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Review

GLP-1 programs the neurovascular landscape

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SUMMARY

Readily available nutrient-rich foods exploit our inherent drive to overconsume, creating an environment of overnutrition. This transformative setting has led to persistent health issues, such as obesity and metabolic syndrome. The development of glucagon-like peptide-1 receptor (GLP-1R) agonists reveals our ability to pharmacologically manage weight and address metabolic conditions. Obesity is directly linked to chronic low-grade inflammation, connecting our metabolic environment to neurodegenerative diseases. GLP-1R agonism in curbing obesity, achieved by impacting appetite and addressing associated metabolic defects, is revealing additional benefits extending beyond weight loss. Whether GLP-1R agonism directly impacts brain health or does so indirectly through improved metabolic health remains to be elucidated. In exploring the intricate connection between obesity and neurological conditions, recent literature suggests that GLP-1R agonism may have the capacity to shape the neurovascular landscape. Thus, GLP-1R agonism emerges as a promising strategy for addressing the complex interplay between metabolic health and cognitive well-being.

INTRODUCTION

Recent insights into the central regulation of homeostatic feeding have spurred the development of pharmaceutical strategies aimed at effectively managing food intake as an obesity treatment. A pivotal discovery highlights the presence of glucagon-like peptide-1 (GLP-1)-expressing neurons primarily located in the caudal nucleus of the tractus solitarius (NTS),[1] crucial for maintaining proper energy balance.[2] Remarkably, these neurons send numerous ascending projections to hindbrain, midbrain, and forebrain areas, integrating them into both the hedonic and homeostatic control of food intake.[3–6] Unsurprisingly, GLP-1 receptor (GLP-1R) agonists emerge as the most promising targets for obesity management, prompting the development of numerous receptor agonists such as liraglutide, semaglutide, and tirzepatide.[7–14] The caveat for exogenous GLP-1 to function as an appetite suppressant is the requirement of a supraphysiological dose with exponentially greater folds in concentration and duration compared to endogenous GLP-1 (Figure 1). Functioning as an incretin hormone, GLP-1 plays a key role in maintaining blood glucose homeostasis by increasing postprandial insulin secretion and reducing glucagon secretion.[15] Endogenous GLP-1 delays gastric emptying, which slows down the rate of glucose absorption and prevents insulin spikes. Beyond this incretin role, GLP-1 signaling significantly contributes to the regulation of diverse behaviors, encompassing metabolic processes and motivated behaviors such as feeding,[3] fluid intake,[16] and drug consumption.[17] Despite the known mediation of these effects by central GLP-1Rs, the precise origins of endogenous GLP-1 responsible for activating these receptors remain a puzzle. This complexity is heightened by GLP-1's production in two distinct locations within the body—peripherally in the gut,[18] released into circulation, and centrally in distinct brain regions, including the NTS and the olfactory bulb.[19,20] GLP-1 binding onto hypothalamic and hindbrain centers induces satiety, yet the exact mechanisms and pathways through which GLP-1 enacts its effects on the brain remain elusive. Furthermore, the concentration of endogenous GLP-1 secreted and the routes by which it enacts its effects depend on the strength of the stimulus. For example, a normal meal leads to a postprandial level of GLP-1 that triggers the afferent vagus nerve and results in a vagus relay that communicates its overall incretin effect.[21] This level of plasma GLP-1 does not stimulate receptors on target organs due to its low concentration and short half-life. Conversely, a large meal, or post-bariatric surgery, will result in a higher level of endogenous GLP-1 that acts on both the vagal system and receptors on target organs. Whether postprandial endogenous intestinal GLP-1 can reach the brain to modulate food intake requires further elucidation. It is plausible that a normal meal does not lead to a level of plasma GLP-1 that can reach the brain via systemic circulation, while a large meal leads to a more robust and prolonged release of intestinal GLP-1 that

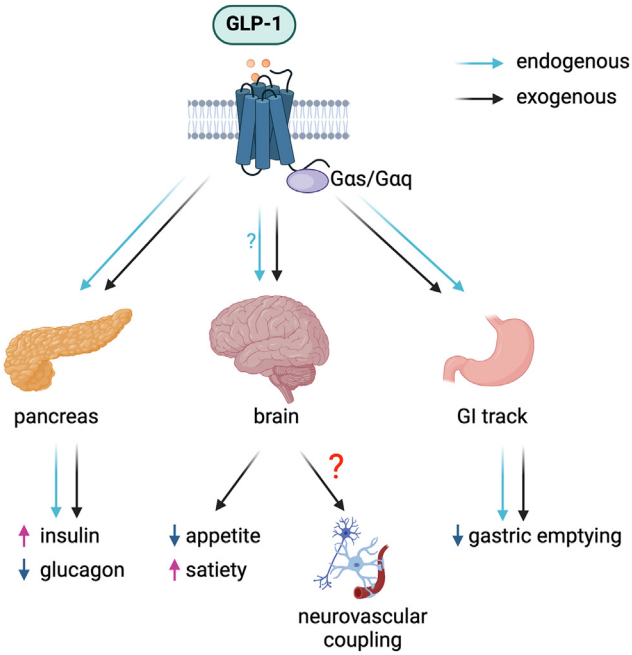

Figure 1. GLP-1R expression and function on the neuro-glial-vascular unit

Endogenous and exogenous GLP-1 (GLP-1R agonist) share overlapping and distinct physiological properties. Both act as incretin hormones to maintain glucose homeostasis and reduce gastric emptying. Exogenous GLP-1 enhances satiety and demonstrates neuroprotection through its anti-inflammatory properties. Whether endogenous GLP-1 can act centrally remains unknown due to its short half-life.

can act on central nodes to regulate satiety. Understanding the interplay between these dual sources (brain and intestine) of endogenous GLP-1 and their respective roles in modulating physiology depending on the stimulus is critical for unraveling the intricate signaling mechanisms associated with GLP-1.

Over the past decades, obesity has surged to pandemic levels in Western societies.[22] GLP-1R agonists have gained prominence for delivering a sustained reduction in weight loss (approximately 10%–20%).[23] Individuals with overweight and obesity often exhibit persistent chronic inflammation, both peripherally and centrally. This inflammatory state is intimately linked to a greater risk of developing neurological diseases, connecting obesity-related metabolic syndrome to cognitive decline and neurodegeneration.[24] Intriguingly, besides its role in appetite regulation, GLP-1R agonism displays neuroprotective and neurotrophic actions and minimizes neuroinflammation, such as reduction in brain insulin resistance, microglial activation, reactive astrogliosis, and neurodegeneration.[25,26] This, coupled with GLP-1's ability to act both peripherally and centrally to regulate metabolic health, has prompted investigations into its potential role in addressing extra-metabolic conditions. In addition to the neuroprotective roles, GLP-1R agonism exerts microvascular protection. GLP-1R agonism alleviates retinal vascular leakage and improves brain-retinal-barrier permeability in models of diabetic retinopathy.[27–29] Given the neurovascular effects on the retina, and the existing parallelism of vascular functions between the retina and the brain, it is logical to extend the focus of GLP-1's roles to extra-metabolic effects on the brain by assessing comprehensively the action of GLP-1 on the neurovascular unit (NVU), where neuronal, vascular, and immune systems actively communicate, coordinated by a diverse group of cells mediating the brain-body crosstalk.[30]

In this review, we discuss the intersection between GLP-1R signaling in metabolic and neurological disorders, exploring its impact on the structure-function relationship of the neuro-glial-vascular unit.

