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REVIEW

GLP-1 Receptor Agonists in Neurological Disorders: From Mechanisms to Clinical Translation

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Abstract: Glucagon-like peptide-1 receptor agonists, or GLP-1RAs, have been used for years to treat type 2 diabetes and obesity. More recently, it has become clear that these receptors are widely distributed throughout the central nervous system (CNS), which has raised the possibility of repurposing these drugs for neurological disorders. In this review we go through the evidence across a range of neurological conditions, discuss the main mechanisms thought to explain their neuroprotective effects, and point out the hurdles that still need to be cleared before they can be used in the clinic. Preclinical work has been fairly consistent. These drugs activate the cAMP/PKA/CREB pathway to boost BDNF expression. They also turn on the PI3K/Akt pathway, which reins in GSK-3β and cuts down tau hyperphosphorylation. At the same time, they put the brakes on NLRP3 inflammasome activation in microglia and get AMPK dependent mitochondrial biogenesis and autophagy going. In animal models of Alzheimer's disease (AD), Parkinson's disease (PD), ischemic stroke, intracerebral hemorrhage (ICH), Huntington's disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), depression, epilepsy, and spinal cord injury (SCI), these cellular changes add up to less protein aggregation, less neuron loss, and better functional outcomes. Clinical data are harder to interpret. Some trials have shown modest improvements in cognition or motor function, but others have found no meaningful effect on disease progression. One thing that does not get enough attention is that different GLP-1 receptor agonists cross the blood–brain barrier at widely varying rates, and these differences could well explain why trial results have been so mixed. Looking ahead, getting these drugs into the clinic will depend on choosing the ones that actually reach the CNS, developing biomarkers that can predict who will respond, and designing trials that take disease heterogeneity into account. Seen this way, this review offers a practical framework for turning mechanistic insights into real patient benefit.

Keywords: GLP-1 receptor agonists, neuroprotection, neuroinflammation, Alzheimer's disease, Parkinson's disease

Introduction

Neurological disorders are a leading cause of death and disability worldwide and place a huge burden on patients, families, and healthcare systems.[1,2] The category covers a lot of ground. Some are slowly progressive neurodegenerative conditions like AD and PD. Others come on suddenly, like stroke. There are also immune mediated conditions such as multiple sclerosis and motor neuron diseases such as amyotrophic lateral sclerosis. Even though these conditions look different and have different causes, they seem to share some common underlying problems, including neuroinflammation, trouble with mitochondria, oxidative stress, and programmed cell death.[3–6] That overlap gives us a reason to look for drugs that might protect the brain across multiple diseases.

Right now, treatment options for most neurological diseases are pretty limited. For AD, doctors mostly use cholinesterase inhibitors and NMDA receptor antagonists. These drugs help a bit with symptoms, but they do not stop the disease from progressing.[7,8] For PD, levodopa can improve movement, but over time, it causes side effects and stops working as well.[9] In stroke, the clot busting drug tissue plasminogen activator (tPA) only works within a narrow time window, so only a small number of patients get any benefit.[10] For conditions like multiple sclerosis and amyotrophic

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lateral sclerosis, the treatments we have either calm the immune system or manage symptoms, but they cannot reverse the damage that is already been done.[11,12] Finding something that can slow down or stop these diseases is a really urgent goal in neurology.

Glucagon-like peptide-1 is a hormone that the gut releases after you eat. It helps keep blood sugar stable by boosting insulin, lowering glucagon, slowing down how fast the stomach empties, and controlling appetite.[13] Glucagon-like peptide-1 receptor agonists are drugs that copy what natural glucagon-like peptide-1 does. The class includes quite a few agents with different pharmacokinetic profiles including exenatide, liraglutide, semaglutide, dulaglutide, lixisenatide, and the dual GIP/GLP-1 receptor agonist tirzepatide.[14] It is worth distinguishing these drugs from other diabetes medications that also target the same pathway, such as dipeptidyl peptidase-4 (DPP-4) inhibitors which raise endogenous GLP-1 levels by stopping its breakdown, and experimental hybrid peptides.[15] These drugs were first made for type 2 diabetes, and later they got approved for obesity because they help people lose weight.

There is a pretty well-established link between metabolic problems and brain diseases. Type 2 diabetes and obesity raise the risk of several neurological disorders. They share things like oxidative stress, chronic inflammation, poor mitochondrial function, and weak insulin signaling. That connection has led some researchers to call Alzheimer's disease "type 3 diabetes".[16] GLP-1 receptors are found in key brain regions that handle cognition and energy metabolism, including the neocortex, hippocampus, and hypothalamus.[17] Studies have shown that GLP-1 receptor agonists can bring dopamine levels back up, protect dopaminergic neurons, cut down on neuronal damage, and improve clinical symptoms in people with Parkinson's disease.[18] The fact that these receptors are in these brain regions, plus the way these drugs affect neural transmission and synaptic plasticity,[19] suggests that they might act directly on the central nervous system. That raises the possibility that their effects go beyond just metabolism and could be useful for treating various central nervous system disorders.

