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Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: implications for neurodegenerative disease treatment

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Abstract

Chronic, excessive neuroinflammation is a key feature of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). However, neuroinflammatory pathways have yet to be effectively targeted in clinical treatments for such diseases. Interestingly, increased inflammation and neurodegenerative disease risk have been associated with type 2 diabetes mellitus (T2DM) and insulin resistance (IR), suggesting that treatments that mitigate T2DM pathology may be successful in treating neuroinflammatory and neurodegenerative pathology as well. Glucagon-like peptide-1 (GLP-1) is an incretin hormone that promotes healthy insulin signaling, regulates blood sugar levels, and suppresses appetite. Consequently, numerous GLP-1 receptor (GLP-1R) stimulating drugs have been developed and approved by the US Food and Drug Administration (FDA) and related global regulatory authorities for the treatment of T2DM. Furthermore, GLP-1R stimulating drugs have been associated with anti-inflammatory, neurotrophic, and neuroprotective properties in neurodegenerative disorder preclinical models, and hence hold promise for repurposing as a treatment for neurodegenerative diseases. In this review, we discuss incretin signaling, neuroinflammatory pathways, and the intersections between neuroinflammation, brain IR, and neurodegenerative diseases, with a focus on AD and PD. We additionally overview current FDA-approved incretin receptor stimulating drugs and agents in development, including unimolecular single, dual, and triple receptor agonists, and highlight those in clinical trials for neurodegenerative disease treatment. We propose that repurposing already-approved GLP-1R agonists for the treatment of neurodegenerative diseases may be a safe, efficacious, and cost-effective strategy for ameliorating AD and PD pathology by quelling neuroinflammation.

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Credit Author Statement

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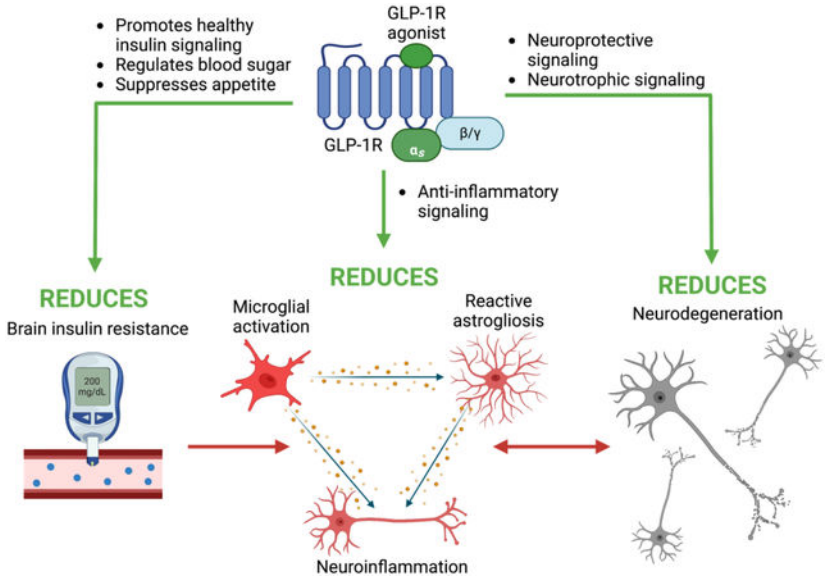
Graphical Abstract



Keywords

Glucagon-like peptide-1 (GLP-1); neurodegeneration; Alzheimer's disease; Parkinson's disease; neuroinflammation; incretin mimetic; glucose-dependent insulinotropic peptide (GIP); insulin resistance

1. Incretin Overview

Across all neurodegenerative disorders and injuries, neuroinflammation plays a key role in disease progression and recovery. There is currently a void in viable US Food and Drug Administration (FDA)-approved medications to treat let alone mitigate disease progression of chronic brain disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD), and more acute brain injuries such as traumatic brain injury (TBI). A recent genome-wide association study (GWAS) provides new genetic insights into AD and related dementias indicating elevation of inflammation-related pathways as a driver of risk for these chronic conditions (1). The repurposing of FDA-approved drugs towards treating inflammation-related central nervous system (CNS) diseases and injuries would be ideal, as their safety profile in humans has already been established. Several FDA-approved incretin mimetics, originally developed for the treatment of type 2 diabetes mellitus (T2DM) (Table 1), are a promising class of drugs currently progressing towards repurposing as a new treatment strategy for a wide variety of brain/neurological disorders. A wealth of preclinical animal studies in models of stroke (2–4), PD (4–6), AD (6–8), glaucoma (9–11), and TBI (12) provide evidence for using incretin mimetics as a treatment option. In addition, several human clinical trials related to CNS diseases are progressing or have been completed (Table 2), with initial phases of trials in PD showing efficacy (13). Incretin mimetics exhibit pleiotropic signaling effects in a variety of different cell types (14), but their potent anti-inflammatory properties, together with their neurotrophic and neuroprotective features,

make them ideal for treating neurodegenerative disease. Within this review article we provide a brief overview of incretin mimetic drugs, both FDA-approved and in clinical and preclinical trials (Tables 1 and 2), and underscore their potent anti-inflammatory capacity that makes them ideal candidates for repurposing and investigation in clinical trials for neurodegenerative conditions.

1.1 Incretins – focus on the endocrine system

The incretin signaling system, constituting the gut-derived metabolic peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), is responsible for blood glucose regulation following food ingestion (15). These peptides act by stimulating the release of insulin. The incretins GLP-1 and GIP are secreted from the small intestinal enteroendocrine L and K cells, respectively, and act on their target receptors present on the β-cells of the pancreas. The GLP-1 receptor (GLP-1R) and GIP receptor (GIPR) are class B G protein-coupled receptors, each with a seven-helix transmembrane domain and an extracellular ligand binding domain. The intracellular face interacts primarily with the $G\alpha_s$ subunit of G proteins and with β-arrestins, as well as various other signaling molecules. GLP-1R and GIPR signaling have several known functions in the endocrine system: GLP-1R activation initiates signaling cascades that promote insulin secretion and β-cell survival; GIPR activation promotes insulin secretion after feeding, glucagon (Gcg) secretion during fasting, triacylglycerol uptake by adipose tissue (16), and reduced bone resorption (17). Both members of the glucagon superfamily, GLP-1 and GIP activity both supplement as well as oppose select actions of Gcg, a structurally related secretin (Figure 1A) synthesized in islet α-cells of the pancreas and within the small intestine, that acts by raising blood glucose levels in periods of fasting. Following their release, GLP-1, GIP, and Gcg are rapidly degraded to end their pharmacological/physiological regulatory action by the enzyme dipeptidyl peptidase-4 (DPP-IV), which is responsible for their short plasma half-lives of 1–2 minutes (18), 2–5 minutes (19), and 6–7 minutes (20), respectively. DPP-IV acts as a relatively unpromiscuous amino-peptidase and releases a dipeptide from the N-terminal end of its substrates. With a preference for an alanine or proline in the penultimate position, it additionally cleaves peptides with other amino acid residues (serine, glycine, valine) albeit more slowly. Discovery of reduced incretin actions in T2DM patients (21) led to robust research into GLP-1 and GIP as potential disease-modifying drug therapies. Although both peptides are highly insulinotropic in healthy individuals (22, 23), only GLP-1 was demonstrated to have preserved insulinotropic effects in patients with T2DM (24, 25). This, combined with the ability of truncated GLP-1 to inhibit Gcg secretion (26), prompted drug developers to target GLP-1R agonists as potential treatments for T2DM.