GLP-1R SIGNALING ACROSS THE DIFFERENT SYSTEMS OF THE NEURO-GLIAL-VASCULAR UNIT

Our brain constitutes only 2% of total body weight; however, it consumes 20% of the body's energy at rest in the form of glucose and oxygen.[31] This is achieved via an intricate network of blood vessels that perfuses the brain and ensures a seamless neuronal-vascular crosstalk known as neurovascular coupling (NVC). Such a sophisticated vascular system intricately interacts with its heterogenic pool of cellular components. This dynamic process involves supplying energy substrates while efficiently eliminating metabolic byproducts to uphold the brain's homeostatic equilibrium. The notion of the NVU underscores the physical location where the structural and functional connection between brain cells and the microvasculature occurs to coordinately regulate the brain-body crosstalk. The diverse expression of GLP-1R on the different cell types of the NVU is indicative of its multifaceted roles in overall brain function (Figure 2).

Neurons

Centrally, GLP-1 is primarily produced by neurons in the NTS, with projections to multiple regions, most notably the hypothalamus.[32] The role of central GLP-1 in feeding behavior is well established, while its influence on glucose homeostasis requires more elucidation.[33] GLP-1R neurons in the dorsomedial hypothalamus (DMH) lower blood glucose levels by increasing insulin release through an NTS^{GLP-1}-DMH^{GLP-1R}-dorsal motor nucleus of the vagus nerve (DMV)-pancreas pathway.[33] In contrast, GLP-1R neurons in the paraventricular hypothalamus (PVH) suppress food intake via an NTS^{GLP-1}-PVH^{GLP-1R} pathway.[34] The divergence in GLP-1R populations in mediating physiological versus pharmacological responses to GLP-1 further highlights the complexity of GLP-1 signaling and introduces the concept of regional and temporal specificity with GLP-1 central nodes responding differently to varying metabolic shifts.[35] Beyond appetite regulation and glucose homeostasis, additional neuronal roles for GLP-1R signaling include the regulation of energy expenditure and the ability to modulate the autonomic nervous system, as well as the brain's reward system. In brief, central stimulation of GLP-1R leads to the activation of brown adipose tissue thermogenesis, resulting in weight loss independently of its effects on food intake.[36] Additionally, central GLP-1R signaling directly regulates adipocyte lipid metabolism by modulating sympathetic outflow.[37] Selective deletion of GLP-1R in the PVH reduces hypothalamic-pituitary-adrenal axis responses to acute and chronic stress.[38] GLP-1R acts on the reward circuitry to diminish cocaine-seeking behavior.[39,40] Such hedonic effects of GLP-1R signaling extend to a less severe form of addiction, such as alcohol use disorder. Treatment

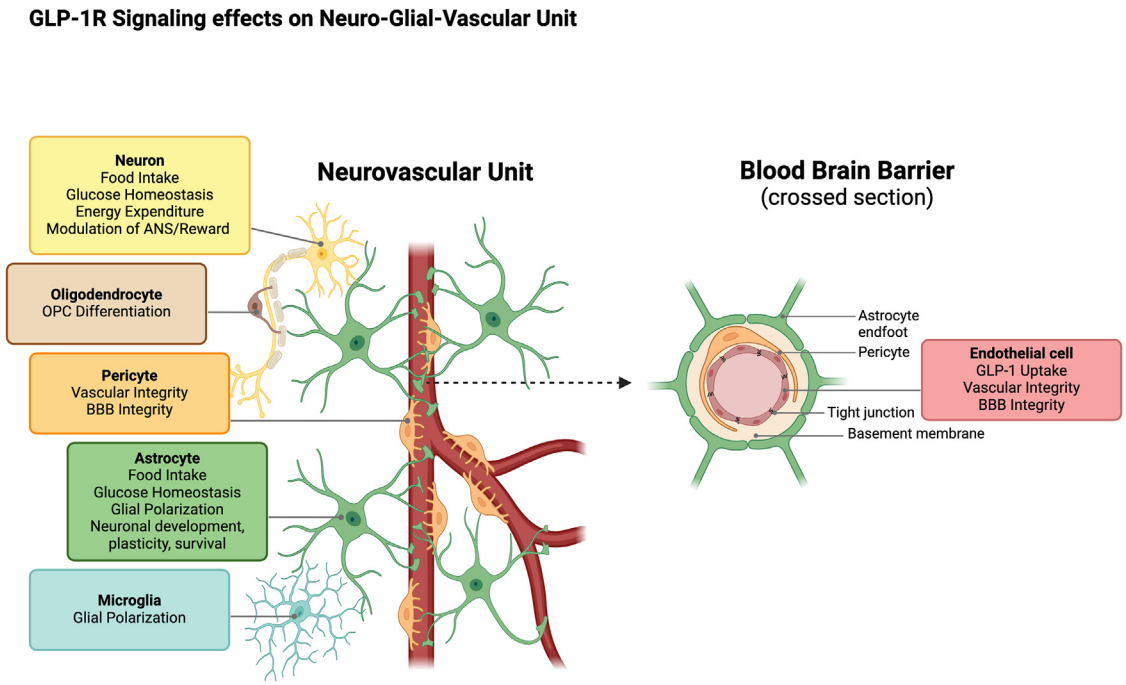

Figure 2. GLP-1R expression and function on the neuro-glial-vascular unit
The broad expression of GLP-1R across the different cell types of the NVU works in tandem to enact its multifactorial effect on the brain and body.

with GLP-1R agonists in alcohol-preferring non-human primates reduces voluntary alcohol drinking.[41] In summary, GLP-1R signaling has a broad effect on the brain to regulate whole-body systemic metabolism. Whether these effects are exclusively conveyed by neurons or are partly mediated by other components of the NVU remains to be elucidated.

Glial cells are a heterogenic pool of cells (astrocytes, microglia, and oligodendrocytes) that integrate all aspects of CNS development and formation. During the maturation process of neural circuits, glial cells allow efficient synaptic communication, adapting to changes in plasticity, maintaining internal homeostasis, and regulating the overall network-level activity within the CNS.[42] Moreover, glial cells are responsible for providing peripheral information into the neuronal network and have a significant impact on whole-body metabolism.[43] Though GLP-1R is primarily expressed in neurons, it is also expressed in a variety of glial cells with distinct roles on each cell type.

Astrocytes

Astrocytes are the most abundant glial cells in the brain. Being a diverse group of cells with regional and temporal specificity, the main role of astrocytes is the maintenance of tissue homeostasis at all levels of CNS organization, extending from molecular (regulation of metabolites and neurotransmitters) to organ (maintenance of the blood-brain barrier (BBB) and glymphatic system).[44] In astrocytes, GLP-1 plays a multifaceted role by inhibiting glucose uptake, promoting fatty acid utilization, and ensuring the maintenance of mitochondrial integrity and function.[45] The absence of GLP-1R signaling in astrocytes leads to the production of fibroblast growth factor 21, resulting in improved systemic glucose homeostasis and memory formation.[45] Furthermore, GLP-1 enhances the supportive capacity of astrocytes to neurons by mediating a metabolic shift from oxidative phosphorylation to aerobic glycolysis.[46] GLP-1-induced astrocytic-lactate generation increases neuronal viability as well as dendrite and axon growth.[46] Notably, the activation of GLP-1R in astrocytes within the NTS is implicated in the control of energy balance through the regulation of food intake.[47] Treatment with GLP-1R agonist liraglutide plays a role in modulating astrocyte polarization by increasing the number of A2 reactive astrocytes, which are crucial for neuronal development, plasticity, and survival.[48] A similar finding is reported in a mouse model of glaucoma, where treatment with GLP-1R agonist NLY01 substantially reduces A1 astrocyte transformation and retinal ganglion cell dealth.[49] Interestingly, GLP-1 (9–36), a natural cleavage product of GLP-1, binds to insulin-like growth factor 1 receptor and activates the downstream phosphatidylinositol 3-kinase (PI3K)/protein kinase B/AKT pathway in astrocytes during oxygen-glucose deprivation/reoxygenation injury.[50] In conclusion, GLP-1R signaling in astrocytes regulates both central and peripheral metabolism, extending from energy balance to neuroplasticity.

