and GLP-1R expression in both brain and gut tissues, elevates superoxide dismutase activity, and diminishes IL-6 expression, significantly mitigating neuroinflammation and oxidative stress. In lipopolysaccharide (LPS)-induced inflammatory models, liraglutide inhibits pro-inflammatory microglial polarization and suppresses cytokine release.[47] These findings collectively indicate that GLP-1/GLP-1R signaling modulates microglial activity, attenuating pro-inflammatory factor production to exert anti-inflammatory effects. Additional research reveals that exendin-4 (Ex-4) activates GLP-1R in vitro to alleviate microglia-driven neuroinflammation, block reactive astrocyte formation, and reduce neuroinflammatory burden.[48] Further studies suggest that poly(ADP-ribose) polymerase-1 (PARP-1) contributes to microglial activation, and GLP-1 analogs mitigate PARP-1 activity by lowering ROS levels, thereby alleviating inflammation.[49] Moreover, GLP-1 analogs exert anti-inflammatory effects via astrocyte protection. Liraglutide has been shown to regulate astrocytic neuroinflammatory responses through a proposed mechanism involving GLP-1R-mediated activation of the cAMP/PKA/CREB pathway. Activated CREB subsequently inhibits transcriptional activation of pro-inflammatory cytokines TNF-α and IL-1β,[50] highlighting a dual anti-inflammatory and neuroprotective role. In summary, GLP-1 and its analogs suppress neuroinflammation by modulating microglial and astrocytic activation, offering novel therapeutic targets for neurocognitive disorders.

GLP-1 and its mimetics exert anti-inflammatory effects via additional molecular pathways. Kim et al.[51] demonstrated in a transient middle cerebral artery occlusion (MCAO) rat model that Ex-4 activates GLP-1R, suppressing JNK-mediated phosphorylation of IB1 (insulin-brain 1)/JIP1 (JNK-interacting protein 1), thereby reducing cyclooxygenase-2 expression to attenuate neuroinflammation. Emerging evidence also indicates that GLP-1R activation elevates intracellular cAMP levels, stimulating the MAPK/ERK signaling pathway to mediate anti-inflammatory responses.[29,43] The regulation of microglial function by GLP-1 analogs may further involve the transcription factor nuclear factor-kappa B (NF-κB), a key downstream effector of the GLP-1R/PI3K/AKT cascade, which governs inflammatory gene expression.[34] Enhanced GLP-1 signaling has been shown to inhibit NF-κB activity, alleviating neuroinflammatory processes.[52] In LPS-induced neuroinflammation models, liraglutide suppresses NF-κB expression, further blocking inflammatory cascades.[47] Similarly, GLP-1/GLP-1R activation in stroke and chronic cerebral ischemia (CI) models inhibits PI3K/AKT-dependent NF-κB signaling, mitigating inflammation-associated pathological sequelae.[39] Collectively, these findings underscore that GLP-1 and its analogs suppress neuroinflammatory responses through diverse in vivo pathways, ameliorating chronic CI-induced neuroinflammation and cognitive dysfunction in AD, PD, and VaD.

Neuroprotective effects of GLP-1R

GLP-1R are widely distributed in the CNS. The GLP-1 signaling system critically regulates CNS functions such as neurotrophic support and neuroprotection. Preclinical studies have validated the neuroprotective efficacy of GLP-1RAs in animal models of AD, PD, cognitive impairment, CI, and diabetic peripheral neuropathy.[27] In PD mouse models, the GLP-1RA NLY01 demonstrates pronounced neuroprotective properties by directly inhibiting microglia-driven astrocyte conversion to the neurotoxic A1 phenotype and modulating microglial activity to preserve dopaminergic neurons.[45] Mechanistic studies reveal that the GLP-1/GLP-1R axis activates diverse intracellular signaling pathways to mediate neuroprotective responses. For example, liraglutide mitigates ischemia-induced neuronal apoptosis by engaging the PI3K/AKT and MAPK pathways, which

upregulate pro-survival effectors (AKT, ERK) while suppressing antisurvival mediators (p38, JNK).[53] Activation of the PI3K/AKT pathway further stimulates mTOR production, enhancing neuroprotection.[39,54] Notably, the dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonist DA5-CH improves hippocampal synaptic plasticity and activates PI3K/AKT signaling in APP/PS1 transgenic AD mice, demonstrating multitarget neuroprotective effects.[55] In conclusion, GLP-1RAs attenuate chronic CI-induced cognitive dysfunction through diversified molecular pathways, underscoring their therapeutic potential for neurodegenerative disorders.