1.2 FDA approval of incretin-based therapies

Various GLP-1 analogs have been developed to lengthen the half-life of the peptide and prolong the beneficial effects of GLP-1R signaling. In 1992, during the early research of incretin effects in diabetes, an endogenous GLP-1 analog, exendin-4, was isolated from the venom of the Gila monster lizard (*Heloderma suspectum*) (27) (Figure 1B). Exendin-4 evades DPP-IV cleavage due to an alanine for glycine substitution at the enzyme cleavage site (Figure 1B) (28) and thus has a prolonged half-life relative to GLP-1 (2.4 hours in plasma) (29). In 2005, exendin-4, under the name “Exenatide”, became the first FDA-

approved GLP-1R agonist for the treatment of T2DM. Since then, many other GLP-1 analogs have been approved by the FDA, including liraglutide, semaglutide, lixisenatide, dulaglutide, and formerly albiglutide (discontinued in July of 2017) (12) (Table 1). In addition to GLP-1R agonist adoption for T2DM treatment, DPP-IV inhibitors, which elevate the levels of endogenously produced incretins throughout the body, have proven efficacious and been FDA-approved to treat the disease (Table 1).

1.3 Multi-agonism

More recent research has investigated the use of drugs that target a combination of secretin receptors (GLP-1R, GIPR, and GcgR) to treat T2DM. In 2009, a dual GLP-1R/GcgR agonist was pioneered for treating metabolic disorders in rodents (30). Later, in 2013, a dual GLP-1R/GIPR agonist, termed “twincretin”, demonstrated efficacy in animal models and humans with T2DM in reducing glycosylated hemoglobin A1c (HbA1c), an average measure of blood sugar levels over the duration of several months (31). Further research led to the development of Tirzepatide, a GLP-1R/GIPR dual agonist, which was found to enhance insulin signaling, reduce blood glucose, and promote weight loss in preclinical and phase 1 and 2 clinical trials (32). Moreover, the beneficial effects of Tirzepatide were significantly greater than the effects of a single GLP-1R agonist or a single GIPR agonist alone (32). A meta-analysis of randomized controlled trials found that Tirzepatide treatment in patients with T2DM significantly reduced HbA1c, fasting blood glucose, postprandial blood glucose, body mass index (BMI), waist circumference, and weight, as compared to single GLP-1R agonist treatment or insulin analog treatment (33). Tirzepatide (Mounjara™) (Table 1) is the only currently FDA-approved incretin multi-agonist (approved in 2022).

Additionally, unimolecular triple incretin-based agonists, or triagonists, have been developed that target the GLP-1, GIP, and Gcg receptors (GcgR). GLP-1R/GIPR/GcgR triagonist treatment in a high-fat diet mouse model system reduced plasma glucose levels, increased plasma insulin levels, and regulated blood glucose levels following food intake (34). Another rodent study demonstrated the heightened potency of a GLP-1R/GIPR/GcgR triagonist and its superior performance to a GLP-1R/GIPR dual agonist in reducing body weight, improving blood glucose regulation, and ameliorating fatty liver disease (35). A novel GLP-1R/GIPR/GcgR triagonist, SAR441255, has been shown to promote weight loss and maintain healthy blood glucose levels in a rodent model, and outperformed a GLP-1R/GIPR dual agonist (36). In a mouse model of obesity, triagonist treatment enhanced weight loss and outperformed single and dual incretin-based receptor agonists (37). Furthermore, preclinical studies of SAR441255 revealed incretin receptor activation and maintenance of normal blood sugar levels in healthy monkeys in response to the drug, as well as the safety and tolerability of the drug in a phase 1 human clinical trial (36) (NCT04521738, 48 participants, aged 18–55 years, lean to overweight). SAR4411255 demonstrated a terminal half-life of 3.5–6.1 hours, which is a relatively short exposure for a proposed once daily subcutaneously administered drug, and doses up to 150 ug were well tolerated, with the most frequent treatment-emergent adverse events being gastrointestinal, in accord with other GLP-1R agonists. Maintaining an appropriately balanced agonism among the three receptor subtypes (GLP-1, GIP, and Gcg) is key for single molecule triagonists to optimize efficacy across measures of glucose and body weight-lowering action, as well

as to maintain tolerability across organ systems. Consequent to business decisions within Sanofi, it is possible that SAR4411255 may not proceed forward in clinical development (38). The first human clinical trial (phase 1 - NCT03374241) of a novel GLP-1R/GIPR/GcgR triagonist, HM15211, was initiated in 2018 in patients with obesity (39) (Table 1). This HM15211 (NCT03374241) trial was a first-in-human study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics after single ascending dose in healthy obese subjects (40 participants, aged 18–65 years). A further phase 1 trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of HM15211 in obese subjects with nonalcoholic fatty liver disease (NAFLD) has been reported as NCT03744182 (66 participants, aged 18–65 years). Finally, an ongoing phase 2 study to evaluate efficacy, safety and tolerability of HM15211 treatment for 12 months in subjects with biopsy confirmed non-alcoholic steatohepatitis (NASH) has been reported as NCT04505436 (217 participants, aged 18–70 years, across multiple US sites with a proposed completion date of November 2025). Currently, no peer reviewed publications of results of any HM15211 clinical study appear available.

Although the dual GLP-1R/GIPR agonist Tirzepatide is the only FDA-approved incretin multi-agonist, unimolecular incretin receptor multi-agonists will likely dominate as treatment options in the future due to growing evidence of their increased efficacy over single GLP-1R agonists (15, 35, 40, 41). Several multi-agonist incretin analogues are in the preclinical or clinical trial phases (Table 1) and are likely to be approved over the coming decade to treat both obesity and diabetes. Interestingly, recent research is unraveling the nuances in intracellular biased agonism these drugs may have, including preferential cAMP and other intracellular pathway induction (42, 43). FDA approval of Tirzepatide and ongoing clinical trials indicate that the multi-agonist approach is safe in humans, which has important implications for treating a range of conditions, including nervous system-related chronic diseases and acute injuries. Preclinical animal models of chronic neurodegenerative disorders such as PD, AD, and glaucoma (9, 44) and acute injury models such as stroke and TBI (12, 45) have robustly demonstrated incretin therapy utility (both single and multi-agonist approaches) as a potential treatment option for these conditions.

1.4 Insulin resistance and introducing incretins in the CNS

In healthy individuals, there is an appropriate balance between the activity of GLP-1, GIP, and Gcg, which is continuously adjusted and maintained by homeostasis. When this fails, a disrupted balance in GLP-1, GIP, and Gcg signaling can lead to chronically elevated blood glucose and subsequent development of insulin resistance (IR) (defined broadly as reduced cellular responsiveness to insulin), a feature of T2DM and obesity (46). Chronically high blood glucose can cause excessive inhibitory phosphorylation of key serine residues of insulin receptor substrates (IRS)-1 and 2 (for example, IRS-1 S312 and S616), resulting in reduced insulin receptor binding sensitivity, and triggers the translocation of IRS-1 and 2 from the cell membrane into the cytoplasm with reduced potential activation of downstream Ak strain transforming (Akt) and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling kinases (47, 48). Insulin can hence play a fundamental role in neurodegeneration through binding to its receptor, which is particularly abundant within the striatum, cerebral cortex, and hippocampus (49, 50). Postmortem studies have reported that

PD patients exhibit a reduced expression of insulin receptors (49, 51) and additionally have revealed a raised IRS-1 pS312 expression within nigral dopaminergic neurons as compared to aged-matched controls (52, 53), symbolic of dysfunctional insulin signaling. Since insulin stimulates glucose uptake into cells, a reduction in insulin sensitivity causes a reduction in glucose uptake; consequently, the elevation in blood glucose levels persists, and IR becomes more severe (54).