Microglia

Microglia are the resident immune cells of the CNS, with the most pronounced diversity during CNS development and following disease or injury.[51] Though the primary source of central GLP-1 stems from the NTS, GLP-1-positive cells colocalize with the microglial marker CD11b and are seen in the mouse cortex, indicating a distinct expression of GLP-1 compared to canonical GLP-1-expressing NTS neurons.[52] In microglia, GLP-1R activation reverses microglial polarization from M1 to M2 subtypes by suppressing AKT and nuclear factor κB (NF-κB) phosphorylation, thereby mitigating microgliosis and astrogliosis.[53,54] This reversal

leads to enhanced neurite complexity and spine morphology in primary cortical neurons.[54] Additionally, the activation of microglial GLP-1R in the trigeminal nucleus caudalis suppresses the central sensitization of chronic migraine by inhibiting the downstream PI3K/AKT pathway.[55] This inhibits microglial cell proliferation, morphological changes, and inflammatory cytokine production, further supporting the role of GLP-1 in inducing a quiescence state in microglial cells.[55] Intriguingly, the neuroprotective effects against microglia-mediated inflammation in neurodegenerative diseases are observed upon the activation of microglial GLP-1R.[56] In a mouse model of sporadic Parkinson's disease, treatment with NLY01 protects against dopaminergic neuronal loss and motor dysfunction primarily through the inhibition of microglial-mediated conversion of astrocytes to an A1 neurotoxic phenotype.[57] However, in a 36-week randomized, double-blind, placebo-controlled study, treatment with NLY01 in participants with early untreated Parkinson's disease did not lead to improvements in motor or non-motor features compared with placebo.[58] It is possible that reduction in microglial activation and astrocytic conversion alone might not alter pathology. Whether modulation of glial activity is more robust in younger participants remains to be elucidated. To conclude, GLP-1R signaling on microglia attenuates neuroinflammation by suppressing the polarization of microglia to a proinflammatory state.

Oligodendrocytes

Myelin is the structure that surrounds individual axons and maintains saltatory impulse propagation.[59] The insulation provided by myelin not only enhances the speed of electrical conduction but also acts as a protective barrier, shielding axons from potential damage caused by external forces or inflammatory responses. Oligodendrocytes are the CNS glial cells responsible for assembling myelin and providing metabolic support to myelinated axons. Using single-cell RNA sequencing, GLP-1R expression in oligodendrocytes is found in the hypothalamus.[60] Mature oligodendrocytes ($Olig2^{+}PDGFRa^{-}$) express GLP-1R in the corpus callosum.[61] Whether GLP-1 has a direct effect on oligodendrocyte and myelin homeostasis or an indirect effect by regulating other components of the NVU still requires clarification. Future studies aimed at characterizing GLP-1R expression in oligodendrocytes on a brain-wide scale will allow us to understand the functions of GLP-1R signaling in oligodendrocytes with spatiotemporal specificity and how this signal is integrated with the rest of the NVU.

Endothelial cells

The brain is one of the most highly perfused organs.[62] Intriguingly, it forms a fundamental structure, the BBB, which selects the size and type of molecules that can access the brain parenchyma. While fundamental for brain function, such a barrier frustrates pharmacological interventions. Importantly, in the context of this review, both GLP-1 and GLP-1R agonists are capable of crossing the BBB.[63] Structurally, the brain vascular layer is comprised of endothelial cells, adjacent vascular smooth muscle cells (VSMCs), and pericytes. Central endothelial GLP-1R regulates the uptake of GLP-1 and its analog into the brain parenchyma.[64] GLP-1R agonists prevent tight junction protein degradation, a protective feature for ischemic stroke in middle cerebral artery occlusion (MCAO) and injury models. This process is achieved via binding to endothelial GLP-1R and stabilizing the BBB.[65] Colocalization of GLP-1R with endothelial cell marker von Willebrand factor (vWF) is observed on microvessels of the ipsilateral basal cortex after subarachnoid hemorrhage induction.[66] Moreover, glutamate excitotoxicity plays a vital role in causing neuronal death during ischemic stroke and is implicated in various neurodegenerative disorders. Studies on animal models of stroke show that administering exendin-4 and liraglutide, either before or after cerebral ischemia, can reduce infarct size, alleviate oxidative stress, and enhance endothelial function.[67] The combination of single-cell RNA-sequencing analysis and immunostaining unveils a high expression of GLP-1R in mouse retinal endothelial cells, which is reduced under diabetic conditions.[68] Treatment with GLP-1R agonist exendin-4 restores receptor expression and leads to improvements in retinal degeneration, vascular tortuosity, avascular vessels, and vascular integrity. Due to the similarity between the retinal and brain vasculature, this finding begs the question of whether GLP-1R's protective effects on retinal endothelial cells can also be observed in brain endothelial cells in the context of metabolic dysfunction. Whether endothelial cells regulate the uptake of endogenous GLP-1 in the context of a strong stimulus to mediate energy balance remains unknown. Further elucidation of GLP-1R signaling in endothelial cells can assist in the explanation of stimulus-dependent endogenous GLP-1 transport to and signaling in the brain.

Mural cells

Mural cells are the counterparts to endothelial cells, located on the abluminal side of the vasculature.[69] The advent of novel tools, including high-resolution intravital optical imaging, calcium imaging, and single-cell transcriptome analysis, has allowed the classification of this heterogeneous cell population.[70] The two broad types of mural cells are VSMCs and pericytes. VSMCs surround 15% of the brain microvessels, primarily arterioles and precapillaries, and express the contractile smooth muscle protein actin. Pericytes, on the other hand, surround 85% of the microvasculature, primarily capillaries, and do not express smooth muscle actin. In the hypothalamus, GLP-1R-expressing mural cells are largely VSMCs, while glucose-dependent insulinotropic polypeptide receptor (GIPR)-expressing mural cells are mostly pericytes.[60] Additionally, GLP-1Rs are expressed by VSMCs lining cortical arterioles.[71] Importantly, the demonstrated protection accomplished by GLP-1R agonism on ischemic stroke may result from vasodilation, impacting tissue perfusion of the infarcted brain tissue—a mural-mediated effect. Transcriptomic assessment quantifies a significant increase in receptor expression under diabetic conditions.[72] Activation of GLP-1R enhances pericyte function, restoring vascular integrity and BBB permeability in diabetic conditions. Exendin-4's effects on alleviating diabetes-induced cognitive impairment in rodents can arise from this mechanism. Recent studies outline a protective role of GLP-1 on pericytes in diabetic retinopathy. In diabetic rats, treatment with GLP-1R agonist lixisenatide prevents retinal pericyte loss.[73] These discoveries uncover the existence of GLP-1R on retinal pericytes.[74] Further investigations on GLP-1R signaling in both brain and retinal pericytes will allow the comparison between regional-specific actions of GLP-1R on the BBB and blood-retinal barrier (BRB).

Overall, the role of GLP-1R signaling on central vascular cells remains relatively unknown in comparison to the peripheral vasculature. Similarly, vascular dysfunction in obesity and metabolic

syndrome has been primarily focused on the periphery. In the following sections, we highlight the effects of overnutrition and obesity on the brain microvasculature and propose microvascular dysfunction as a nexus between obesity and neurological diseases.