That said, there is still a debate about whether these drugs protect the brain mainly by acting directly on the central nervous system or indirectly through improving metabolism throughout the body.[20] Different GLP-1 receptor agonists cross the BBB at very different rates, and that variability probably explains why clinical trial results have been so inconsistent.[17] Sorting out these differences is really important for choosing which drugs to use and how to design trials.

Here is where we stand with clinical trials right now. In PD, the positive Phase 2 Exenatide PD2 trial was followed by a negative Phase 3 Exenatide PD3 trial, whereas the LIXIPARK trial showed modest motor benefits.[21] In Alzheimer's disease, the recent ELAD trial did not find any significant effect on the main endpoint of brain glucose metabolism.[22] Taken together, these mixed results tell us that we need to be careful about picking the right patients, develop good biomarkers, and pay attention to drug specific properties in future studies.

Distribution of GLP-1 Receptors in the Central Nervous System

GLP-1 in the CNS comes from two places. One is the gut, where intestinal L cells secrete it and it can cross the BBB to get into the brain.[23] The other is made right inside the brain, mostly in preproglucagon neurons of the caudal hindbrain, specifically the nucleus tractus solitarius (NTS) and the adjacent intermediate reticular nucleus.[24]

Even though GLP-1 is only made in a few spots, its receptors are spread all over the brain. You can find GLP-1 receptors in the hippocampus, cerebral cortex, hypothalamus, thalamus, amygdala, striatum, nucleus accumbens, and the nucleus tractus solitarius.[20] At the subcellular level, these receptors sit on neuronal cell bodies, dendrites, and presynaptic terminals,[25] which lets GLP-1 directly control neural transmission, how excitable neurons are, and synaptic plasticity. All of these functions are tied closely to how brain diseases start and get worse.

It is worth noting that GLP-1 receptor distribution is not the same in rodents and humans, and that has big implications for how we interpret preclinical studies and whether they will translate to people.[26] In rodents, you see a lot of GLP-1 receptors in the area of postrema and subfornical organ, which are involved in energy balance and autonomic regulation.[27] But human brain studies show a more widespread distribution in the cortex and striatum, with relatively less in brainstem nuclei. We need to keep these species differences in mind when we try to extrapolate preclinical neuroprotective effects to human neurological disorders.

Neuroprotective Mechanisms of GLP-1 Receptor Agonists

Activation of Classical Signaling Pathways

GLP-1 receptors belong to the Gs protein coupled receptor family. When you activate them, they raise intracellular cyclic AMP (cAMP) levels, which then activates protein kinase A (PKA).[28] PKA goes on to phosphorylate cAMP response element binding protein (CREB), a transcription factor that turns on genes that make neurotrophic factors and anti-apoptotic proteins. Activating this pathway helps neurons survive, strengthens synaptic connections, and makes neurons more resistant to injury.

Taking GLP-1 receptor agonists over the long term boosts BDNF production and activity,[29] thereby facilitating learning and memory processes and supporting neuronal survival. Even when neurons are exposed to toxic amyloid-β aggregates, GLP-1 and exendin-4 can still increase BDNF levels and promote its transport along axons.

Activating GLP-1 receptors can also trigger Akt downstream through the PI3K pathway.[30] Once Akt is activated, it can block pro-apoptotic proteins and cut down on tau hyperphosphorylation by putting the brakes on GSK-3 beta,[31] and tau hyperphosphorylation is a key feature of Alzheimer's disease.[32] At the same time, Akt can turn on the mTOR pathway, which helps with protein synthesis and keeps cells growing and stable.

On top of that, GLP-1 receptor agonists can also activate the MAPK and ERK pathways, which control a number of genes involved in neuronal growth, repairing damage, and functional differentiation.[33]

Regulation of Neuroinflammation

Inflammation plays a role in how many brain diseases start and progress. In conditions like Alzheimer's disease and Parkinson's disease, ongoing damage signals keep microglia stuck in a state of chronic overactivation, pushing them toward a pro-inflammatory phenotype and making them release a lot of inflammatory factors.[34,35] GLP-1 receptor agonists can fight back against this. They cut down the number of overactivated microglia, which reduces the release of inflammatory factors,[36] and they also push microglia toward an anti-inflammatory phenotype.[37]

What is more, when microglia get too activated, they can turn astrocytes into a toxic form that damages nearby neurons.[38] By holding back microglial overactivation, these drugs can stop astrocytes from going toxic, which in turn protects neurons.[39]

Here is an interesting finding. A new GLP-1 receptor agonist called DA5-CH has been shown to protect the brain in a neonatal mouse model of hypoxic ischemic injury. It works by blocking signaling pathways involving TLR2, NF-κB, and NLRP3.[40] In this model, DA5-CH lowered levels of TNF-α, IL-1β, and IL-6, and it also stopped the NLRP3 inflammasome from forming, which reduced neuroinflammation.[40]