IR may be present in the brain and is a common feature of neurodegenerative diseases (55–58). Extensive research indicates that T2DM is a risk factor for AD (8, 59–62) and PD (58, 63–65). However, brain IR may occur in AD in the absence of a T2DM diagnosis, as indicated by reduced insulin and insulin-like growth factor-1 (IGF-1) responses in patients with AD and without T2DM (66). These findings suggest that, while peripheral IR as observed in T2DM can contribute to neurodegenerative disease pathology, IR in the CNS may occur via its own independent mechanisms as a separate entity. Yet, it is notable that increased weight circumference, mid-life adiposity, and metabolic syndrome (all allied to peripheral IR and systemic inflammation) are associated with an elevated risk of PD (67–69). In relation to acute neurodegenerative disorders, T2DM in patients challenged with TBI is a significant predictor of mortality—in a study of 51,585 TBI patients, those with T2DM exhibited a significantly higher mortality rate (14.4%) than those without T2DM (8.2%) (70). Furthermore, brain glucose metabolism is dramatically altered following a TBI, with an acute increase in cerebral glucose metabolism typically followed by an extended decline in glucose metabolism (71). Aligned with this, there are multiple reports of hyperglycemia following TBI, with uncontrolled blood glucose levels resulting in poorer outcomes for recovery and an increased mortality risk (72–74). IR is a marker of increased risk for ischemic stroke (75) and, additionally, is associated with poorer functional outcomes (76).

Incretin receptors are prominent in the brain and are intricately associated with peripheral insulin regulation through increased control of feeding behaviors (77, 78). GLP-1R signaling in the hippocampus and hypothalamus improves memory function (79, 80) and is additionally linked to reduced appetite and regulation of food intake (77). GIPR is expressed in neurons and glial cells in the paraventricular nucleus (PVN), dorsomedial nucleus (DMN), and arcuate nucleus (ARC) of the hypothalamus, and reduces food intake in cooperation with GLP-1R signaling (78). GIPR signaling in cortical regions likely has a role in progenitor cell proliferation (81). The expression of incretin receptors in the CNS as well as the link between brain IR and neurodegeneration have fueled scientific interest in the use of GLP-1R and GIPR agonist treatments to promote neural health.

GLP-1R stimulation has been associated with neuroprotective and neurotrophic properties in several foundational studies conducted in the early 2000s (82–84). Rat hippocampal neurons treated with GLP-1 (82, 84) or exendin-4 (84) were more resistant to glutamate excitotoxicity, and both treatments enhanced neural growth and differentiation in a rat neuroendocrine cell model (83)—findings that have been replicated numerous times across cell types of neuronal origin and multiple animal models. In contrast, GLP-1R deficient mice have a learning deficit that can be restored by hippocampal *Glp1r* gene transfer (85), and have impairments in synaptic plasticity, long-term potentiation (LTP), and memory formation (86). GLP-1R overexpression results in a great resilience to a host

of physiological and pathological challenges—compared with parent SH-SY5Y cells, in a human neuroblastoma cell line (SH-SY5Y) overexpressing GLP-1R (by as little as 2-fold) and challenged with hydrogen peroxide and 6-hydroxydopamine (6-OHDA), GLP-1R stimulation significantly enhanced cell viability and proliferation, clearly illustrating the neurotrophic and anti-apoptotic properties of GLP-1R signaling (87). The observed neuroprotective properties of GLP-1R-targeting drugs suggested the potential of incretin receptor agonists in treating diseases of the brain and, since the foundational studies, numerous studies with single, dual, and triple agonists have been undertaken across neurodegenerative and neuropsychiatric conditions preclinically and are now extending into clinical research trials.

An important consideration in GLP-1R/GIPR/GcgR agonist drug development and, indeed, in all neurological therapeutic development (88), is blood-brain barrier (BBB) penetration. GLP-1, GIP, and Gcg are large peptide molecules and thus have limited BBB penetration. Nevertheless, early studies by Kastin and colleagues (89, 90) as well as by Banks and colleagues (91) demonstrated that GLP-1, as well as many alike peptides (92), can access the brain in small but pharmacologically relevant amounts. GLP-1 influx was rapid, associated with simple diffusion and not a saturable transport system (89). A recent study confirmed the rapid brain uptake and pharmacological action of systemically administered GLP-1 and exendin-4, and suggested the presence of a saturable BBB transporter that potentially involves the GLP-1R, as antagonists reduced brain uptake (93). Notably, this same study confirmed the abundance of the GLP-1R on brain vascular endothelial cells (93, 94) that has been reported to potentially mediate arteriolar dilation and, thereby, regulate tissue perfusion (95). The same study additionally demonstrated that resection of the vagus nerve (i.e., complete vagotomy) had no effect on brain GLP-1 uptake and pharmacological action (as evaluated by elevated protein kinase A (PKA) in rat brain), thus suggesting that such pharmacological action required the presence of drug in the brain and was not mediated via the peripheral (vagal) nervous system (93)—as vagal afferent neuron GLP-1Rs have been shown to have a role in facilitating the actions of GLP-1 on food intake and glycemic control (96).

Certain synthetic GLP-1R agonists described below, likewise, have varying ability to cross the BBB. In a study by Banks and colleagues (97) comparing the brain uptake pharmacokinetics of GLP-1R agonists, the acylated GLP-1R ligands liraglutide and semaglutide did not measurably cross the BBB, whereas the non-acylated and non-PEGylated GLP-1R ligands exendin-4 and lixisenatide did measurably cross the BBB (97). However, despite the lack of evidence of semaglutide crossing the BBB, semaglutide has been reported to access the brain through interactions with certain ventricular sites and circumventricular organs, and can directly access the brainstem, hypothalamus, and septal nucleus (98). In separate studies involving the administration of exendin-4 (in the form of sustained-release exenatide as Bydureon®) to humans with PD (13) and as a twice daily immediate release form (BID Byetta®) in AD (99), cerebrospinal fluid (CSF) concentrations of exendin-4 were approximately 2.1% and 1.4% of concomitant plasma levels, respectively. In this regard, the maintenance of long-term steady-state plasma levels of exendin-4, as achieved by sustained-release PT320/PT302 in preclinical studies or by pump where peptide

plasma and CSF levels were quantified, results in greater levels in CSF and a higher CSF/plasma ratio than the immediate release exendin-4 form (100, 101).

Several dual GLP-1R/GIPR agonists were also evaluated in the study by Banks and colleagues (97), and the non-acylated and non-PEGylated dual agonists Peptide 17 and Hölscher peptides DA3-CH and DA-JC4 were found to cross the BBB, with exendin-4 and DA-JC4 exhibiting the best BBB penetration of the peptides assessed (97). This is not to say that PEGylated GLP-1R ligands cannot cross the BBB—novel GLP-1R agonist NLY01 is a PEGylated formulation reported to be effective in treating a mouse model of multiple sclerosis (MS) (102) and of PD (103) and is currently in a phase 2 clinical trial for PD treatment (104) (Table 1), highlighting the drug's promise for potentially treating neurological disorders. In contrast, recent studies by Hölscher and colleagues (105) indicate that the brain delivery of NLY01 is very low, far less than that of exendin-4 and dual GLP-1R/GIPR dual agonists. This is likely consequent to NLY01's attachment to a 40 kDa PEGylation to extend its systemic half-life but simultaneously making it the size of a small protein (with a consequentially lower BBB permeability than far smaller peptides such as GLP-1 (molecular mass 3,298.7 Da) and Exenatide (4,186.6 Da)). With the many variations of GLP-1R-based drugs on the market and in development, BBB penetration is a paramount consideration for treatment of neurodegenerative diseases and injuries (5).