OBESITY-INDUCED NEUROVASCULAR UNCOUPLING AND MICROVASCULAR DYSFUNCTION

A hallmark of human obesity is chronic exposure to a high-fat diet (HFD), which can trigger neuroinflammation and cognitive decline, posing a risk factor for neurodegeneration. A HFD's impact on the cerebral vasculature includes compromised BBB integrity and neurovascular uncoupling and remodeling.[75–78] Higher BMI is associated with decreased cerebral perfusion in resting and concentration single-photon emission computed tomography scans.[79] Young adults with metabolic syndrome exhibit decreased macrovascular and microvascular cerebral blood flow (CBF) due to smaller vessel cross-sectional area and lower mean blood velocity.[80] The CBF reduction is attributed to a loss of cyclooxygenase (COX) vasodilation, with similarities in cerebrovascular impairments observed in middle-aged adults with metabolic syndrome.[81,82] The reduction in CBF in younger adults with metabolic syndrome mirrors the reduction seen in normal aging for middle-aged adults, indicating that metabolic syndrome accelerates cerebrovascular health deterioration.[83] Additionally, the albumin quotient, indicating the ratio of cerebrospinal fluid (CSF) albumin to serum albumin, is higher in patients with type 2 diabetes mellitus (T2DM), positively correlating with CSF biomarkers of angiogenesis and endothelial cell dysfunction such as vascular endothelial growth factor (VEGF).[84] While it is evident that reduced CBF serves as a marker for vascular dysfunction, it is crucial to emphasize that both an increase and decrease in CBF can indicate a shift in homeostasis and act as markers for a disease state.[85]

The ability of overnutrition to shape the neurovascular landscape raises questions about the reversibility of diet-induced microvascular dysfunction. As for all interventional studies, it is crucial to determine the appropriate age of the subjects and the optimal dose and length of treatment. For example, in juvenile mice, 8 weeks of HFD is insufficient to induce neurovascular impairments; however, alterations are observed after 16 weeks of HFD.[86] Likewise, 11 weeks of HFD leads to cognitive impairments only in juvenile mice but not in adult mice.[87] These discrepancies in phenotypes are crucial to avoid any false positives and negatives. With that in consideration, recent studies have demonstrated improvements in diet-induced NVU impairments using pharmacotherapy. Treatment with telmisartan, a common angiotensin II receptor blocker, normalizes diet-induced neurovascular uncoupling and CBF reduction in juvenile mice.[86] The potential to use GLP-1R agonism as a pharmacological tool to shape the neurovascular landscape is explored in the following sections.

GLP-1R AGONISM REPAIRS METABOLIC-ASSOCIATED NEUROVASCULAR UNCOUPLING AND MICROVASCULAR DYSFUNCTION

The extensive impact of central GLP-1 on feeding behavior, glucose homeostasis, and cognitive function prompts an exploration of the mechanisms through which GLP-1 enacts its extensive neurophysiological effects. This section dives into the impact of GLP-1 signaling on the intricate relationship between the neuro-glial-vascular unit.

Postprandial increases in plasma GLP-1 align with increased regional CBF in the left dorsolateral prefrontal cortex and hypothalmaus.[88] Under basal and hyperglycemia conditions, GLP-1 (1–37) improves BBB integrity, elevating the expression of the tight junction proteins occludin and claudin-5 via the cyclic AMP/protein kinase A (PKA) pathway in cultured brain microvascular endothelial cells (BMVECs).[65] In HFD-fed mice, exenatide (a long-acting GLP-1R agonist) mitigates cortical neuroinflammation and behavioral deficits by modulating microglial M2 polarization.[89] Cultured human astrocytes treated with exenatide exhibit reduced glial fibrillary acidic protein (GFAP) expression in both normo- and hyperglycemic conditions.[90] Treating diabetic rats with exendin-4 ameliorates functional and structural alterations in the BBB and blood-CSF barrier by increasing protein levels of tight junctions and aquaporins.[91] In patients with T2DM, liraglutide demonstrates cognitive improvement by activating the dorsolateral prefrontal cortex and orbitofrontal cortex brain regions.[92] Liraglutide treatment also reverses the reduced diameter and functional density of brain capillaries in HFD-fed rats.[93] In streptozotocin (STZ)-induced diabetic rats, liraglutide attenuates inflammatory markers in the cerebral microvasculature without impacting blood glucose levels or body weight.[94] In a mixed murine model of Alzheimer's disease (AD) and T2DM, 20 weeks of liraglutide administration reduces vascular damage, brain atrophy, and neuronal loss and alleviates cognitive impairment.[95] Linagliptin, a dipeptidyl peptidase-4 inhibitor, improves diabetes-induced cerebrovascular dysfunction by reducing endothelin-1 (ET-1) plasma levels and cerebrovascular hyperreactivity.[96,97] In 12-month HFD-fed mice, linagliptin treatment restores BBB integrity and pericyte coverage and counters the angiogenic effect of T2DM.[98] Moreover, using diabetic Goto-Kakizaki rats, treatment with linagliptin for 4 weeks restores cerebral perfusion and improves insulin-induced cerebrovascular relaxation and vascular remodeling but does not affect short-term hippocampus-dependent learning.[99] In this case, the lack of cognitive improvement might be attributed to the duration of intervention. Linagliptin does not cross the BBB and increases GLP-1 levels; therefore, its associated neuroprotection is hypothesized to arise from GLP-1R signaling.[100] Notably, chronic linagliptin treatment demonstrates neuroprotective effects even in mice lacking GLP-1Rs, suggesting a central action for linagliptin beyond its role in incretin regulation.[101]

In sum, GLP-1R agonism demonstrates promising effects to counteract obesity-induced neurovascular uncoupling and microvascular dysfunction by ameliorating CBF, BBB integrity, and vascular remodeling in humans, rodents, and *in vitro* models (Figure 2). A pilot study assessing the effect of a single dose of exenatide on healthy nondiabetic subjects found no effect on cerebral and peripheral vasculature or on inflammatory biomarkers.[102] This indicates that the effect of GLP-1R agonism on NVC and the cerebral vasculature might require long-term treatment in the context of metabolic shifts to have a clinically relevant effect. Further research is needed to optimize the onset

and duration of GLP-1R agonism to both prevent and treat an altered microvasculature.

EFFECT OF METABOLIC DYSFUNCTION ON CEREBROVASCULAR RISK AND RECOVERY

Cerebral ischemia-reperfusion injury (CIRI) exacerbates stroke outcomes due to rapid reperfusion, posing a persistent challenge in recovery due to the limited treatment options and a narrow time window for intervention.[103] The obesity paradox suggests better cardiovascular outcomes for patients with obesity or overweight compared to lean individuals,[104] a notion that is still debated in the cerebrovascular field. This pattern is also seen in AD, where midlife weight gain increases the risk of neurological complications, while late-life weight gain is proposed as a protective factor.[105] Metabolic syndrome prevalence worsens cerebral microvascular rarefaction and endothelial dysfunction induced by CIRI.[106] In rats, early exposure to HFD correlates with impaired NVC and cerebrovascular dysfunction, leading to increased cerebral injury and unfavorable stroke outcomes.[107] Hyperglycemia, an independent risk factor for poor ischemic stroke outcomes, heightens BBB disruption and activates matrix metalloproteinase-9 (MMP-9), a family of extracellular matrix remodeling endopeptidases.[108,109] Inhibiting MMP-9 activity counteracts HFD-induced cerebrovascular remodeling, reducing hemorrhagic volumes and improving neurological outcomes post-stroke.[109] Hyperglycemia also elevates hypoxia-inducible factor 1 alpha (HIF-1α) and VEGF expression, markers of angiogenesis, in brain microvessels after ischemic reperfusion.[110] Knocking out endothelial HIF-1α ameliorates BBB leakage and brain infarction in diabetic mice.[110] Hyperbaric oxygen preconditioning attenuates brain infarct and hemorrhagic transformation (HT) by downregulating HIF-1α and MMP-1 in hyperglycemic MCAO rats.[111] Weight loss before stroke enhances recovery by normalizing fasting glucose and insulin resistance.[112] With T2DM being a major risk factor for stroke development, diabetes treatments addressing cerebrovascular risk and recovery have garnered significant attention. To optimize interventions, understanding spatiotemporal variations in cerebrovascular changes associated with metabolic-induced neurological impairments is essential for targeted interventions.[113]