Regulation of Mitochondrial Function and Autophagy

Mitochondria are essential for making energy in cells, and they often start to malfunction early in brain diseases. You see this not only in chronic neurodegenerative conditions like AD and PD[41,42] but also in acute ones like stroke.[43] The GLP-1 receptor signaling pathway affects mitochondrial function by activating AMP activated protein kinase (AMPK) through calcium/calmodulin dependent protein kinase kinase 2 (CaMKK2).[44]

Once AMPK is activated, it does two main things. First, it kicks off mitochondrial biogenesis, helping cells make new healthy mitochondria;[45] Second, it puts the brakes on beta secretase 1 (BACE1), an enzyme that helps make amyloid beta, which is particularly relevant in Alzheimer's disease.[46]

In stroke, after ischemia and then reperfusion, mitochondria do not work as well, which means less energy and a flood of harmful reactive oxygen species, and that leads to cell damage and death.[47] Studies have shown that GLP-1 receptor agonists can improve how mitochondria work and keep the outer mitochondrial membrane stable, which lowers oxidative stress and protects neurons after an injury.[48]

Also, the GLP-1 signaling pathway helps cells clear out damaged components through autophagy, which keeps the inside of the cell healthy and stable.[49] By keeping mitochondrial function and cellular balance in check, these drugs protect neurons in both chronic neurodegenerative diseases and acute conditions like stroke.