2. Neuroinflammation Overview

2.1 Neuroinflammation

Although inflammation is part of the body's healthy response to pathogens and injury, excessive inflammation can have detrimental health effects. In the brain, neuroinflammation is the product of cytokine, chemokine, reactive oxygen species (ROS), and second messenger signaling, involving interactions between neurons, microglia, and astrocytes (Figure 2) (106, 107). Generally, in response to a physiological or environmental trigger (for example, pathogens/pathogen-associated molecular patterns (PAMPs), infection, neurotoxins, neuronal damage, or injury), resting microglia (i.e., in their physiological state) are activated (106) (Figure 2A, B). Microglia exist in context-dependent activation states. In a healthy brain, microglia are homeostatic or quiescent when not activated by a stimulus and patrol for aberrant signaling and other cues of damage; when an insult is detected, microglia are activated into a pro-inflammatory state (12) and express a spectrum of associated phenotypes (Figure 2B). In the literature, pro-inflammatory microglia are often termed "M1" as opposed to "M2" microglia, which comprise a subtype of activated microglia (commonly referred to as "alternatively activated" or "anti-inflammatory") that secrete anti-inflammatory cytokines and exhibit other reparative functions; however, it is important to note that the "M1" and "M2" terms are falling out of favor due to growing evidence of a spectrum of microglial phenotypes (108). M1 microglia release inflammatory molecules, ROS, chemokines (including C-X-C motif chemokine ligand 1 (CXCL1), C-C motif chemokine ligand 1 (CCL1), and CCL5), prostaglandin E_2 (PGE_2), and cytokines (including interleukin (IL)-1 beta (IL-1β) and tumor necrosis factor (TNF)-alpha (TNF-α)); which, when excessive, can damage neurons by activating intracellular inflammatory pathways involving nuclear factor kappa-light-chain-enhancer of activated

B cells (NF-κB), cyclooxygenases (COX) 1 and 2, and ROS, among other signaling molecules (109, 110) (Figure 2D). In response, the damaged and dying neurons release damage-associated molecular patterns (DAMPs), adenosine triphosphate (ATP), cell debris, neuroinflammatory cytokines, and microglial activators, further activating microglia and continuing the inflammatory cycle (80, 109) (Figure 2H). DAMPs include myelin sheath fragments, tau, amyloid-β, α-synuclein, advanced glycation end products (AGEs), and neuron-specific enolase (80). Astrocytes may exacerbate or ameliorate neuroinflammation depending on the signals present: interferon gamma (IFNγ), transforming growth factor β (TGF-β), signal transducer and activator of transcription 3 (STAT3), glycoprotein gp130, Fas ligand (FasL), and brain-derived neurotrophic factor (BDNF) stimulate protective pathways, but sphingolipids, IL-17, NF-κB, tropomyosin receptor kinase B (TrkB), suppressor of cytokine signaling 3 (SOCS3), vascular endothelial growth factor (VEGF), and chemokines can trigger harmful pathways that worsen inflammation (111). CNS disease or injury can induce astrocytes to convert to their reactive form (112) through a process termed reactive astrogliosis (113) (Figure 2F). More specifically, M1 microglia induce astrocytes to convert to their reactive state through the release of cytokines, particularly IL-1α, TNF-α, and complement component 1, subcomponent q (C1q) (112, 114) (Figure 2E). Reactive astrocytes are neurotoxic and can potentially destroy neurons and oligodendrocytes through release of saturated lipids in apolipoprotein (APO) E and APOJ lipoparticles (115) (Figure 2G). This subtype of astrocytes, previously termed “A1” reactive astrocytes, have been identified in human Huntington’s disease, amyotrophic lateral sclerosis (ALS), AD, PD, and MS, with common gene markers of these cells becoming significantly upregulated in several brain regions (112). This “A1” state is typified by inflammatory transcriptional responses, a downregulation of phagocytic function, and neurotoxic activity that likely involve activation of toll-like receptor (TLR) 4 on the cell membrane and the downstream triggering of the inhibitor of κB kinase (IKK)-NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways. Even in the absence of disease states, normal aging induces A1 astrocyte formation (116). Although neuroinflammation involves an incredibly complex interplay between stimuli (context dependent cascades), cell types, and organism health, we have briefly overviewed several key neuroinflammatory mechanisms in the following sections.

2.2 NF-κB signaling

Microglia initiate the first stages of neuroinflammation through the activation of NF-κB, a Rel family transcription factor. There are 5 members of the NF-κB family; 2 subunits, alike or different, may dimerize, translocate to the nucleus, and act as a transcription factor for a wide variety of inflammation-related genes (109). In the cytoplasm, NF-κB is inhibited by its interaction with inhibitor of κB (IκB)—only free NF-κB may translocate into the nucleus (117). The canonical NF-κB signaling pathway is initiated by a pro-inflammatory molecule such as IL-1, lipopolysaccharide (LPS), or TNF-α forming rimmers and binding to its respective receptor on the cell. This induces a signaling cascade that culminates in the inhibitory phosphorylation of IκB by the IKK complex (117, 118). Phosphorylated IκB is ubiquitinated and subsequently degraded, thereby freeing NF-κB for nuclear translocation (117, 118). In this manner, NF-κB is activated by cellular stresses (such as oxidative stress, cytokines, toxins, and carcinogens). Activation of receptors belonging to the TNF

superfamily induces the noncanonical pathway of NF-κB signaling, in addition to the aforementioned canonical pathway (117, 118). Following stimulation of the noncanonical pathway, NF-κB inducing kinase (NIK) is freed from its inhibitory interactions with TNF receptor-associated factors (TRAF) 2 and 3 and is thus stabilized; NIK accumulates and induces a signaling cascade through IKKα homodimers that allows a different NF-κB dimer to freely translocate into the nucleus (118). Once in the nucleus, dimerized NF-κB binds to κB elements on gene promoters, which augments the expression of downstream genes for various enzymes (such as COX-1 and COX-2, implicated in neuroinflammation and neurodegeneration), adhesion molecules, chemokines, and cytokines involved in the inflammatory response (119).

2.3 Pro-inflammatory cytokines

Pro-inflammatory cytokines, such as TNF-α and IL-1β, have important roles in neuroinflammation and apoptosis. Other cytokines are anti-inflammatory and counter these inflammatory responses to provide homeostatic regulatory control. A large imbalance between pro- and anti-inflammatory cytokines is problematic. Pro-inflammatory cytokine TNF-α activates various receptors that induce apoptosis, including TNF receptors (TNFR) 1 and 2 and cluster of differentiation (CD) 95, whereas IL-1β activates IL-1 receptor (IL-1R) which induces signaling pathways leading to inflammation, excitotoxicity, and neurodegeneration (109, 120). Various TNF-α inhibitors have been examined in rodent models of CNS diseases and were found to improve neuronal survival, minimize neuroinflammation, maintain synapses, reduce apoptosis, and enhance cognitive function (121–125), implying detrimental effects of excessive TNF-α activity on CNS health and neuronal survival. IL-1β injections in the striatum of rats increased adhesion molecule expression, broke down the BBB, and promoted diffusion of toxic nitric oxide (NO) (126). Additionally, chronic neuroinflammation, activation of microglia, impaired cognitive function, and reduced neurogenesis were observed in mice engineered to overexpress IL-1β (127). In humans, elevated levels of these pro-inflammatory cytokines have been linked with various neurological disorders, including AD, PD (128, 129), stroke (130), TBI (12), and a host of psychiatric disorders that include major depressive disorder, generalized anxiety disorder, post-traumatic stress disorder, bipolar disorder, and schizophrenia (131–133). Furthermore, pro-inflammatory cytokines increase production of inducible NO synthase (iNOS), which in turn elevates levels of NO. NO exhibits multiple mechanisms of neurotoxicity, including formation of peroxynitrite and resulting DNA damage, glutamate excitotoxicity, and activation of apoptosis signaling cascades (134). In addition to the cytotoxic effects of high concentrations of NO, greater abundance of iNOS and NO allows for enhanced nitrotyrosination of neural proteins, a common feature of neurodegenerative diseases (135, 136).

2.4 ROS

Additional consequences of neuroinflammation include DNA damage, greater oxidative stress, and increases in ROS. Conversely, neuroinflammation can be a consequence of ROS. ROS are produced by mitochondrial dysfunction (137), and frequently observed in neurodegenerative disease (138–141). Oxidative stress and ROS co-occur with neuroinflammation, AD, and T2DM (142). Ferroptosis, an iron-dependent form of cell

death resulting from excess accumulation of intracellular lipids peroxidation, is linked to increased neuroinflammation, and is associated with several neurological disorders (143). ROS activate NF-κB and thus exacerbate neuroinflammatory gene and subsequent protein expression (144). Antioxidant treatments, such as N-acetyl cysteine (NAC), have demonstrated anti-ROS and anti-inflammatory capacity across a wide range of animal models of acute brain injury (TBI and stroke) and resulted in improved symptoms of military personnel who suffered a TBI in the Iraq war theater (145, 146).