REPURPOSING OF GLP-1 AGONISTS FOR THE TREATMENT OF CEREBROVASCULAR DISEASES

Stroke

Stroke stands as a major contributor to both fatalities and incapacitation, placing a substantial economic burden on Western societies.[114] Thrombolysis has been a standard treatment for acute ischemic stroke for a quarter century. However, its efficacy is confined to less than 10% of patients treated within a 4-h window from stroke onset.[115] In recent decades, endovascular thrombectomy has emerged as a valuable therapy, showcasing benefits in early recanalization and reperfusion, but its widespread use and enduring effectiveness remain constrained.[116] Despite these strides, there persists a need for neuroprotective agents to extend the treatment time window and enhance functional outcomes in ischemic stroke. Diabetes exacerbates the risk of stroke and is implicated in roughly 20% of diabetes-related deaths, underscoring the interconnected mechanisms of diabetes and stroke. Given the broad usage of GLP-1R agonists for the treatment of obesity and T2DM and its roles in neuroprotection, it offers a promising avenue for future therapeutic breakthroughs in cerebrovascular therapy. In a mouse cerebral ischemia model, there is an increase in GLP-1R expression in the CA1 region after stroke, suggesting a compensatory mechanism for neuronal protection.[117] Interestingly, GLP-1R expression exhibits a biphasic response, peaking within 24–48 h after the ischemic insult, followed by a drop, and then a subsequent increase after 1–2 weeks.[117] This biphasic response parallels findings for VEGF-A in response to ischemia.[118] However, conflicting reports indicate a decrease in GLP-1R expression at various time points after stroke induction.[119] A possible explanation is that GLP-1R expression increases as a compensatory mechanism to the physiological insult and drops back to the homeostatic level after vascular remodeling is established. The parallelism between GLP-1R and VEGF-A expressions further reinforces the link between GLP-1R signaling and cerebral vascular plasticity.

Preclinical studies indicate treatment with GLP-1R agonists as potential complementary interventions to canonical cerebrovascular interventions. Exendin-4 treatment in hyperglycemic mice inhibits MMP-9 activation, reducing infarct growth after cerebral ischemia.[108] In a rat MCAO model, exendin-4 attenuates neurological deficits, brain edema, infarct volume, and BBB permeability, attributed to GLP-1R activation of the Wnt/β-catenin signaling pathway involved in sprouting and nonsprouting angiogenesis, vasculogenic mimicry, and mosaic vessel formation.[120,121] This pathway inhibits MMP-9 activation, lowers reactive oxygen species (ROS), and mitigates leukocyte infiltration.[120] Exendin-4's protective effects extend to cortical arterioles with lasting increases in brain tissue partial pressure of oxygen (pO_2) via modulation of CBF.[71] Warfarin-associated HT after cerebral ischemia is a consequence attributed to increased BBB permeability.[122] Exendin-4 ameliorates warfarin-associated HT, preserves BBB integrity, and suppresses oxidative DNA damage, lipid peroxidation, microglial activation, and neutrophil infiltration through the inhibition of the PI3K/AKT/glycogen synthase kinase 3 beta (GSK-3β) pathway.[122] Astrocyte-dependent mechanisms mediate exendin-4's ability to preserve BBB integrity, reducing astrocyte-derived VEGF-A and increasing tight junction protein expression.[123] Chronic exendin-4 treatment normalizes microvessel density, pericyte coverage, and fibrotic scar formation in MCAO T2DM mice.[124] In retinal ischemia-reperfusion injury, exendin-4 suppresses BRB breakdown by targeting inflammatory genes (e.g., interleukin-1 beta [IL-1β], tumor necrosis factor alpha [TNF-α], and C-C motif chemokine ligand 2 [CCL2]).[125] Long-lasting exendin-4-loaded microspheres demonstrate greater improvement in various neurovascular parameters when compared to regular exendin-4, such as cortical CBF, cerebral microcirculation, cognitive deficits, brain edema area, and levels of ROS, aquaporin, and GFAP expression.[126] In an acute ischemic stroke, liraglutide dose-dependently reduces infarct size.[127] Proteomics mass spectrometry analysis post-MCAO in mice reveals alterations in oxidative stress, cell growth, apoptosis, and inflammatory response after liraglutide administration.[128] The neuroprotective effect of liraglutide involves inhibiting

pyroptosis via the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3)/Caspase-1/IL-1β pathway.[129] GLP-1R knockdown abolishes liraglutide's protective effect, implicating nuclear factor erythroid 2-related factor 2 (Nrf2) activation and M2 polarization.[130] NLRP3 inhibition improves diabetes-mediated cognitive impairment and vascular integrity, preventing the hypoxia-mediated decrease in BDNF (brain-derived neurotrophic factor) secretion.[131] GLP-1 alleviates NLRP3 inflammasome-associated inflammation in perivascular adipose tissue, suggesting a similar interaction between GLP-1 and NLRP3 in the cerebral vasculature.[132] Of note, BDNF-mediated mitophagy alleviates hyperglycemia-induced BMVEC injury.[133] Interestingly, GLP-1R/BDNF/(tropomyosin receptor kinase B) TrkB signaling modulates hippocampal neuroplasticity in HFD-induced diabetic mice,[134] contributing to GLP-1's neuroprotective effects on cerebrovascular remodeling.[134–136] In diabetic rats with MCAO, treatment with liraglutide augments Nrf2 and heme oxygenase 1 (HO-1) expression in the cerebral ischemic tissue.[137] Pretreatment for 2 weeks reduces infarct volume in both diabetic and nondiabetic rats,[138] while post-treatment enhances VEGF expression without altering cortical CBF.[139] Delayed administration of liraglutide improves microvessel density and endothelial cell proliferation and upregulates the expression of VEGF.[140] When the administration is extended, liraglutide treatment increases the number of neuronal nuclei, GFAP, vWF, and GLP-1R in the cerebral ischemic area.[141] In both delayed scenarios, there is neurovascular remodeling accompanied by improvements in glucose metabolism and neurological function.[140,141] Both exendin-4 and liraglutide enhance CBF and reduce oxidative stress and cognitive deficits in MCAO diabetic mice.[142] In short, GLP-1's influence on the cerebral vasculature is primarily mediated by its anti-inflammatory properties that prevent detrimental insults from an overactive inflammatory response.