GLP-1R inhibits neuronal apoptosis and promotes neuronal regeneration

As previously noted, CCH promotes neuronal apoptosis. Damaged or apoptotic neurons release neuroinflammatory mediators, including cytokines and microglial activators.[43] These activated microglia subsequently trigger astrocytic transformation into neurotoxic A1-type astrocytes, initiating inflammatory cascades.[22,56] Both activated microglia and astrocytes contribute to neuronal loss in neurodegenerative pathologies.[27] GLP-1 counteracts these processes by enhancing neurotrophic factor expression, attenuating apoptosis, suppressing pro-inflammatory cytokines, and restoring neurite plasticity.[44] Mechanistically, GLP-1R exhibit dual expression in both neurons and microglia. Enhanced GLP-1R signaling promotes neuronal proliferation and differentiation.[22,48] Activated GLP-1R suppresses microglia-derived inflammatory factors (e.g., TNF-α), preserving neurite complexity—including branch length, neuronal counts, and secondary branching—to exert neuroprotection.[57] In vitro neuronal studies confirm that GLP-1RAs increase neurite density, stimulate axonal growth, and enhance neurite elongation.[58] Notably, NLY01 selectively inhibits microglial activation by targeting their surface GLP-1R, blocking TNF-α-mediated induction of reactive astrocytes, and protecting murine/human neurons in vitro.[21] Crucially, NLY01's neuroprotective mechanism operates indirectly via microglial modulation rather than direct neuronal GLP-1R engagement.[45]

Bertilsson et al.[59] demonstrated in a primary rodent neural culture system that pharmacological activation of GLP-1R (using Ex-4 and native GLP-1) significantly enhanced the proliferative capacity of murine neural stem cells in vitro. This observation was complemented by evidence showing that GLP-1RAs can induce lineage commitment of neural stem cells toward neuronal phenotypes,[24] thereby stimulating both neuroproliferation and differentiation processes. While the precise mechanism underlying GLP-1R-mediated regulation of neuronal expansion remains incompletely elucidated, experimental data suggest potential involvement of the PI3K/AKT signaling pathway. This pathway appears to regulate protein stabilization and transcriptional activation of the proneural factor Achaete-scute homolog 1 (Ascl1, also termed Mash1).[60] The neurogenic factor Achaete-scute complex-like 1 (Ascl1/Mash1) functions as a pioneer transcription factor. It drives neural progenitor cells and non-neuronal cells to exit the cell cycle and promotes neuronal differentiation through the activation of neuronal target genes. As such, it plays a pivotal role in neuronal differentiation.[22,61] Notably, rodent studies demonstrate that liraglutide-induced hippocampal neurogenesis correlates with upregulated Ascl1/Mash1 expression, establishing its critical role in neuronal progenitor pool expansion.[62] Importantly, Ascl1/Mash1 exhibits therapeutic potential by redirecting stroke-induced proliferative reactive astrocytes toward neuronal differentiation trajectories, thereby mitigating pathological CNS damage associated with reactive astrogliosis.[61,63]

Multiple studies have indicated that the activation of AKT serves to promote the activation of mTOR. This promotion occurs through the enhancement of protein synthesis, pyrimidine synthesis, and the prevention of autophagy, as detailed Athauda and Foltynie.[34] Such mechanisms support neuronal differentiation and growth, thereby alleviating the development of neurodegenerative diseases triggered by chronic CI. Additionally, the activation of GLP-1R has been shown to promote neuronal survival. This is achieved by mediating tyrosine-216 dephosphorylation and inactivating glycogen synthase kinase-3β (GSK-3β) via the PI3K/Akt signaling pathway, as reported in Krafft et al.[64]