2.5 Pericyte loss

In addition to neurons, astrocytes, and microglia, pericytes are a fourth cell type with evidence of GLP-1R expression and demonstrated roles in regulating neuroinflammation and neurodegeneration (147, 148). Pericytes are contractile cells found on capillaries that confer several important functions, including blood flow control through constriction and dilation of capillaries, BBB integrity through regulation of BBB protein expression, regulation of leukocyte entry into the brain, angiogenesis, and CNS injury responses (149–151). Loss or dysfunction of pericytes has been repeatedly associated with BBB damage, consequent neurodegeneration, and several CNS diseases (149, 152–156). For instance, capillary abnormalities and reduced cerebral blood flow are known characteristics of AD and are linked with pericyte dysfunction (149, 157, 158). Pericyte activity is a significant component in regulating neuroinflammation and neurodegenerative disease pathology, yet few studies examine the therapeutic potential of GLP-1R signaling in pericytes, highlighting a need for future research in this realm.

2.6 Neuroinflammation in CNS disease

Neuroinflammation can exacerbate neurodegenerative disorders, and neurodegeneration routinely feeds further neuroinflammation (159) (Figure 2). Although healthy aging can naturally stimulate neuroinflammatory signaling in the brain (160, 161), AD patients exhibit notably higher levels of neuroinflammation (128, 162). Chronic neuroinflammation can impair neuroplasticity and cognition, damage neurons, and culminate in neurodegenerative diseases epitomized by AD (106) (Figure 2H). AD is the most common neurodegenerative disorder and is identified by the accumulation of amyloid-β plaques and neurofibrillary tau tangles, which form when tau protein becomes hyperphosphorylated (163). Microglial exposure to these plaques elevates pro-inflammatory cytokine production (Figure 2A, B, C, D, E), further aggravating the disease and contributing to hippocampal dysfunction and associated memory problems in patients (164). Neurotoxic amyloid-β is produced when amyloid precursor protein (APP) is disproportionally cleaved by β-site APP cleaving enzyme 1 (BACE1) (163). Amyloid-β deposits in the AD brain activate microglia through binding to TLR4 and 6 and CD36 receptors (Figure 2A, B), initiating release of pro-inflammatory cytokines and chemokines that can then damage neurons (Figure 2D); the neuronal debris itself can also activate microglia (Figure 2C), perpetuating a cycle of chronic neuroinflammation and neurodegeneration (165) (Figure 2H). Furthermore, mass cytokine release also may disrupt microglial clearance of extracellular amyloid-β deposits by reducing the number of amyloid-β receptors expressed on the microglial cell surface (166). Transgenic mouse AD models exhibit increased markers of neuroinflammation relative to healthy controls, including elevated brain levels of IFNγ and IL-1β (166–

168). Recent research proposes that treatments targeting neuroinflammation, particularly through reduction of TNF-α activity and resulting reduction in activated microglial activity and astrocyte reactivity, may outperform treatments targeting amyloid-β pathology in AD clinical trials (114). Although the amyloid-β hypothesis has persisted as a main contributor to AD pathology and morbidity, anti-amyloid therapies have not proven effective in preventing disrupted cognition (169). A recent GWAS examining common genetic features of AD has identified neuroinflammatory pathways (mainly associated with TNF) to be a key feature of AD (1), offering perhaps a more viable target for treating the disease.

PD is the second most common neurodegenerative disorder and features characteristic neuroinflammation and dopaminergic degeneration in the substantia nigra region of the midbrain—neuroinflammation exacerbates PD progression through interactions with PD-linked gene products, mitochondrial dysfunction, and oxidative stress (170). Drugs targeting inflammatory pathways have been proposed as treatments to slow PD progression (171). In the PD brain, increased pro-inflammatory cytokine levels, microglial activation, ROS, and elevated α-synuclein in neurons are indicative of a neuroinflammatory environment (5). This neuroinflammation aggravates pre-existing noxious genetic factors and contributes to degeneration of dopaminergic neurons in PD (5, 171).

3. GLP-1R Signaling and Neuroinflammation

3.1 Brain IR and neuroinflammation

In the brain, IR exacerbates neuroinflammation (Figure 3). IR produces chronically elevated blood sugar levels and an unhealthy imbalance of lipids in the blood (Figure 3A), conditions which can damage and increase the permeability of the BBB (48) (Figure 3B). In response to BBB damage, free fatty acids, and high blood glucose (Figure 3C), microglia are activated into a pro-inflammatory state (Figure 3D), which can lead to cytokine release (Figure 3E) and downstream neuroinflammatory cascades (Figure 3F) and reactive astrogliosis (Figure 3G) (48). In turn, neuroinflammation further damages the BBB, making it increasingly permeable (172)—this enhanced permeability elevates the already-high blood glucose concentrations in the brain and contributes to a vicious cycle of neuroinflammation as a result of hyperglycemia (173) (Figure 3H). Other neuroinflammatory consequences of brain IR include vascular dysfunction (which has been linked to dementia accompanying neurodegenerative disease (174)), greater NO production, oxidative stress, and consequent neuroinflammation (99). Additionally, chronic hyperglycemia and IR worsen neuroinflammation by stimulating excessive mitochondrial respiration in the brain, which leads to increased production of ROS and downstream activation of NF-κB, cytokine production, and corresponding neuroinflammatory signaling cascades (172).

3.2 Brain IR, neuroinflammation, and AD

Brain IR is a risk factor for neurodegenerative diseases such as AD as well as motor disorders such as multiple system atrophy (formerly known as Shy-Drager syndrome), a sporadic and progressive neurodegenerative condition commonly identified by motor abnormalities (ataxia and parkinsonism) and autonomic dysfunction (175), and PD

(176–179). Several studies using animal models provide strong evidence that IR and neuroinflammation feed AD neuropathology (167, 180–182). For example, in a double transgenic mouse model of AD (APP/PS1), brain levels of pro-inflammatory cytokines (IFNγ, IL-1β, and IL-4), reactive astrocytes, and IRS-1 phosphorylated at serine 616 (a marker of IR (99, 178)) were raised, suggesting that neuroinflammation and IR interact in the AD brain (167). Other studies in transgenic mouse models of AD (5xFAD; APN−/− and APP23) have found that disruptions in insulin signaling increase microglial activation, neuroinflammatory signaling, cognitive deficits, and AD neuropathology (181, 182). Brain IR also promotes the hyperphosphorylation of tau, leading to the formation of tau neurofibrillary tangles characteristic of AD (99). Conversely, certain neurobiological characteristics of AD can aggravate IR and neuroinflammation. Amyloid-β oligomers stimulate serine phosphorylation of IRS-1, thus worsening brain IR, and a feed-forward cycle of IR and amyloid-β plaque formation ensues (99). Moreover, solubilized amyloid-β can trigger pro-inflammatory signaling cascades that amplify vascular inflammation and vasoconstriction (183). The unhealthy interactions between IR, inflammatory signaling cascades, amyloid-β deposition, endothelial dysfunction, and tau yperphosphorylation largely contribute to the progression of neuroinflammation and neurodegeneration in AD in both animal models and humans (66, 184).