Other GLP-1 analogs also have been demonstrated to reduce ischemic damage after CIRI. Semaglutide, with a longer half-life than liraglutide, demonstrates greater protection against ischemic damage.[127] Semaglutide treatment reduces inflammatory M1 microglia and A1 astrocytes after ischemic stroke.[143] In this context, complement (C)3d$^+$ A1 astrocytes block BBB permeability in the neuroinflammatory response. The capability of semaglutide to block the astrocyte phenotype conversion suggests that GLP-1R agonists may treat uncontrolled neuroinflammatory-induced neurological disorders[143] since the extinction of neuroinflammation is complemented by improved growth factor signaling and neurogenesis in hippocampal areas.[144] Immediate and delayed lixisenatide treatment, an analog of exenatide, upregulates VEGF and endothelial nitric oxide synthase (eNOS) expression. This effect is blocked by exendin (9–39).[145] Similarly, lixisenatide administration in diabetic rats reduces cerebral infarct volume, neuronal apoptosis, oxidative stress, and inflammation.[146,147] Chronic treatment with linagliptin pre- and post-stroke decreases ischemic brain damage in both middle-aged diabetic and nondiabetic mice.[148] In the genetically diabetic-obese (*db/db*) mice, chronic post-treatment with linagliptin improves CBF, BBB integrity, and cognitive performance and attenuates cerebral oxidative stress and brain atrophy.[149] The improvement in functional outcome after stroke is attributed to the stromal cell-derived factor 1 alpha (SDF-1α)/C-X-C motif chemokine receptor 4 (CXCR4) pathway involved in wound healing, angiogenesis, and proliferation.[150,151] Using *in vitro* BMVECs, linagliptin ameliorates the lack of proliferative and migratory abilities of BMVECs by enhancing the sirtuin 1 (SIRT1)/HIF-1α/VEGF pathway.[152] Sitagliptin, with a shorter half-life relative to linagliptin, offers protection against CIRI through the GLP-1R-mediated transient recptor potential (TRP)/calcitonin gene-related peptide (CGRP) signaling pathway involved in vasodilation.[153,154] Of note, overexpression of CGRP protects against hyperglycemia-induced BMVEC damage by suppressing extracellular signal-regulated kinase (ERK)/HIF-1/VEGF signaling.[155] The pathways mediated by GLP-1R signaling converge into a common theme: anti-inflammatory-mediated cerebral vascular remodeling.

Traumatic brain injury

Compared to CIRI, traumatic brain injury (TBI) due to mechanical impact is caused by different primary insults with similarities in the pathogenesis of these cerebral injuries.[156] TBI induced by controlled cortical impact (CCI) mimics cerebral edema seen in human TBI. Chronic HFD feeding worsens functional outcomes and decreases brain recovery post-TBI by aggravating neuroinflammation and oxidative stress.[157] Higher plasma GLP-1 levels are associated with a greater risk of TBI-induced mortality and may indicate severe central resistance to endogenous GLP-1 in non-survivors compared to survivors.[158] Expression of GLP-1R levels decreases significantly after TBI.[159] Exendin-4 restores BBB integrity, reduces neuronal apoptosis, and improves cognitive impairment after mouse TBI induction.[160] A similar effect is seen in rats, with exendin-4 treatment promoting neurological, cognitive, and CBF recovery by attenuating inflammatory responses.[161] Impairment of the glymphatic system is a major contributor to the neuropathological changes and cognitive impairment following TBI due to the accumulation of various neurotoxic substances such as amyloid beta and tau protein.[162] Intriguingly, GLP-1R activation in TBI improves glymphatic system dysfunction, alleviating reactive astrogliosis and loss of perivascular aquaporin-4.[160] Post-treatment with liraglutide after CCI improves BBB integrity and sensorimotor function, reduces cerebral edema, and limits cortical tissue loss.[163,164] Neuroinflammation reduction is evident in lower microglial expression, although astrogliosis remains unaffected, possibly due to the observed time point.[165] Additional research contrasting the effect of GLP-1R agonism on different types of cerebrovascular disease will clarify the overlapping and distinct pathways impacted by GLP-1's anti-inflammatory-induced vascular plasticity.

Overall, repurposing GLP-1 for cerebrovascular diseases offers an innovative approach to address these challenging health issues (Figure 3). More research is needed to explore the usage of other metabolic drugs, such as sodium/glucose cotransporter 2 (SGLT2) inhibitors and metformin, to lower cerebrovascular risk factors and treat cerebrovascular diseases and their associated comorbidities.

EXTENSION OF NEUROVASCULAR REMODELING TO MYELINATION AND CSF DYNAMICS

The capability of GLP-1 to influence the neurovascular landscape suggests a connection to its role in mediating cognitive

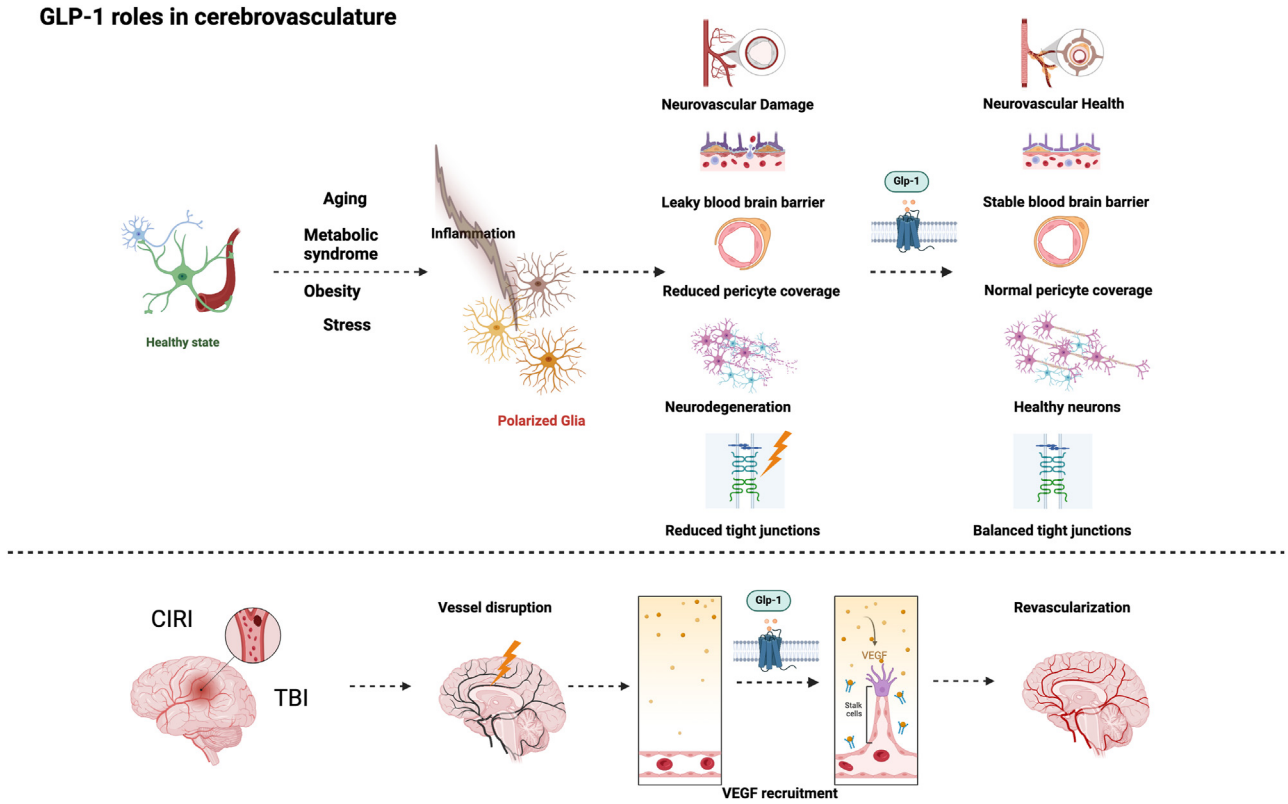

Figure 3. GLP-1 ameliorates neurovascular uncoupling and promotes cerebrovascular remodeling

GLP-1R signaling ameliorates obesity-induced neurovascular uncoupling and cerebrovascular risk through improvements in CBF, BBB integrity, and vascular remodeling. Treatment with GLP-1R agonists in both humans and rodents mitigates glial polarization and neuroinflammation. The induction of an anti-inflammatory state reduces vascular damage and neuronal loss and increases tight junction expression, pericyte coverage, and insulin-induced cerebrovascular relaxation. GLP-1 treatment upregulates the expression of VEGF and induces vascular plasticity in cerebrovascular diseases such as CIRI and TBI.