In a research investigation focusing on ischemia-reperfusion injury in mice, it was demonstrated that the stimulation of GLP-1R led to the activation of the cAMP/PKA and Akt/GSK3 signaling pathways, promoted the expression of proteins

associated with neurogenesis.[65] Yang et al.[66] identified a previously uncharacterized role of GLP-1 in enhancing DNA repair mechanisms within cortical neurons of ischemic stroke model rats, mediated through upregulated expression of APE1—a base excision repair enzyme critical for mitigating oxidative stress-induced neuronal damage. In summary, GLP-1 analogs exert neuroprotective effects through sequential activation of GLP-1R-dependent signaling pathways, promotion of neuronal survival via enhanced differentiation/proliferation mechanisms, and attenuation of ischemia-associated neuronal injury, thereby preserving both structural and functional integrity of neural networks.

GLP-1R promotes synaptogenesis and improves memory function

Synapses constitute the fundamental structural and functional junctions between neurons, comprising three distinct components: presynaptic membranes responsible for neurotransmitter release, synaptic cleft enabling chemical diffusion, and postsynaptic membranes equipped with specialized receptors. Synaptic plasticity represents the activity-dependent modification of interneuronal connection efficacy, serving as the cellular substrate for cognitive processes. GLP-1 and its mimetics demonstrate efficient BBB permeability to bind neuronal GLP-1R, thereby enhancing memory consolidation through synaptic integrity preservation.[29] Experimental evidence reveals that GLP-1R activation potentiates spatial learning performance, whereas genetic ablation of GLP-1R induces memory deficits accompanied by impaired long-term potentiation (LTP)—a canonical electrophysiological correlate of synaptic plasticity.[67]

Emerging evidence underscores the neuromodulatory role of GLP-1RAs in potentiating synaptic plasticity. Studies demonstrate that lixisenatide exerts its therapeutic effects by allosterically activating GLP-1R signaling cascades, thereby upregulating hippocampal expression of neurotrophic tyrosine kinase receptor type 2 (TrkB) and mechanistic target of rapamycin (mTOR) genes in high-fat diet-induced murine models—molecular mediators critically regulating synaptic plasticity parameters and LTP maintenance.[68]

GLP-1RAs play a significant role in enhancing synaptic plasticity. Multiple studies have demonstrated that lixisenatide is capable of activating GLP-1R. In high-fat-fed mice, this activation leads to the upregulation of the hippocampal neurotrophic tyrosine kinase receptor type 2 and mTOR genes. These genes are intricately involved in the regulation of synaptic plasticity and LTP.[68] Liraglutide, as a GLP-1RA, has garnered increasing recognition for its therapeutic potential in ischemic cerebrovascular disorders. A clinical trial investigating postoperative delirium following cardiac surgery demonstrated that liraglutide attenuates surgery-induced synaptic loss and synaptic plasticity impairment, thereby reducing delirium incidence.[69] A study demonstrated that liraglutide enhances synaptic plasticity by activating mTORC1 signaling and potentiating AMPA receptor (AMPAR) activity, which increases dendritic arborization, spine density, and synaptic protein expression in primary hippocampal neurons exposed to neurotoxic conditions in rats.[70] Furthermore, liraglutide ameliorates cognitive dysfunction in diabetic patients by suppressing oxidative stress, lipid peroxidation, and iron overload, thereby attenuating hippocampal neuronal damage and synaptic plasticity deficits while restoring cognitive performance.[71] Klugmann et al.[72] demonstrated that central GLP-1R activation triggers ERK phosphorylation, subsequently downregulating D-box binding protein (DBP) expression, which modulates hippocampal synaptic plasticity, learning capacity, and neuroprotective efficacy. This identifies DBP as a novel transcriptional regulator of hippocampal neuroplasticity. The dual GLP-1/GIP receptor agonist DA4-JC activates GLP-1R signaling, reversing memory deficits in AD mouse models via enhanced hippocampal synaptic plasticity (evidenced by LTP augmentation), amyloid plaque clearance, and suppression of cerebral pro-inflammatory cytokine production.[73] Pharmacological evidence further confirms that sitagliptin improves cognitive outcomes in AD mice through GLP-1R-dependent activation of BDNF-TrkB signaling cascades coupled with synaptic plasticity modulation.[74]