3.3 GLP-1R agonists as treatment for neurodegeneration

Drugs that target brain IR by promoting healthy incretin and insulin signaling are a promising research direction for the treatment of neurodegenerative disease (185–188). GLP-1R has evidenced expression in neurons, microglia, and astrocytes across key brain regions (10) (Figure 4: right panel) and GLP-1R agonists have demonstrated neuroprotective and anti-inflammatory properties (189–191). GLP-1R and other secretin receptors GIPR and GcgR signal via multiple anti-inflammatory pathways (192, 193) that could be stimulated to reduce neuroinflammation and ameliorate conditions of neurodegenerative diseases (Figure 4: left panel). Ligand binding-induced activation of the $G\alpha_s$ subunit of a secretin receptor's associated G protein stimulates adenylyl cyclase and consequently elevates cyclic adenosine monophosphate (cAMP) levels. cAMP activates exchange protein activated by cAMP (Epac) which has downstream anti-inflammatory and antiapoptotic effects (194, 195). cAMP also stimulates protein kinase A (PKA), which stimulates MAPK/ERK anti-inflammatory signaling and phosphorylates and activates the transcription factor cAMP response element (CRE)-binding protein (CREB) (196, 197). Another signaling pathway, the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, likewise amplifies CREB signaling (198). CREB binds to CRE promoters and enhances expression of downstream genes, several of which are anti-inflammatory and neuroprotective, such as B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra large (Bcl-xL) (199). Bcl-2 and Bcl-xL are antiapoptotic molecules that inhibit the activity of pro-apoptotic proteins including Bcl-2 associated agonist of cell death (BAD), p53, and caspases (12, 199, 200). CREB also activates apurinic/apyrimidinic endonuclease 1 (APE1), with downstream effects of ameliorating oxidative stress-associated DNA damage (201). Notable in Figure 4 is that key signaling proteins, particularly Akt, act as a control center and thereby are master regulators of downstream biochemical cascades that can impact cell survival, metabolism, protein homeostasis, and inflammation—these proteins are a central hub of both insulin and GLP-1 signaling.

The relevance of Akt in PD development is backed by reports of selective loss of dopaminergic neurons associated with a decreased expression of Akt pS473 in the PD brain (202, 203). Additionally, PD risk factor genes, such as PINK1, appear to converge and interact with Akt; while inhibition of this cascade promotes neurodegeneration (204, 205). The site of action of incretin receptor activation on PI3K/Akt signaling has not been definitively elucidated but could be downstream of IRS-1 activation by incretin signaling (12). In addition to CREB regulation, the PI3K/Akt pathway also inhibits NF-κB inflammatory signaling; inhibits Forkhead box protein O1/O3 (FOXO1/O3)-, Jun N-terminal kinase (JNK)-, and glycogen synthase kinase-3β (GSK-3β)-mediated apoptotic signaling; and stimulates mammalian target of rapamycin (mTOR) neuroprotective signaling (12, 206, 207). As in Figure 4 and above, GLP-1R stimulation as well as insulin also trigger the MAPK pathway. This is comprised of three primary arms, the JNKs, the ERKs, and p38 kinases that, together, can either augment survival and proliferation or engender stress and apoptosis, depending on the cell type and stimulus. With considerable cross talk and feedback between these pathways, these potentially protective signaling cascades downstream of GLP-1R, GIPR, and GcgR indicate the great potential in targeting these receptors for anti-inflammatory and anti-neurodegenerative drug treatments.

Numerous GLP-1R, GIPR, and/or GcgR agonists have been developed for the treatment of T2DM and obesity and have the potential to be repurposed for the treatment of neurodegenerative diseases (Table 1). GLP-1R agonists have been tested in preclinical and clinical studies to investigate whether restoring brain insulin signaling is a viable treatment option for neuroinflammation and corresponding neurodegeneration.

3.4 GLP-1R agonism reduces neuroinflammation in preclinical studies

The link between IR and neuroinflammation is highlighted by a multitude of cell culture and animal studies that utilize various incretin receptor-stimulating treatments to maintain healthy insulin signaling and reduce markers of neuroinflammation and neurodegeneration. Such preclinical studies are briefly overviewed in the following sections.

GLP-1—In the brain, GLP-1R stimulation by GLP-1 is associated with neuroprotective benefits to the CNS. Research in SH-SY5Y human neuroblastoma cells found that GLP-1 treatment promoted neuronal viability through anti-apoptotic, anti-oxidative, and neurotrophic mechanisms, involving elevated PKA and PI3K pathway activity, decreased expression of apoptotic factors, and increased expression of anti-apoptotic factors (87, 191). Furthermore, GLP-1 activity has been demonstrated to have anti-neuroinflammatory and anti-neurodegenerative effects in preclinical model systems. Cultured rat primary hippocampal neurons treated with GLP-1 were protected against amyloid-β-induced neurotoxicity (218). In mice pretreated with LPS to simulate AD-like neuroinflammation, GLP-1-increasing treatments reversed inflammation-induced synaptic impairments in the hippocampus (219); reduced amyloid-β deposition, inflammatory glial activation, and expression of inflammatory molecules COX-2, TNF-α, IL-1β, and TLR4 (220); and inhibited activity along the inflammatory NF-κB/TLR4 and Akt/GSK-3β signaling pathways (221). Moreover, increasing GLP-1 levels in mice pretreated with LPS reduced memory impairment (221) and improved cognitive performance (219); in mice pretreated

with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to simulate motor dysfunction characteristic of PD, GLP-1 augmentation improved motor abilities (221). The potential for GLP-1 to improve AD and PD pathology was reinforced in experiments using primary mouse mixed neuronal cultures challenged with amyloid-β (modeling AD) or α-synuclein (modeling PD), in which GLP-1 metabolite (9–36) enhanced cell survival and decreased M1-like microglia numbers (191). Additionally, the metabolite reduced IL-6 and TNF-α levels secreted by LPS challenged human HMC3 and mouse IMG microglial cells lines (191). Hence, multiple studies have independently demonstrated that GLP-1R stimulation by GLP-1 and, more recently, by its primary metabolite GLP-1(9–36) (191) are anti-inflammatory and neuroprotective.

Exendin-4/Exenatide—Neuroprotective and neurotrophic effects of exendin-4 treatment have been observed in mouse models of various neural diseases, including middle cerebral artery occlusion-induced stroke (4), ALS in SOD1 G93A mutant mice (222), and T2DM-related neuropathies induced by pyroxidine (223). Furthermore, a study in cultured SH-SY5Y human neuroblastoma cells demonstrated greater neuronal viability and proliferation with exendin-4 treatment (87). Exendin-4 treatment has been found to exhibit significant anti-inflammatory effects as well, especially in the context of neurodegenerative disease—exendin-4 treatment in cultured primary rat astrocytes (224) and neurons (225) reduced amyloid-β-induced oxidative stress, cytotoxicity, and neuroinflammation. In transgenic mouse models of AD (5xFAD and 3xTg-AD) as well as in human cortical neurons obtained post-mortem, GLP-1R stimulation using an engineered exendin-4 treatment reduced amyloid-β-induced microglial activation, thus limiting neuroinflammation; inhibited reactive astrogliosis through the reduction of inducers TNF-α, C1q, and IL-1α; and improved neuronal viability (226). Similar effects, using the same GLP-1 mimetic, were demonstrated in a mouse PD model (103). Furthermore, GLP-1R activation through exendin-4 treatment was found to improve recognition memory impairment by dampening signaling along the AMPK/NF-κB pathway, reducing levels of neuroinflammatory cytokines IL-1β, IL-1β p17, and TNF-α, and increasing synaptic protein levels in mice with spared nerve injury modeling neuropathic pain (227). Markers of AD (amyloid-β deposition, abnormal glycoprotein glycan expression, and cognitive and memory impairments) and of brain IR (IRS-1 serine phosphorylation and elevated blood glucose levels) were reduced with exendin-4 treatment in transgenic mouse models of AD (225, 228, 229). With relevance to PD, MPTP and 6-OHDA mouse models of PD treated with exendin-4 exhibited enhanced motor function and dopamine signaling and minimized neurodegeneration (4, 101).