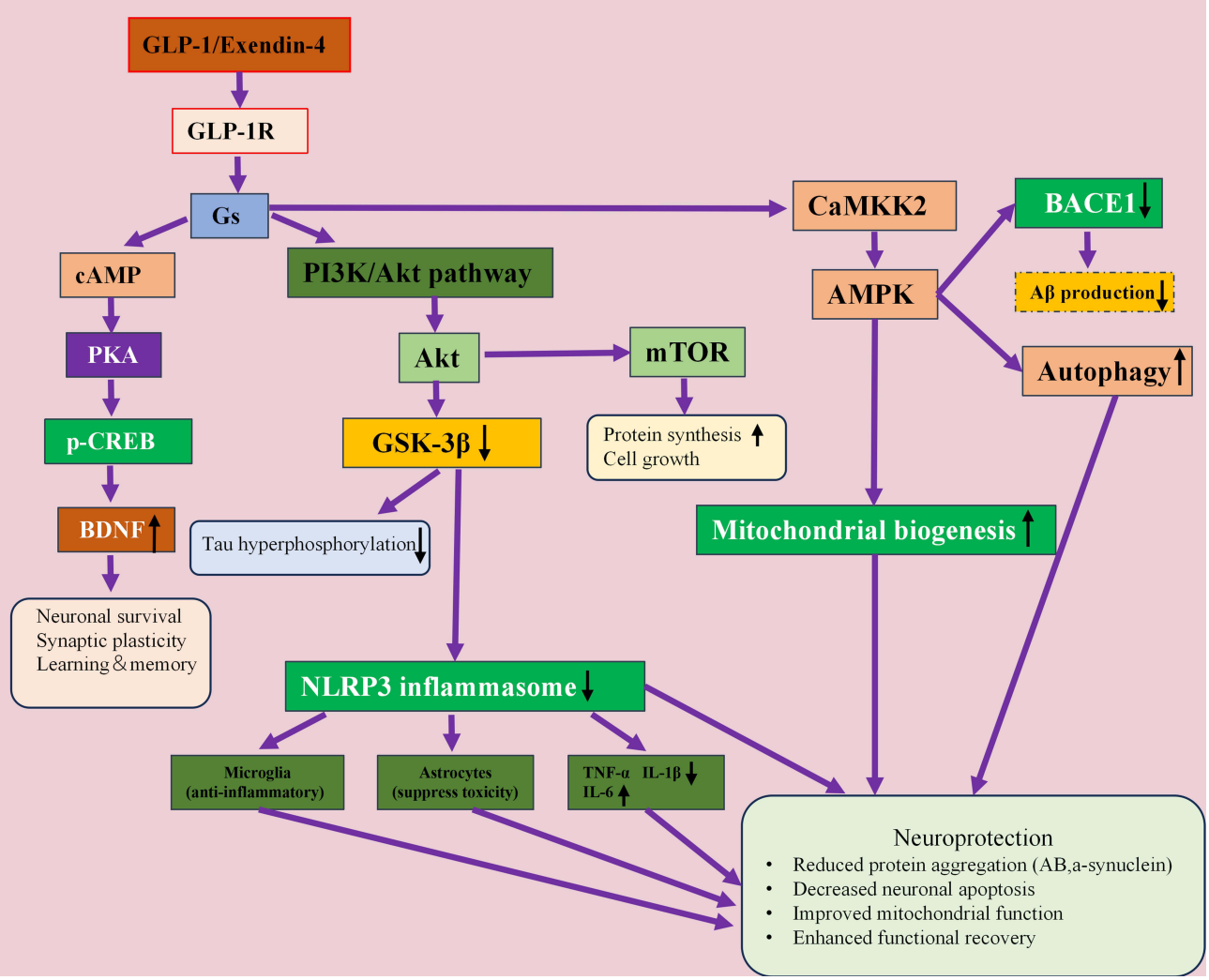

Figure 1 Schematic diagram of the neuroprotective mechanisms of GLP-1 receptor agonists. Upon activation, GLP-1 receptors engage several downstream signaling pathways. These include the cAMP/PKA/CREB pathway, which drives BDNF expression and supports neuronal survival; the PI3K/Akt pathway, which limits GSK-3β activity and reduces Tau hyperphosphorylation; suppression of microglial activation and neuroinflammation; and AMPK mediated regulation of mitochondrial function and autophagy. Together, these interconnected pathways account for the multi-target neuroprotective effects of GLP-1 receptor agonists. In the figure, black upward arrows indicates promotion, and black downward arrows indicates inhibition.

To sum up, GLP-1 receptor agonists protect neurons through several pathways including the classic cAMP/PKA/CREB pathway, the PI3K/Akt pathway, controlling inflammation, and keeping mitochondria working as shown in Figure 1. These pathways work together and form the molecular basis for the many ways this class of drugs protects the brain.

Role of GLP-1 Receptor Agonists in Neurological Diseases

Alzheimer's Disease

AD is one of the most common neurological disorders in older people.[50] Right now, about 55 million people worldwide are living with dementia, and that number is expected to hit 131.5 million by 2050.[51] What does Alzheimer's disease look like in the brain? Outside neurons, amyloid beta clumps together into sticky plaques. Inside neurons, tau gets hyperphosphorylated and twists into tangles. Meanwhile, connections between neurons break down, and the neurons themselves slowly die off. Not surprisingly, patients lose their ability to think and remember, and as the disease gets worse, they eventually cannot do daily activities on their own.[52–54]

There are several ideas about what causes AD, including the amyloid beta cascade hypothesis, the tau hypothesis, and the cholinergic hypothesis. More recently, people have been paying more attention to metabolic dysfunction. Studies have found that people with type 2 diabetes are more likely to develop Alzheimer's disease. Also, brain tissue from Alzheimer's patients shows less insulin signaling. Because of this link, some researchers have called AD "type 3 diabetes".[55]

A lot of animal studies suggest that GLP-1 receptor agonists can help with AD. In mice that carry Alzheimer's related genes, these drugs improve cognitive function.[56] They cut down on amyloid beta plaques by lowering the activity of BACE1, an enzyme that helps make amyloid beta. They also help microglia clear out existing plaques.[57,58] These drugs also reduce tau phosphorylation by blocking GSK-3 beta, which stops tangles from forming.[59] After treatment, the brain has fewer overactive microglia and astrocytes, and more neurons survive. These drugs also make neurons respond better to insulin, which helps bring PI3K/Akt signaling back to normal.[60] One study even looked at a dual CCK/GLP-1 receptor agonist. It improved cognitive performance in Alzheimer's mice, reduced amyloid beta buildup, and protected mitochondria by helping clear out damaged ones.[61] In short, GLP-1 receptor agonists seem to protect the Alzheimer's brain through multiple mechanisms.

Parkinson's Disease

PD is the second most common progressive neurodegenerative disorder. More than 10 million people have it worldwide.[62] In PD, dopamine producing neurons in the substantia nigra slowly die off. The ones that survive often contain clumps of alpha synuclein, called Lewy bodies.[63] Patients have trouble moving. They might shake, feel stiff, move slowly, or lose their balance. They also have non-motor problems like loss of smell, constipation, depression, and trouble thinking.[64]

We still do not fully understand what causes Parkinson's disease. Both genes and the environment play a role. Mitochondrial problems, too much oxidative stress, brain inflammation, and protein clumping all contribute.[65] Current treatments mostly just manage symptoms. Levodopa improves movement, but over time it causes side effects and stops working as well. It does not slow the disease down.[66] There is a real need for treatments that can change the course of the disease. Recent reviews have pointed to GLP-1 receptor agonists as a potential option, and they have also highlighted the need for biomarker guided ways to pick the right patients.[67,68]

Many studies show that these drugs can help in PD. In animals treated with chemicals that damage dopamine neurons, these drugs protect those cells, bring dopamine levels back up, and improve movement.[69,70] Newer studies suggest they also help clear out alpha synuclein clumps.[71] Overall, a lot of animal research indicates that GLP-1 receptor agonists can protect dopamine neurons and ease both movement and non-movement symptoms.[18] All this preclinical work has given us a good reason to try these drugs in people.