Neuronal communication is mediated through synaptic transmission, with LTP of synaptic efficacy established as the canonical cellular correlate of memory formation.[20] Emerging from synchronized neuronal activation, LTP serves as a critical biomarker for memory consolidation. Its functional impairment in AD and VD correlates with clinical manifestations of memory dysfunction. These observations underscore the therapeutic relevance of preserving LTP integrity in neurological

disorders. Experimental evidence demonstrates that GLP-1 enhances LTP induction in cerebral circuits, ameliorating cognitive deficits in neurodegenerative disease models. Conversely, GLP-1R knockout murine models exhibit learning impairments concomitant with hippocampal LTP attenuation.[67,75] In AD, β-amyloid (Aβ) accumulation is recognized as a defining neuropathological hallmark of the AD-affected brain. Investigations using AD rat models demonstrate that GLP-1R activation induces synaptic mechanisms that simultaneously potentiate LTP magnitude and antagonize Aβ-mediated suppression of synaptic plasticity.[76] The novel GLP-1 analog CJC-1131—engineered with extended pharmacokinetic stability—effectively mitigates Aβ-induced cognitive deficits and synaptic plasticity impairments, suggesting its therapeutic potential for AD intervention.[77] Furthermore, GLP-1R activation mediates hippocampal plasticity and facilitates long-term memory consolidation via induction of the cAMP/PKA/pCREB signaling cascade, enhancing prolonged maintenance of LTP in the hippocampal CA1 region.[78] Current evidence demonstrates that GLP-1Rs primarily act at postsynaptic sites in the hippocampal CA1 subregion, enhancing the induction of LTP and sustaining glutamatergic neurotransmission by promoting synaptic membrane insertion of AMPARs and restoring physiological glutamate release dynamics at presynaptic terminals.[36] In conclusion, GLP-1RAs can improve synaptic plasticity and protect synaptic function, promoting the restoration of synaptic function in nervous system diseases.

GLP-1R and mitochondrial damage

Mitochondria serve as essential organelles responsible for maintaining cellular energy metabolism and redox homeostasis.[79] Sustained mitochondrial structural integrity is critical for ensuring cellular viability. Research has demonstrated that GLP-1R activation exerts multifaceted protective effects on mitochondrial dynamics. One study demonstrated that GLP-1R signaling is necessary for maintaining the integrity and functionality of astrocyte mitochondria, particularly in hypothalamic astrocytes. The absence of GLP-1R signaling modestly compromises mitochondrial function and activates cellular stress responses in these cells.[80] The GLP-1R stabilizes the outer mitochondrial membrane, inhibits cytochrome c efflux into the cytoplasm, and suppresses the activation of caspase-3 and caspase-8. Collectively, these mechanisms attenuate apoptosis, mitigate oxidative stress, and preserve mitochondrial functional integrity.[81,82] Emerging evidence from CNS disease models demonstrates that GLP-1 analogs modulate SIRT1 expression in neurons. The activation of SIRT1 counteracts 3-nitropropionic acid (3-NP)-induced motor coordination impairments and behavioral deficits in mice models, with mechanistic studies revealing enhanced PGC-1α activity and mitochondrial biogenesis as critical contributors to functional recovery.[58,83] In summary, activation of GLP-1R improves mitochondrial function through multiple pathways, attenuates mitochondrial dysfunction caused by chronic CI, and mitigates the onset and progression of cognitive impairment.