function, as neurovascular dysfunction is correlated with cognitive impairments in various neurological diseases.[166] Alterations in the brain vasculature correlate with changes in myelin composition, impacting cognitive performance.[167,168] Chronic overnutrition is associated with lower white matter integrity and cerebral myelin content,[169] indicating a possible link between obesity and neurological diseases.[170] Consumption of excess HFD leads to oligodendrogliopathy and impedes oligodendrocyte differentiation in the brain and spinal cord.[171] HFD-induced demyelination is mediated through astrocyte-linked indirect nicotinamide adenine dinucleotide (NAD^+)-dependent mechanisms.[172] Inhibition of cluster of differentiation 38 (CD38), an NAD^+-degrading enzyme, enhances remyelination in regular chow-fed mice and increases astrocytic expression of *Glp1r* and *Igf1*, indicating improved lipid metabolism and insulin signaling.[45,172] While a minimal effect of CD38 inhibition is seen in HFD-induced demyelination, a combination of CD38 inhibitor and GLP-1R agonist might work in tandem to induce remyelination in obesity. Moreover, caloric restriction promotes remyelination by increasing oligodendrocyte survival and differentiation and decreasing astrogliosis and microgliosis.[173] Supplementation with nicotinamide, a caloric restriction mimetic, induces myelin production and ameliorates gliosis.[174] The intimate link between the brain vasculature and nutrient consumption on myelin composition indicates that GLP-1 might have an impact on the myelination process.

Myelination

Neurovascular dysfunction with BBB breakdown and reduced CBF is a prominent feature in demyelinating diseases, and therapeutics to modulate the NVU is a potential avenue for preventing demyelination and inducing remyelination.[175] Obesity is a risk factor for multiple sclerosis (MS), and obesity in patients with MS is associated with higher disease severity and a poorer outcome.[176] GLP-1's impact on myelination is evident in preclinical studies where GLP-1R agonists promote remyelination in models of MS. In a cuprizone-induced mouse model of MS, co-treatment with cuprizone and liraglutide for 4 weeks induces remyelination by stimulating oligodendrocyte progenitor cell (OPC) differentiation via anti-inflammatory mechanisms.[177] Co-treatment with cuprizone and NLY01 does not impact demyelination in the corpus callosum.[61] Additionally, post-treatment with NLY01 after cuprizone intoxication does not alter myelin composition or the number of mature oligodendrocytes.[61] Of note, the inflammatory environment and immune trafficking are stable between the vehicle and the treated groups, indicating that post-treatment with NLY01 fails to minimize neuroinflammation and might overshadow its direct impact on oligodendrocytes. In a chronic experimental autoimmune encephalomyelitis (EAE)

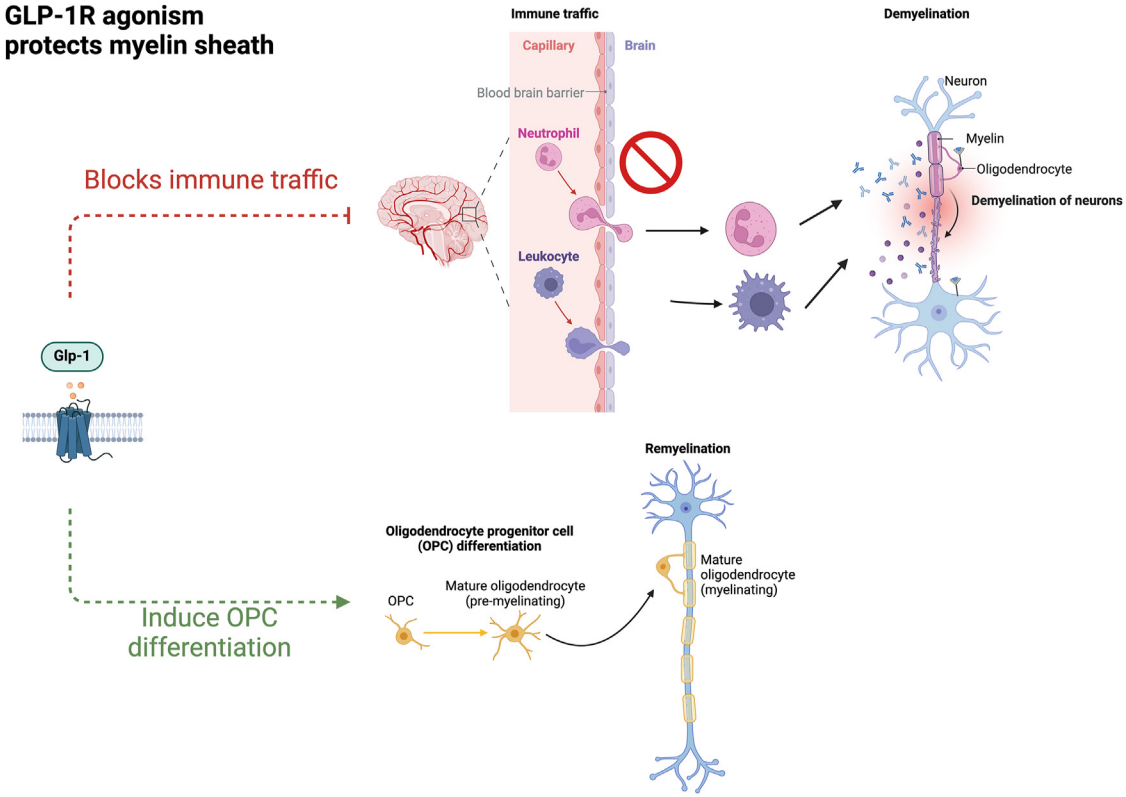

Figure 4. GLP-1 restores CNS remyelination capacity
GLP-1R agonism enhances remyelination by stimulating OPC differentiation. Treatment with GLP-1R agonists inhibits immune cell trafficking into the CNS and attenuates inflammation-induced demyelination.

mouse model of MS, pretreatment with NLY01 delays the onset and attenuates the severity of EAE by inhibiting immune cell trafficking into the CNS.[178] The reduction in leukocyte recruitment is likely attributed to the anti-inflammatory effects of NLY01, leading to improvements in BBB integrity. In symptomatic EAE mice, treatment with exendin-4 leads to remyelination in the lumbar spinal cord.[179] Linagliptin reduces cuprizone-induced demyelination by modulating the adenosine 5′ monophosphate-activated protein kinase (AMPK)/SIRT1 and Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3)/NF-κB pathways.[180] The potential of GLP-1R agonism to prevent demyelination or induce remyelination is promising, with further research needed to dissect the role of GLP-1R signaling on oligodendrocytes and OPCs (Figure 4). Whether GLP-1 has a direct effect on myelin composition or indirectly through the alterations of the other components of the NVU remains to be elucidated.