That said, clinical trial results in Parkinson's disease have been mixed. As of 2025, no GLP-1 based therapy has been shown to definitely modify the disease. The phase 2 Exenatide PD2 trial reported a 3.5-point improvement on the Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (MDS UPDRS Part III), and the benefit lasted through a 12-week washout, which suggested possible disease modification.[72] But the phase 3 Exenatide PD3 trial that followed could not replicate those findings. It found no difference between exenatide and placebo on the primary outcome or any secondary outcomes.[73] A post hoc analysis suggested that a higher proportion of insulin-resistant patients in the phase 2 trial may have contributed to the discrepant results, because Exenatide PD3 showed a non-significant trend toward benefit only in the small insulin-resistant subgroup.[73]

The phase 2 LixiPark trial showed that lixisenatide, a GLP-1 receptor agonist with measurable brain penetration, slowed motor progression in early Parkinson's disease compared with placebo.[74] In AD, the ELAD trial found that liraglutide did not significantly affect brain glucose metabolism, although exploratory analyses suggested some benefits on cognitive function and brain atrophy.[22] Similarly, the large phase 3 EVOKE and EVOKE+ trials of oral semaglutide in early Alzheimer's disease failed to slow cognitive decline on the primary endpoint, despite positive effects on certain disease-related biomarkers.[75]

Taken together, these mixed results suggest that GLP-1 receptor agonists still have a biological rationale for treating Parkinson's disease, but recent phase 3 trials have not yet delivered consistent evidence of disease modification.

Lixisenatide can cross the blood-brain barrier, which may set it apart from other GLP-1 receptor agonists that have limited central nervous system penetration. Future trials should take into account metabolic status, especially insulin resistance, and give priority to drugs that can reach the brain. Careful patient selection, better biomarkers, and attention to drug-specific properties will all be important for future development.

Ischemic Stroke

Stroke remains a major cause of death and disability worldwide. Over the past thirty years, despite research advances, the burden of stroke remains high.[76] As the population ages, the number of strokes is likely to rise.[77] Stroke damages the brain through multiple mechanisms including oxidative stress, neuroinflammation, blood-brain barrier damage, and cell death, all of which lead to neuron loss and lasting disability.[78–81]

GLP-1RAs, initially developed for diabetes, have recently shown potential in stroke treatment. Animal studies have demonstrated that these drugs can improve functional recovery after cerebral ischemia reperfusion by inhibiting inflammatory responses, reducing apoptosis, and promoting neurogenesis.[82] However, neuroprotection is only one aspect of stroke therapy. Restoring blood flow to the ischemic region is just as important. The current standard of care for acute ischemic stroke is recombinant tPA, which can open up large arteries but often does not do much for microvascular flow, which limits brain tissue repair. A recent study found that exendin-4 significantly improves microcirculatory blood flow through multiple signaling pathways including AC cAMP, PGE2 EP4, and non-cGMP dependent nitric oxide pathways, offering a new strategy for stroke treatment.[83]

In addition, progress has been made in studies looking at the protective effects of dual-receptor agonists on the blood-brain barrier. Tirzepatide, for example, activates C/EBP alpha, which in turn upregulates expression of the tight junction protein claudin-1, thereby keeping the blood-brain barrier intact and functional.[84] Figuring out how these drugs work will give us new ideas for clinical stroke therapy.

Intracerebral Hemorrhage

ICH is a major subtype of stroke caused by bleeding directly into the brain tissue.[85] Unlike ischemic stroke, which comes from a blocked vessel, intracerebral hemorrhage involves mechanical damage from the expanding blood clot, followed by secondary injury from hemoglobin toxicity, oxidative stress, blood-brain barrier disruption, and inflammation.[86] Intracerebral hemorrhage accounts for a significant share of all strokes but has a much higher death rate, and effective treatments are very limited.[87]

Recent real-world evidence suggests that GLP-1 receptor agonists may help in ICH.[88] A large multi-institutional study of patients with spontaneous intracerebral hemorrhage showed that those taking these drugs had significantly lower death rates during follow-up, as well as fewer rebleeding episodes, seizures, and cases of hydrocephalus.[88]

Beyond improving outcomes after the hemorrhage, these drugs may also reduce the risk of a first ICH. A nationwide study of patients with type 2 diabetes found that GLP-1 receptor agonist use was linked to a lower risk of non-traumatic ICH.[89] The protective effects seem to work through less inflammation, sturdier brain blood vessels, and blood-brain barrier protection, largely independent of blood sugar control.[90] We still need prospective randomized trials to confirm whether these drugs can improve outcomes in patients with intracerebral hemorrhage.

Huntington's Disease

HD is an inherited neurodegenerative disorder caused by a CAG repeat expansion in the huntingtin gene. This mutation leads to progressive loss of medium spiny neurons in the striatum, as well as cortical atrophy in later stages. Affected individuals develop uncontrolled choreiform movements, cognitive decline, and psychiatric symptoms including depression and anxiety.[91,92] There is currently no cure for Huntington's disease, and existing treatments only provide symptomatic relief.