Exenatide, a synthetic version of exendin-4, exhibits similar anti-neuroinflammatory and anti-neurodegenerative benefits in preclinical models. In a 3xTg-AD mouse model, exenatide treatment reversed high fat diet-induced impairments of BDNF signaling and reduced levels of NF-κB and peroxisome proliferator-activated receptor proteins (PPARs) α and γ, indicating reduced inflammation; however, there was no significant effect on systemic metabolism nor cognitive performance in response to exenatide treatment in this experiment (230). Exenatide has also been found to combat neuroinflammation and AD as indicated by reduced ‘nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain containing 2’ (NLRP2; a component of the inflammasome in

astrocytes) levels in the piriform cortex, reduced amyloid-β deposition, and improved cognition in 5xFAD transgenic mice modeling AD (224). PD mice respond to exenatide treatment as well—6-OHDA and MitoPark PD mouse models treated with a sustained release exenatide formulation (PT320) experienced neuroprotective effects of the drug, including improved motor function (231) and enhanced dopamine signaling activity in midbrain networks (232). Additionally notable in these two PD preclinical studies was an exenatide-mediated reduction in L-3,4-dihydroxyphenylalanine (L-DOPA)-induced abnormal involuntary movements (AIMs) in the rat 6-OHDA model and a slowing of disease progression, dopamine loss, and motor deficits in the MitoPark mouse when administered a clinically translatable drug dose (231).

Liraglutide—Liraglutide is structurally similar to GLP-1; however, its acylation (supporting binding to serum albumin) increases the peptide's half-life by slowing absorption and evading recognition by DPP-IV (233). Although FDA-approved for the treatment of T2DM, research indicates that liraglutide may provide neuroprotective effects. For example, in cultured SH-SY5Y human neuroblastoma cells, liraglutide pretreatment decreased oxidative stress and promoted neuroprotection and neurotrophy, likely through a cAMP-dependent PKA/CREB signaling pathway (234). Results of preclinical studies of liraglutide have important implications for treating AD and neuroinflammation. Interestingly, a 2016 study reported no significant effect of liraglutide treatment in reducing amyloid-β plaque load in transgenic APP/PS1 mouse models (235). This could potentially be due to relatively poor BBB penetration of liraglutide and highlights the need for the research into the development of GLP-1R-stimulating drugs that can measurably reach the brain from the periphery. However, other research has found that liraglutide appears capable of crossing the BBB in pharmacologically relevant amounts and acting on GLP-1R in the CNS (236). More recently, in a study using a streptozotocin (STZ)-induced insulin resistant and a 5xFAD mouse model, liraglutide treatment reversed markers of neuroinflammation (particularly astrocyte reactivity and microglial activity in the cortex and hippocampus) and amyloid-β plaque deposition (237). Furthermore, liraglutide pretreatment in human SH-SY5Y neuroblastoma cell culture protected against the apoptotic effects of okadaic acid and limited tau activation and BACE1 expression, and in a rat model of okadaic acid-induced AD, liraglutide improved rat memory function and cognition and reduced neuronal apoptosis, tau phosphorylation, and BACE1 levels (163). These more recent studies suggest that liraglutide may be efficacious in improving certain markers of neuroinflammation and AD when administered in a sufficiently high dose. However, since relatively few studies evaluate plasma drug levels, how drug doses selected for evaluation in preclinical studies relate to those safely tolerated in and translatable to humans remains unknown.

Lixisenatide—Fewer studies have investigated neuroprotective effects of lixisenatide, a long-lasting GLP-1R agonist confirmed to be capable of measurably crossing the BBB and exerting neuroprotective effects (236). These neuroprotective effects of lixisenatide treatment include reductions in amyloid-β plaques, tau neurofibrillary tangles, and neuroinflammation (measured by microglial activation in the hippocampus), as demonstrated by a study utilizing an APP/PS1/tau mouse model of AD (238). These effects were a result of augmented PKA/CREB pathway and inhibited p38/MAPK pathway

signaling due to GLP-1R stimulation (238). Lixisenatide has also been found to enhance LTP in the hippocampus, improve working memory, maintain synapses, reduce amyloid-β plaque levels, and combat neuroinflammation in AD rodent models (APPswe/PS1ΔE9 mice and rats) (239–241). Furthermore, in a MPTP PD mouse model, lixisenatide treatment was associated with neuroprotective benefits and reduced PD-related motor impairment (242).

DPP-IV Inhibitors—Although not GLP-1R agonists, DPP-IV inhibitors block the action of DPP-IV and therefore reduce the rate of breakdown of GLP-1 and GIP, consequently raising levels of endogenous incretins and promoting healthy incretin hormone signaling. Numerous DPP-IV inhibitors are FDA-approved for the treatment of T2DM, and DPP-IV inhibition has demonstrated efficacy in reducing neuroinflammation and AD markers—DPP-IV inhibition in an STZ-induced rat model of AD elevated GLP-1 levels and decreased levels of amyloid-β, total tau, phosphorylated tau, and pro-inflammatory cytokines TNF-α and IL-1β in a dose-dependent manner (243). Furthermore, treatment of Zucker diabetic fatty (ZDF) rats with the DPP-IV inhibitor alogliptin raised the expression of CREB target genes and decreased blood glucose in the hippocampus, thus dampening the neuroinflammatory response (244). Anti-neuroinflammatory effects were also observed with DPP-IV inhibitor sitagliptin, which significantly quelled the neuroinflammatory response in various rodent models by reducing levels of the pro-inflammatory molecules TNF-α, IL-6, IL-17, and CD163 and by raising levels of the anti-inflammatory molecules TGF-β and IL-10 (207). With regard to neurodegenerative disease treatment, sitagliptin has also been found to reduce amyloid-β deposition, have antiapoptotic and antioxidative properties, and improve scores on mini-mental state exam (MMSE) tests for dementia of elderly people with and without AD (207). Linagliptin, another DPP-IV inhibitor, was found to increase levels of GLP-1 and GIP in the brain; reduce amyloid-β, tau phosphorylation, and neuroinflammation (indicated by reduced glial fibrillary acidic protein (GFAP) immunoreactivity); and improve cognitive deficits of AD in a 3xTg-AD mouse model (245). Similarly, DPP-IV inhibitor Gramcyclin A treatment in a recent APP/PS1/tau triple transgenic mouse model of AD stimulated GLP-1R signaling, promoted glucose uptake in the brain, decreased levels of activated microglia and neuroinflammation in the hippocampus, and reduced amyloid-β plaques, soluble amyloid-β–40, and soluble amyloid-β–42 levels (246). As a cautionary note, drug levels were not evaluated in majority of the above studies, and how the selected doses in these preclinical studies relate to those translatable to humans remains unknown.

Dual Agonists—Dual incretin agonists co-stimulate both GLP-1R and GIPR and, in general and when well-designed, have been found to outperform single GLP-1R agonists in ameliorating markers of neuroinflammation and neurodegeneration (247–249). Several GLP-1R/GIPR dual agonists generated by Hölscher and colleagues have been found to have anti-neuroinflammatory and anti-neurodegenerative benefits in preclinical studies (247–250). Treatment of APP/PS1 and APP/PS1/tau mouse models of AD with the Hölscher dual agonist DA-JC4 reduced pro-inflammatory cytokine levels, phosphorylated tau levels, and amyloid-β plaque load; improved memory impairments and mitochondrial volume and numbers; and strengthened synapses and LTP in the hippocampus (249, 250). DA-CH5, another of the Hölscher dual agonists, outperformed liraglutide in reducing neuroinflammation (as evaluated by reduced levels of activated microglia and astrocytes),

apoptosis, and oxidative stress in a MPTP mouse model of PD (247). Similarly, DA-JC1 outperformed liraglutide in reducing oxidative stress and ROS, enhancing neuronal viability and neurogenesis, and reducing reactive astrocytes and neuroinflammation, both in an APP/PS1 mouse model of AD and in cultured SH-SY5Y human neuroblastoma cells challenged with hydrogen peroxide (248). Anti-neuroinflammatory benefits have also been observed using the original GLP-1R/GIPR agonist of DiMarchi and colleagues (termed "twincretin"). In cultured SH-SY5Y human neuroblastoma cells, twincretin has been demonstrated to enhance neurotrophic signaling through stimulating the CREB pathway and promote neuronal survival in conditions modeling neuroinflammation (251). Additionally, twincretin's actions on elevating levels of cAMP (the initial event in the cascade triggered by receptor engagement, binding, and activation) and inducing neurotrophic activity were significantly greater than equimolar concentrations of single GLP-1R or GIPR agonists (251). Dual agonists also offer numerous other neuroprotective benefits including reduced oxidative stress and improved memory function, synaptic health, and neurogenesis in mice (252), as well as neuroprotective and antioxidant properties in rodent models of TBI (12, 100, 251). Interestingly, the human dose of liraglutide (single GLP-1R agonist) and twincretin (dual GLP-1R/GIPR agonist) in T2DM is the same: 1.8 mg subcutaneously daily. In the preclinical evaluation of twincretin in concussive head injury by Bader and colleagues (100), a direct comparison was made to liragultide treatment—a 247.6 μg/kg dose of liraglutide in mouse, which translates to a 1.8 mg dose in an 88.8 kg human, provided similar efficacy to a 5-fold lower dose of twincretin (50 μg/kg) to mitigate TBI-induced neuroinflammation, neuronal loss and behavioral impairments.