Glymphatic homeostasis

The intricate relationship between GLP-1R signaling and the cerebral vasculature extends to CSF dynamics, crucial for nutrient delivery and waste removal. Neuronal activity-induced functional hyperemia drives CSF dynamics during sleep, and neural activity driven by visual stimulation modulates CSF flow, emphasizing the role of a healthy cerebral vasculature in maintaining cerebral metabolic levels and turnover.[181,182] Interestingly, dynamic changes in arterial diameter in the absence of neural activation drive perivascular glymphatic CSF inflow and clearance.[183] Furthermore, alterations in CSF homeostasis and intracranial pressure (ICP) heighten the susceptibility to and are observed in various neurological diseases.[184] In T2DM rats, glymphatic dysfunction contributes to cognitive decline by hindering the clearance of neurotoxic molecules.[185,186] Idiopathic intracranial hypertension (IIH), characterized by increased ICP and optic disc swelling, is linked to CSF circulation failure and sinus vein obstruction.[187,188] Obesity is a major risk factor for IIH development, with greater occurrence in women with obesity.[189] In overweight women with IIH, there is an increase in intracranial CSF volume that accumulates in the extraventricular subarachnoid space with greater venous outflow resistance.[190] In rats, HFD increases CSF secretion without changes in the resistance to CSF drainage compared to the control diet.[191] The sexual dimorphic phenotype is observed only in female rats, consistent with the high rates of female patients with IIH and obesity, and demonstrates a 55% increase in ICP.[192] Importantly, weight loss interventions are effective approaches to minimize the risk of IIH and treat patients with IIH.[193] GLP-1R agonism demonstrates potential in IIH management, with GLP-1R expression in the choroid plexus influencing CSF secretion.[194] In fact, exendin-4 modulates CSF production *in vitro*.[194] In rodents, this CSF lowering effect translates into exendin-4 reducing ICP in a dose-dependent manner, with effects lasting for 24 h.[194] Intriguingly, clinical studies support the efficacy of GLP-1R agonists in reducing

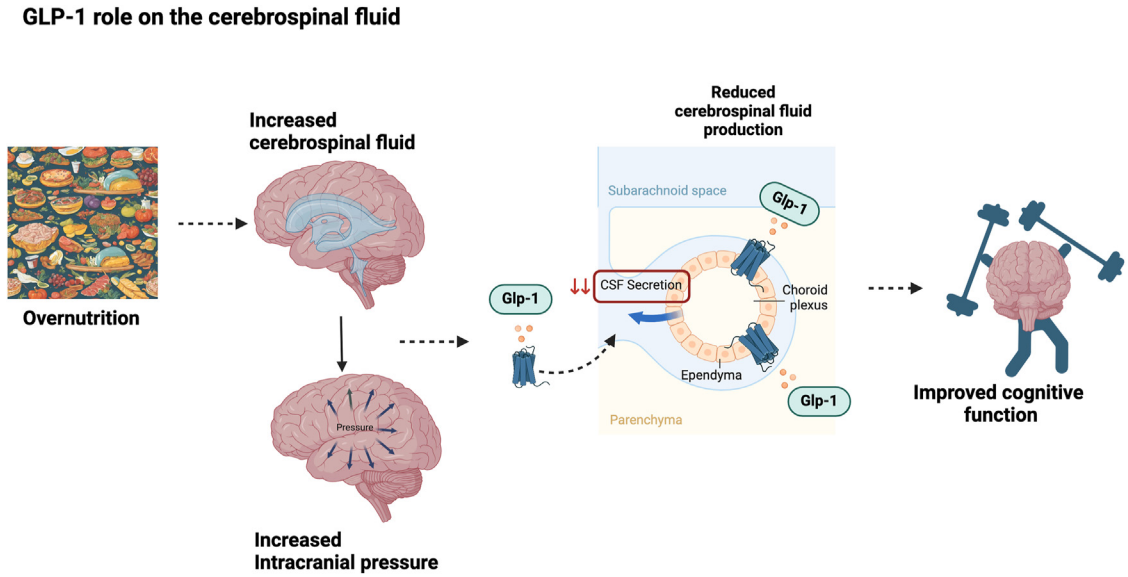

Figure 5. Modulation of glymphatic flux via GLP-1 treatment

Chronic overnutrition increases CSF secretion and ICP, which increases the risk of neurological complications. GLP-1R expression on the choroid plexus functions as a dial that reduces CSF secretion. In human and rodent studies, GLP-1R agonism is capable of lowering CSF secretion and ICP, resulting in improved cognitive function.

ICP, highlighting their potential in treating conditions with elevated ICP. For instance, a case report of IIH caused by Ramadan intermittent fasting led to the hypothesis that a drop in GLP-1 concentration triggers a decrease in GLP-1R activation in the choroid plexus.[195] This results in increased CSF secretion and ICP. Furthermore, in a phase II randomized, double-blind, placebo-controlled trial, exenatide treatment results in clinically meaningful reduction in ICP with improvements in headaches and visual acuity.[196] Unsurprisingly, GLP-1R agonism is now being explored in IIH as a phase III clinical trial to overcome raised ICP (NCT05347147). Lastly, in an open-lab, single-center, case-control pilot study, supplementing semaglutide or liraglutide with usual care weight management improves headache frequency compared to usual care weight management alone.[197] In patients with IIH after bariatric surgery, there is an association between a reduction in ICP and an increase in meal-stimulated GLP-1 levels.[198]

Together, it is evident that GLP-1R signaling impacts CSF dynamics and ICP (Figure 5). Commonly used off-label ICP-lowering drugs, such as acetazolamide, spironolactone, and topiramate, worsen cognitive function. However, treatment with exenatide in a cohort of patients with IIH reduces ICP without affecting cognition.[199] Nevertheless, while these results are encouraging, whether GLP-1R agonism can improve cognitive function through a decrease in ICP for IIH still needs to be validated. Evaluating the mechanistic differences of GLP-1R signaling on various neurological conditions characterized by increased ICP is a critical first step. The capacity of GLP-1 to impact the glymphatic system is currently an early but promising approach to target neurological disorders with glymphatic dysfunction. Being that the glymphatic system is intimately intertwined with the neuro-glial-vascular unit, cerebral vasculature, and myelin composition, the potential of GLP-1 to affect all these different modalities of the brain due to a positive domino effect highlights GLP-1 as an ideal representative of drug repurposing.

CONCLUSIONS

The intimate link between metabolic and cognitive health sheds light on brain-body communication and redefines certain disorders as neurometabolic. The concept of repurposing antidiabetic drugs for the treatment of neurological diseases is gaining popularity, with metabolic disorders being a major risk factor for neurodegeneration. In recent years, repurposing of GLP-1 mimetics to treat neurological diseases holds promise due to their anti-inflammatory, neuroprotective, and neurotrophic properties. The expression of GLP-1R on diverse cell types and its ability to influence the neurovascular landscape make GLP-1 an ideal candidate to bridge the brain-body and neuro-metabolic crosstalk. Whether GLP-1's effects on these cell types are direct or indirect still requires further clarification, as well as the precise mechanisms by which GLP-1 activates NVC, cerebral vascular remodeling, myelination, and CSF dynamics. A deeper understanding of the pivotal role played by GLP-1R signaling enhances the potential to address both metabolic and neurological disorders, potentially complementing treatments for both types of conditions simultaneously.

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DECLARATION OF INTERESTS

A.M.J. serves on scientific/medical advisory boards for Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Pfizer, Rhythm Pharmaceuticals, WW, and IntelliHealth; serves as a consultant for Scholar Rock; and receives institutional research support from Eli Lilly, Novo Nordisk, and Rhythm Pharmaceuticals. M.H.T. was a Research Cluster Advisory Panel (ReCAP) member of the Novo Nordisk Foundation between 2017 and 2019. He received funding for his research projects by Novo Nordisk (2016–2020) and Sanofi-Aventis (2012–2019). He consulted twice for Boehringer Ingelheim Pharma GmbH & Co. KG (2020 and 2021) and delivered a scientific lecture for Sanofi-Aventis Deutschland GmbH (2020). As CEO and CSO of Helmholtz Munich, he is co-responsible for numerous collaborations of the employees with many companies and institutions worldwide. In this capacity, he discusses potential projects with and has signed/signs contracts for the Helmholtz institute(s) related to research collaborations worldwide, including but not limited to pharmaceutical corporations like Boehringer Ingelheim, Novo Nordisk, Roche Diagnostics, Arbormed, Eli Lilly, SCG Cell Therapy, and others. As the CEO and CSO of Helmholtz Munich, he was/is further overall responsible for commercial technology transfer activities. M.H.T. and A.M.J. confirm that, to the best of their knowledge, none of the above funding sources or collaborations were involved in or influenced the preparation of this manuscript.

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