Preclinical evidence for GLP-1 receptor agonists in Huntington's disease remains limited but is growing. In cellular models of overexpressing mutant huntingtin, liraglutide has been shown to restore insulin signaling, activate AMPK, enhance autophagy, and reduce protein aggregation. In the N171-82Q transgenic mouse model, exendin-4 treatment improved motor function, prolonged survival, and reduced mutant huntingtin aggregation in the brain.[93]

It is important to distinguish between direct GLP-1 receptor agonists and DPP-4 inhibitors. DPP-4 inhibitors such as vildagliptin indirectly raise endogenous GLP-1 levels by preventing its breakdown, but they also affect other substrates.

One study looked at vildagliptin in rats with a Huntington's like condition and found improved motor and cognitive performance and less striatal damage through the PI3K/Akt pathway.[94] However, these findings do not directly test GLP-1 receptor activation and should not be equated with the effects of direct GLP-1 receptor agonists.

Overall, research on GLP-1 receptor agonists in Huntington's disease is still at an early stage. Direct human data are absent, and no clinical trials have been conducted to date. More work is needed to figure out which patients might benefit, how these drugs might be combined with other therapies, and whether they are safe over the long term.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disease where the immune system attacks the myelin sheath of nerves. Myelin is essential for fast nerve conduction, and its disruption leads to neurological problems. In the clinic, patients may have a relapsing remitting course or a progressive disease pattern.[95]

Early studies suggest that GLP-1 receptor agonists have potential therapeutic value for multiple sclerosis, with mechanisms that include immunomodulation and helping myelin repair.[96] In animal models of MS, these agents significantly reduce disease severity. One study observed that in mice with demyelinating injury, liraglutide promoted the proliferation and maturation of oligodendrocyte precursor cells, activated the p-AMPK/SIRT1 signaling pathway, enhanced autophagy, and inhibited neuroinflammatory responses.[97] When the researchers blocked AMPK, these protective effects disappeared, which tells us that AMPK is key to how this drug works.

Another study looked at the natural compound 4-hydroxyisoleucine, which helped myelin repair in a rat model by raising GLP-1 levels.[98] These findings suggest that the GLP-1 signaling pathway represents a potential therapeutic target for promoting neural repair in MS.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease where you progressively lose motor neurons. These neurons are found in the brain, brainstem, and spinal cord. As they die, patients gradually lose muscle control and eventually develop life-threatening respiratory failure.[99] The pathogenesis of amyotrophic lateral sclerosis remains incompletely understood. Current research points to several contributing factors including glutamate excitotoxicity, oxidative stress, mitochondrial problems, and abnormal protein clumping.[100]

In animal models of amyotrophic lateral sclerosis, GLP-1 receptor agonists have shown benefits. They protect motor neurons, reduce inflammation, and help animals live longer.[2] One study looked at 4-hydroxyisoleucine in rats with an amyotrophic lateral sclerosis-like condition and found better movement and less oxidative stress and cell death through insulin-like growth factor 1 (IGF-1) and GLP-1 pathways,[101] Taken together, these findings suggest that targeting the GLP-1 signaling pathway might be a way to treat amyotrophic lateral sclerosis.

Depression

Depression is a serious psychiatric illness that affects mood, thinking, and daily functioning. Lots of factors are involved including monoamine imbalances, too little neurotrophic support, brain inflammation, and changes in how neurons connect with each other.[102]

GLP-1 receptors are found in brain regions that handle reward and pleasure. That has made researchers wonder whether GLP-1 receptor agonists might also influence mood.[103] Animal studies have reported antidepressant like effects with these drugs. One study tested liraglutide in mice exposed to chronic stress. The drug reduced depression-like behaviors in these mice and also improved learning and memory when they were not under stress.[104] Many other animal studies have reported similar antidepressant-like effects with GLP-1 receptor agonists. These effects often come along with better brain plasticity, less inflammation, and changes in neurotransmitter levels.[105]

In another study, exendin-4 helped mice that had both diabetes and depression. It worked by activating GLP-1 receptors, improving how mitochondria function, and clearing out damaged parts inside cells. This stopped microglia from overreacting and causing inflammation.[106] Putting it all together, these early findings suggest that GLP-1 receptor agonists might one day be used to treat depression.