GLP-1 and the BBB

CCH induces BBB dysfunction and elevated permeability through diverse pathophysiological mechanisms. BBB impairment is implicated in multiple neurodegenerations, including AD, VaD, and PD. Ex-4 is a GLP-1 agonist. A study demonstrates that in MCAO rats, the GLP-1RA Ex-4 improves neurological deficit scores, reduces infarct volume, mitigates BBB disruption, and downregulates astrocyte-derived VEGF-A, MMP-9, CXCL-1, and MCP-1.[84] Experimental investigations demonstrate that Ex-4 treatment restores diabetes-altered expression of BBB-related proteins (occludin and aquaporin-4) and blood–cerebrospinal fluid barrier components, reverses pathological permeability in both barriers, and ameliorates cognitive dysfunction in diabetic rats.[85] Experimental evidence demonstrates that sodium butyrate enhances colonic GLP-1 secretion and upregulates cerebral GLP-1R expression. Subsequent GLP-1R activation attenuates BBB disruption in PD models by modulating tight junction proteins, including occludin and zonula occludens-1.[86] Furthermore, GLP-1 ameliorates oxidative stress via suppression of ROS and enhances BBB integrity.[44] Mechanistically, GLP-1 enhances BBB stabilization through PI3K/Akt pathway-mediated inactivation of GSK-3β, which upregulates key BBB-protective proteins including tight junction components (claudin-3, claudin-5) while downregulating endothelial adhesion molecules (VCAM-1, ICAM-1). However, this effect can be completely abolished by Wortmannin (a specific PI3K inhibitor).[87–89] In summary,

GLP-1 analogs exert neuroprotective effects by activating the GLP-1), which preserves BBB integrity and sustains neurological function.

GLP-1R and neurotrophic factors

Brain-derived neurotrophic factor (BDNF), a key neurotrophin predominantly expressed in the CNS and enriched in the hippocampus, exhibits multifaceted neuroprotective properties. BDNF rescues dopaminergic neurons, reverses synaptic degeneration in neurodegenerative pathologies, enhances neural progenitor cell differentiation and survival. BDNF critically supports neuronal survival in neurodegenerative pathologies by exerting anti-apoptotic, antioxidant, and autophagy-modulating effects, as evidenced by prior mechanistic investigations.[90] Research has demonstrated that exenatide restores BDNF axonal transport in Aβ-treated neurons by upregulating GLP-1R expression, thereby activating insulin-signaling pathways.[91] Sayed et al.[92] demonstrated that vildagliptin upregulates neurotrophic factor expression (e.g., BDNF) in the striatum via the GLP-1/PI3K/Akt pathway in a 3-NP rat model. In the hippocampus, BDNF is transcriptionally regulated by the CREB. Activation of the GLP-1R synergistically activates multiple signaling pathways, including the PI3K/Akt, MEK/ERK, and cAMP/PKA axes. This integrated signaling enhances CREB activation and promotes BDNF synthesis in hippocampal neurons under both in vivo and in vitro conditions, even in nonpathological states.[36,93]

Glial cell line-derived neurotrophic factor (GDNF), which is widely expressed in multiple regions of the CNS, plays a multifaceted role in neuroprotection, including the maintenance of astrocyte viability. Notably, GDNF has been demonstrated to exert robust neuroprotective effects against ischemic brain injury.[94] Reduction of GDNF levels in the brain contributes to glutamate excitotoxicity within murine dopaminergic neurons, as evidenced in rodent models.[95] Notably, the clinically utilized GLP-1RA liraglutide demonstrates significant upregulation of GDNF expression in established PD models, suggesting its therapeutic potential for modifying disease-associated neuropathological processes.[96] Another study demonstrated that GLP-1 and GIP upregulate the expression of BDNF, GDNF, and nerve growth factor in microglia through activation of PI3K and PKA-dependent phosphorylation pathways, thereby exerting neuroprotective effects.[97] Substantiating this mechanism, Glotfelty et al.[98] provided functional evidence that pharmacological activation of GLP-1R directly potentiates the BDNF/GDNF signaling axis, concomitant with amelioration of both motor dysfunction and cognitive impairment in PD models. The biosynthesis and regulatory pathways of BDNF and GDNF are not mechanistically distinct but exhibit dynamic interplay through shared signaling cascades. Pharmacological activation of the GLP-1R by its synthetic analogs elevates both BDNF and GDNF expression, enabling these neurotrophic factors to function synergistically in maintaining neuronal network integrity and mitigating neurodegenerative pathology.