Epilepsy

Epilepsy is one of the most common neurological disorders, affecting millions of people worldwide.[107] It is characterized by repeated seizures caused by abnormal electrical activity in the brain.[108] While many patients do well on anti-seizure medications, a good number still have seizures even with treatment.[109] The underlying mechanisms of epilepsy involve brain inflammation, mitochondrial dysfunction, and oxidative stress, all pathways that GLP-1 receptor agonists are known to target.[110]

Large scale clinical studies have recently given us strong evidence that GLP-1 receptor agonists are linked to lower epilepsy risk.[111] A recent meta analysis of many randomized controlled trials, including a large number of patients with type 2 diabetes showed that these drugs significantly cut the combined risk of late onset seizures and epilepsy compared with placebo.[112] This protective effect was seen only with GLP-1 receptor agonists and not with other diabetes drugs. Large observational studies have confirmed this finding, with semaglutide showing the strongest effect.[113]

Animal studies provide the mechanism to back up these clinical observations. In a rat model of temporal lobe epilepsy, liraglutide treatment dampened NLRP3 inflammasome activation, turned on the Nrf2 antioxidant pathway, and brought mitochondrial protein levels back up.[114] These actions fit nicely with the known anti-inflammatory and mitochondria protective effects of GLP-1 receptor agonists. There are still questions we cannot answer, like whether these benefits apply to patients without diabetes and whether the fact that semaglutide looks better is because it gets into the brain more or for some other reason. Even so, the convergence of large-scale human data and mechanistic animal studies puts epilepsy on the map as a promising new use for GLP-1 receptor agonists.

Spinal Cord Injury

Spinal cord injury (SCI) is a devastating condition that often leads to permanent loss of movement and feeling below the level of the injury.[115,116] The initial mechanical damage is followed by a secondary wave of injury marked by inflammation, cell death, and scar formation, which together stop axons from growing back.[117] Current treatments are mostly surgery and rehab, and there are no drugs that effectively limit the secondary damage or help the body recover function.

Preclinical studies have started to look at whether GLP-1 receptor agonists can help with SCI.[118] A recent study in a rodent spinal cord injury model showed that liraglutide puts the brakes on microglial pyroptosis, a specific type of inflammatory cell death, through the GLP-1 receptor mediated PI3K/Akt/TFEB/FANCC/p38 signaling pathway.[117] That is a previously unknown mechanism linking GLP-1 receptor activation to controlling inflammatory cell death in the injured spinal cord. Another study found that exendin-4 pushes immune cells to switch toward an anti inflammatory phenotype while cutting down the harmful pro inflammatory phenotype, and that came along with better hindlimb motor function.[119]

These effects fit with the broader anti-inflammatory and cell protective actions of GLP-1 receptor agonists described throughout this review.[120] But all the evidence so far comes from animal studies, and we do not have human data. Important questions still need answers, including what the right dose is, when to give the drug after the injury, and whether these preclinical benefits will actually show up in human patients.[121] Going forward, we need more translational studies to see whether GLP-1 receptor agonists can really improve outcomes in spinal cord injury.

Overall, GLP-1 receptor agonists look promising across a range of neurological disorders. Table 1 summarizes the main features of each disease, how these drugs protect the brain, and the improvements seen in preclinical models.

Table 1 Summary of GLP-1 Receptor Agonists in Neurological Diseases

Disease	Key Pathological Features	Core Protective Mechanisms	Functional Improvements
AD	Aβ plaques, tau tangles, insulin resistance	Reduce Aβ and tau; restore PI3K/Akt signaling	Cognitive improvement
PD	Dopamine neuron loss, α-synuclein aggregates	Protect dopamine neurons; enhance autophagy	Motor improvement with mixed trial results
Ischemic stroke	Infarction, BBB disruption, microcirculatory failure	Improve microcirculation; protect BBB	Reduced infarct volume and better recovery

(*Continued*)

Table 1 (Continued).

Disease	Key Pathological Features	Core Protective Mechanisms	Functional Improvements
ICH	Hematoma, hemoglobin toxicity, BBB disruption	Reduce inflammation; stabilize vessels	Lower mortality and rebleeding from real world data
HD	Striatal neuron loss, mutant huntingtin	Activate AMPK; enhance autophagy	Better motor function and longer survival from preclinical studies
MS	Inflammatory demyelination	Promote remyelination via AMPK/SIRT1	Reduced disease severity from preclinical studies
ALS	Motor neuron loss	Protect motor neurons; reduce inflammation	Extended survival from animal models
Depression	Monoamine imbalance, neuroinflammation	Improve mitochondrial function; suppress microglial pyroptosis	Antidepressant effects from preclinical studies
Epilepsy	Recurrent seizures, neuroinflammation	Suppress NLRP3; activate Nrf2	Lower seizure risk from clinical data with semaglutide strongest
SCI	Secondary inflammation, glial scar	Inhibit microglial pyroptosis; promote M2 polarization	Improved motor function from preclinical studies

Challenges and Perspectives

GLP-1 receptor agonists look really promising for treating neurological disorders, but there are several obstacles that need to be overcome before they can be widely used.

One challenge is blood-brain barrier penetration. Different GLP-1 receptor agonists cross the barrier with very different efficiency. Small peptides such as exenatide and lixisenatide get into the central nervous system at measurable levels, whereas larger or chemically modified analogues such as liraglutide and semaglutide barely get in under normal conditions. This variability probably affects how well they work in brain diseases. More work is needed to figure out how each drug gets across the barrier and what that means for treatment.