GLP-1R and GM

The bidirectional interplay between GM and the CNS has emerged as a pivotal area of biomedical research. Evidence suggests that the GM regulates the development and function of the immune, metabolic, and nervous systems through dynamic bidirectional communication along the microbiota–gut–brain axis.[99] The CNS regulates the metabolic axis of the microbiota through vagal nerve branches and the hypothalamic–pituitary–adrenal cortex.[100] CCH not only causes brain injury but also leads to gastrointestinal complications such as constipation, fecal incontinence, and gastrointestinal bleeding.[101] Studies have demonstrated that ischemic stroke rapidly induces GM dysbiosis, characterized by an overgrowth of Enterobacteriaceae, thereby exacerbating cerebral infarction.[102] Xiao et al.[103] demonstrated that rats subjected to bilateral common carotid artery occlusion exhibited not only cognitive impairment and depression-like behaviors but also gut barrier dysfunction and microbiota dysbiosis. Furthermore, CCH induces gut dysbiosis by reducing the abundance of Romboutsia, Turicibacter, and Prevotella and decreasing the concentration of short-chain fatty acids (SCFAs), particularly acetate and propionate.[7] Dysbiosis is implicated in the onset and progression of AD. Studies have demonstrated that GM dysbiosis diminishes bacterial diversity, increases bacteria producing LPS, and damage gut barrier integrity. The translocation of LPS into systemic circulation (endotoxemia) induces elevated levels of proinflammatory cytokines, including interleukin-1β

(IL-1β), interleukin-6 (IL-6), and TNF-α. Additionally, LPS directly disrupts enzymatic activity and promotes tau protein hyperphosphorylation, establishing a pathological milieu that facilitates the formation of β-amyloid plaques and neurofibrillary tangles.[104] In summary, GM dysfunction is mechanistically linked to neurocognitive disorders, including CCH, PD, and AD.

Gastrointestinal hormone signaling pathways constitute integral components of the gut–brain axis, a complex bidirectional communication network between the intestinal microbiota and the CNS, is a critical neuroendocrine modulator of gut–brain crosstalk; notably, probiotic interventions targeting gut microbiome dysregulation can upregulate GLP-1 secretion.[46] Upon ligand-receptor binding to GLP-1R, GLP-1 exerts multifaceted neuroprotective, anti-inflammatory, and metabolic regulatory effects within the CNS.

Short-chain fatty acids

SCFAs, crucial metabolic byproducts of the GM, are primarily composed of acetate, propionate, and butyrate. These molecules are generated through microbial anaerobic fermentation of non-digestible dietary fibers and other fermentable substrates in the colon.[7] SCFAs, key signaling molecules within the microbiota–gut–brain axis,[105] mediate bidirectional communication across this axis. Experimental evidence indicates that SCFAs directly influence the CNS by traversing the BBB and indirectly modulate neurophysiological processes through immunoregulatory, endocrine, vagus nerve-mediated, and circulatory pathways. These multifaceted mechanisms affect synaptic plasticity, cognitive performance (learning and memory), and emotional regulation.[106] Histone deacetylases (HDACs) are critically involved in CNS pathologies, where elevated HDAC6 activity has been causally linked to memory deficits.[107] Experimental data demonstrate that CCH markedly elevates HDAC6 protein expression, whereas SCFAs suppress HDAC6 levels, thereby partially attenuating CCH-induced neurocognitive dysfunction.[108] Experimental studies reveal that diminished acetate (a SCFA) production correlates with microglial activation and induce cognitive decline.[109] Experimental data demonstrate that CCH induces marked reductions of acetate levels in both fecal samples and hippocampal tissues. These deficits trigger hippocampal microglial activation, phenotypic polarization toward a pro-inflammatory state, and significant cognitive impairment. Notably, supplementation with SCFAs counteracts these pathological changes by suppressing microglial/astrocyte hyperactivity and reprogramming microglial polarization from M1 (pro-inflammatory) to M2 (anti-inflammatory) phenotypes, thereby mitigating neuroinflammatory cascades.[108] In rodent models of depression, exogenous acetate administration rescues hippocampal synaptic plasticity deficits through HDAC inhibition.[110] Correspondingly, in experimental CI models, butyrate supplementation attenuates acute ischemic injury-induced synaptic plasticity impairment.[111] Acetate as a dominant metabolic substrate fueling acetyl-CoA synthesis, whereby sustaining oxidative phosphorylation capacity and mitochondrial ATP production during prolonged CI progression.[112,113] SCFAs increase the levels of acetate, acetyl-CoA, and ATP, normalize mitochondrial membrane potential, reduce ROS accumulation, and restore hippocampal mitochondrial function.[108] Previous studies have demonstrated that GM transplantation mediated by elevated SCFAs levels not only alleviates neuroinflammation but also ameliorates cognitive decline and depression-like behaviors following BCCAO through suppression of hippocampal neuronal apoptosis.[103] Conclusively, SCFAs exhibit potential for alleviating neurocognitive disorders through multifaceted mechanisms, including suppression of neuroinflammatory responses, preservation of BBB integrity, and maintenance of neuronal function. Nevertheless, current evidence predominantly originates from preclinical investigations. Clinical studies evaluating SCFAs in neurocognitive disorders remain sparse, with existing trials limited by insufficient sample sizes and methodological heterogeneity. To establish translatable clinical relevance, the reproducibility and generalizability of these findings must be rigorously validated through large-scale, multicenter randomized controlled trials, which would further elucidate the therapeutic efficacy and long-term safety profiles of SCFAs.

GLP-1R and SCFAs

Research has found that GM-mediated production of SCFAs via enteroendocrine L cells plays a critical role in stimulating GLP-1 secretion.[26,114] SCFAs are recognized to influence GLP-1 release by activating the G-protein coupled cell surface receptors (GPR) GPR41 and GPR43.[115,116] However, this hypothesis remains scientifically

contentious. Christiansen et al.[117] employed an ex vivo perfused rat colon model to investigate colonic endocrine function, demonstrating that in vitro SCFA-induced GLP-1 secretion is mechanistically independent of free fatty acid receptors FFA2 (GPR43) and FFA3 (GPR41). Subsequently, the study by Bolognini et al.[118] confirmed the role of GPR43 in the release of GLP-1 in enteroendocrine cells. These findings indicate that SCFAs induce the release of intestinal hormones, such as GLP-1, at least partially through the GPR43 receptor pathway. This hypothesis aligns with the findings reported by Moţăţăianu et al.[119]

SCFAs (acetate, butyrate, and propionate) regulate the expression and secretion of GLP-1 in L cells through free fatty acid receptor 2 (FFAR2/GPR43) and free fatty acid receptor 3 (FFAR3/GPR41).[120] Butyrate can bind to GPCRs GPR41 and GPR43 to modulate microbial activity associated with colonic L cells. The GLP-1R is widely expressed in the brain, and its activation exerts neuroprotective effects in AD, PD, and stroke.[115] A study indicated that butyrate could activate the GPR41/Gbc/PI3K/Akt pathway, reducing neuronal apoptosis following cerebral infarction in MCAO rats.[121] The GM is crucial for the maturation and activation of microglia. The GM is crucial for the maturation and activation of microglia. A study demonstrated that both germ-free mice and mice treated with antibiotics for 4 weeks exhibited immature microglia.[122] This finding aligns with the observation by Heiss et al.[123] demonstrating that GM regulates microglial maturation and activation through partial involvement of GLP-1R signaling. *Clostridium butyricum* (Cb), a butyrate-producing probiotic, facilitates the enhancement of butyrate production and secretion of the intestinal hormone GLP-1, ultimately ameliorating host brain damage.[124] Research indicates that Cb, a probiotic strain, enhances GLP-1 production and upregulates cerebral GLP-1R, consequently ameliorating MPTP-induced motor deficits and mitigating dopaminergic neuron loss in mouse models.[125] In conclusion, SCFAs modulate GLP-1 expression via multifaceted mechanisms and target the GLP-1R, thereby exerting neuroprotective effects in neurocognitive disorders.