Then there is the problem that we do not have reliable biomarkers to tell which patients are most likely to benefit. Neuroimaging and cerebrospinal fluid analyses might give us some clues, but more research is needed to identify the right patient populations for these therapies. Recent reviews have stressed that future progress depends on biomarker driven, biologically enriched trial designs.

When you treat also matters. For most neurological conditions, starting earlier probably gives better results, but we still do not know the best time to start GLP-1 receptor agonist therapy. Long term safety is another thing we do not know much about. Most existing studies have followed patients for relatively short periods, so we do not know what happens with chronic use.

Side effects are also a practical concern. Lots of people taking these drugs get gastrointestinal symptoms, especially nausea, which can make them stop taking the medication. Plus, weight loss, while good in some situations, might be bad or even harmful for certain patients with neurological diseases.

Looking ahead, there are several strategies that could help get around these problems. One approach is to design new GLP-1 receptor agonists that get into the brain better by tweaking their structure. Another direction is developing multi-target drugs. Dual GIP/GLP-1 receptor agonists and even triple agonists are currently being tested and might work better because they hit multiple signaling pathways at once. Combining these drugs with other neuroprotective agents also looks promising, as different drugs might work together to give a stronger effect. Finally, a precision medicine approach could be a big help. By putting together genetic information, biomarker profiles, and disease-specific characteristics, doctors might one day be able to match the right drug to the right patient at the right time. Despite these challenges, GLP-1 receptor agonists still represent a genuinely promising way to treat brain disorders. These challenges and corresponding future directions are summarized schematically in Figure 2.

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Figure 2 Challenges and future directions of GLP-1 receptor agonists in neurological diseases. The left panel highlights key barriers to clinical translation. These include variable blood brain barrier penetration across different GLP-1RAs, a lack of reliable biomarkers to guide patient selection, uncertain timing of treatment relative to disease stage, limited long term safety data, and gastrointestinal side effects that often interfere with adherence. The right panel outlines corresponding paths forward: developing new agents with better central nervous system access, testing multi-target agonists, combining GLP-1RAs with other therapeutic strategies, and applying precision medicine to match each patient with the most suitable treatment.

Conclusion

GLP-1 receptor agonists started out as glucose lowering drugs. Twenty years later, they are increasingly recognized as potential disease modifying treatments for a range of neurological disorders. Their receptors are widely expressed across the brain, providing a direct anatomical substrate for neuroprotection. Mechanistically, these drugs act on multiple fronts. They suppress neuroinflammation, support mitochondrial function, enhance BDNF signaling, interfere with pathological protein aggregation, and improve cellular energy metabolism. This polypharmacological profile allows them to address several pathogenic processes simultaneously.

Preclinical evidence has been robust. Animal models of AD, PD, ischemic stroke, ICH, HD, MS, ALS, depression, epilepsy, and SCI have all shown benefits following GLP-1 receptor agonist treatment. However, the strength of clinical evidence varies considerably across these conditions. For Alzheimer's disease and Parkinson's disease, several randomized controlled trials have been completed, yielding mixed results. While some trials have reported modest cognitive or motor benefits, others including recent phase 3 trials have shown no significant effect on disease progression. For Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, and depression, the evidence remains largely preclinical or sparse, and no firm conclusions can be drawn at this stage.

Several key barriers currently limit clinical translation. Different GLP-1 receptor agonists cross the blood-brain barrier with widely varying efficiency, and this variability likely influences therapeutic outcomes. For example, exenatide and lixisenatide show measurable CNS penetration, whereas liraglutide and semaglutide exhibit minimal detectable uptake under normal conditions. Biomarkers that could identify likely responders are largely missing. The optimal timing of intervention remains unclear. Long-term safety data are sparse, and tolerability issues, particularly gastrointestinal side effects, often interfere with adherence.

The broader implications of these findings are twofold. First, the variability in CNS penetration across different GLP-1 receptor agonists suggests that drug selection should be guided by brain exposure data rather than assuming class effects. Second, the mixed clinical trial results indicate that patient stratification based on metabolic status, particularly insulin resistance, may be essential for demonstrating efficacy. Future trials should prioritize centrally penetrant molecules and incorporate biomarker driven, biologically enriched designs.

Looking forward, better brain penetrant compounds are needed. Multi-target agonists that engage additional receptors may prove more effective than single target drugs. Rational combinations with other neuroprotective agents could yield synergistic effects. A precision medicine framework, matching drug to patient based on genetic, biomarker, and metabolic profiles, may eventually guide treatment decisions. For patients with neurological conditions that currently

have few treatment options, the possibility of repurposing GLP-1 receptor agonists as disease modifying therapies remains an important goal worth pursuing.

Consent for Publication

All authors consent to publication.

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Disclosure

The authors declare that they have no competing interests.

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