Side effects of GLP-1R

While activation of the GLP-1R demonstrates therapeutic benefits in glycemic control and amelioration of chronic CI-induced neurocognitive deficits, emerging evidence suggests potential adverse effects. Notably, pharmacological agonists of GLP-1R exhibit a statistically significant association with gastrointestinal complications, particularly intestinal obstruction. Clinical study data indicate that compared to sodium-glucose cotransporter-2 inhibitors, GLP-1RAs are associated with an increased risk of intestinal obstruction (1.9 vs 1.1 per 1000 person-years; hazard ratio (HR): 1.69, 95% confidence interval (CI): 1.04–2.74). The highest HR is observed after 1.6 years of use (HR: 3.48, 95% CI: 1.79–6.79).[126] This adverse effect may be related to the persistent increase in intestinal length and villus height caused by GLP-1RAs, which can lead to reduced elasticity and fibrosis of the small intestine, resembling the mechanical properties of a loose spring.[127] Additionally, GLP-1R activation induces transient neurogastrointestinal symptoms (e.g., nausea and vomiting).[128] This effect is likely attributable to the widespread distribution of GLP-1Rs within appetite-regulating brain regions, particularly the nucleus tractus solitarius and area postrema, which coordinate central anorexigenic signaling cascades.[25] The side effects associated with GLP-1R activation may alter the dietary intake of experimental rats, consequently influencing study outcomes. Hence, to eliminate this confounding factor, methodological adjustments—such as the implementation of enemas—should be incorporated during experimentation to control its impact on results. In summary, GLP-1RAs demonstrate therapeutic potential for neurocognitive disorders. However, their adverse effects require rigorous clinical evaluation during therapeutic application. Tailored dosing strategies and systematic monitoring protocols should be implemented, guided by patient-specific factors (e.g., comorbidities, tolerance thresholds, and pharmacokinetic profiles).

Conclusion and outlook

This article provides a review and analysis of the neurological damage caused by chronic CI, summarizing the anti-inflammatory, neuroprotective, neuron regeneration-promoting, synapse formation, and mitochondrial function-maintaining effects of the GLP-1/GLP-1R axis in various CNS diseases. It highlights the role of protecting the functions of microglia and astrocytes, thereby maintaining the homeostasis of the CNS. It also elucidates the potential side effects induced by GLP-1R activation. Based on research data

obtained from GLP-1 and its analogs in animal models of AD, PD, and VaD, this new therapeutic strategy shows potential as a treatment for human neurocognitive disorders. However, the methods by which GLP-1 and similar drugs activate GLP-1R, their mechanisms of action in the CNS, and possible side effects still require further exploration. Currently, the therapeutic application of such drugs remains at the animal model research level, and more clinical evidence is needed to confirm their specific mechanisms, clinical efficacy, and potential adverse events in humans.

Declarations

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Appendix

Abbreviations

AD	Alzheimer's disease
Ascl1/Mash1	Achaete-scute complex-like 1
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
CCH	chronic cerebral hypoperfusion
CNS	central nervous system
CREB protein	cAMP response element-binding
GDNF	glial cell line-derived neurotrophic factor
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
GPCR	G-protein-coupled receptor
IL-1α	interleukin-1 alpha
LTP	long-term potentiation
MAPK/ERK	mitogen associated protein kinase/extracellular signal-regulated kinase
MCAO	middle cerebral artery occlusion
HDACs	histone deacetylases
3-NP	3-nitropropionic acid
PD	Parkinson's disease
ROS	reactive oxygen species
SCFA	short-chain fatty acids
TNF-α	tumor necrosis factor-alpha
VaD	vascular dementia