Triple Agonists—"Triagonists" are unimolecular peptide drugs that simultaneously target GLP-1R, GIPR, and GcgR. While primarily in development for treating metabolic disease (37), these triple agonists have also been linked with reduced neuroinflammation and neurodegeneration. A novel triple agonist stimulated CREB pathway signaling in hippocampal neurons in a 3xTg-AD mouse model of AD and produced improvements in cognition, working memory, and long-term spatial memory (253). The triple agonist was also found to reduce amyloid-β plaques, neuroinflammation, and oxidative stress and increase neurogenesis, number of synapses, and BDNF expression in APP/PS1 mice (254), indicating a potential for treating AD. In SH-SY5Y human neuroblastoma cells, a GLP-1R/GIPR/GcgR triagonist reduced oxidative stress, enhanced neuronal health and viability, and minimized glutamate excitotoxicity, highlighting the neurotrophic/protective effects of secretin receptor stimulation (255). The ability of the triagonist to elevate cAMP levels was dramatically greater than that of a single GLP-1R agonist on an equimolar basis (255), and selective antagonists for each of the three secretin receptors were required to inhibit the triagonist mediated neurotrophic/protective actions, thereby suggesting balanced pharmacological action across these receptors (255). Moreover, the triagonist significantly reduced TNF-α secretion in primary mouse microglia challenged with LPS (255). Additionally, in a 30-gram weight drop close head injury mouse model of mild concussive TBI, the triagonist improved memory function following injury (255). These findings support the successful translation of neuroprotective and anti-neuroinflammatory properties from cellular to animal studies for this promising drug.

3.5 GLP-1R agonists in human trials

Use of incretin receptor-targeting drugs for the treatment of CNS diseases is further supported by meta-analyses revealing that T2DM patients' prescribed GLP-1R stimulating medications may promote CNS health. Cohort studies of T2DM patients using GLP-1R stimulating drugs, either through GLP-1R agonism or DPP-IV inhibition, exhibited decreased risk of developing PD (271, 272). Another cohort of T2DM patients taking GLP-1R agonists had a reduced risk of stroke relative to patients who were taking GLP-1R-stimulating drugs (3, 273). These analyses suggest CNS disease modifying capability of drugs that promote GLP-1R signaling. Thus, clinical studies in humans have been proposed and completed to investigate the potential for GLP-1R agonists in treating neurodegenerative diseases (Table 2) and will be overviewed in the following sections.

GLP-1R agonists liraglutide (Victoza®), semaglutide (Ozempic®, Rybelsus®), exenatide (Bydureon®, Byetta®, PT320, NLY01), and lixisenatide (Adlyxin®/Lyxumia®) have been FDA-approved or are in trials for the treatment of T2DM and are currently being investigated to determine their potential efficacy in treating neurodegenerative diseases. Only trials of liraglutide and exenatide have reached completion. In a phase 2 clinical trial investigating liraglutide treatment in patients with AD, 6 months of liraglutide treatment significantly increased glucose transport at the BBB, elevating the cerebral metabolic rate for glucose and reversing the abnormalities in brain glucose transport commonly associated with AD pathology (274). In addition, a human study found that 12 weeks of liraglutide treatment improved brain connectivity but had no measurable effect on cognition (275). Furthermore, this research revealed a negative association between fasting plasma glucose level and bilateral hippocampal and anterior medial frontal connectivity (275), indicating a potential relationship between incretin signaling (regulates plasma glucose) and neural abnormalities. Most recently, a 52-week phase 2 clinical trial of liraglutide in PD patients found that liraglutide treatment was safe and well-tolerated and improved non-motor symptoms, mobility, and quality of life (276). Currently awaited is the peer-reviewed analysis of the Evaluating Liraglutide in Alzheimer's Disease (ELAD) study, a 12-month, multi-center, randomized, double-blind, placebo-controlled, phase 2b clinical trial of liraglutide in mild to moderate Alzheimer's dementia (204 patients; NCT1843075) where the primary outcome is to measure changes in cortical glucose metabolic rates during the 12-month liraglutide treatment versus the placebo group (277). In a preliminary correspondence, there was no significant change in this primary marker; however, liraglutide was found to be well-tolerated, and positive numerical outcomes were evident amongst secondary outcome measures that comprise various markers of AD and neuroinflammation, including changes in several cognitive measures, brain volume and connectivity, microglial activation, tau phosphorylation, and amyloid-β levels (278). Another trial that is currently in progress investigates the safety and efficacy of liraglutide in treating patients with PD (279).

At present, exenatide is the most prevalent GLP-1R agonist in clinical trials for AD and PD treatment. In an 18-month phase 2 clinical trial investigating the safety and efficacy of exenatide (administered as BID Byetta®) in treating early AD, extracellular vesicles isolated from the patients exhibited reduced amyloid-β–42 concentrations with exenatide treatment (257). However, in the same study, there were no significant differences between exenatide

treatment and placebo in patients' cognition, cortical thickness and volume, or biomarkers of AD in CSF or plasma (257). This was a small double-blind, randomized, placebo-controlled clinical trial whose primary outcome was to assess safety and tolerability. A total of 18 patients completed the study, and partial outcomes were available on 21 patients prior to the premature termination of the study when the sponsor withdrew provision of drug and matched placebo pens. Exenatide proved to be well-tolerated but the study was underpowered to truly evaluate markers of efficacy and drug action (257). Hence, further research is required to elucidate the effects of exenatide and related drugs in AD patients.

Exenatide may also be efficacious in treating PD—a proof of concept, single-blinded phase 2 clinical trial assessed 45 moderate PD patients randomly delegated to receive subcutaneous exenatide (BID Byetta®) or to act as controls for 12 months. The trial evaluated overnight off-medication motor scores at baseline, time-dependently over the study, and following a 2-month washout period and found a significant exenatide-mediated improvement in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 that persisted through the washout period (258). A follow up of available patients indicated that the exenatide actions endured over 12 months following drug cessation (280). This open label clinical trial spurred a larger double-blind, randomized, placebo-controlled trial by the same group that evaluated once weekly extended-release exenatide (Bydureon®) in moderate PD patients and reported significantly improved off-medication motor scores (13) assessed by MDS-UPDRS part 3, the primary outcome measure. In accompanying studies evaluating the contents of blood sampled, neuronal-derived exosomes demonstrated that the efficacious exenatide interactions were mediated through the brain insulin, Akt, and mTOR signaling pathways in PD patients (281). Moreover, in a post-hoc analysis, 12 weeks of exenatide treatment in patients with moderate stage PD was found to improve mood and reduce indicators of depression, and these beneficial effects persisted up to 48 weeks following exenatide treatment (282). Following the success of these single-center exenatide PD clinical trials, Foltynie and colleagues have initiated a multi-center, phase 3 clinical trial to evaluate once weekly extended-release exenatide (Bydureon®) over a 96-week period to define whether exenatide's advantageous actions are symptomatic or disease-modifying to potentially impact disease progression, or combined elements of both (Exenatide-PD3; NCT04232969). A sustained-release exenatide phase 2, multi-center clinical trial involving a once weekly and once every other week administration (PT320; Peptron; NCT04269642) has recently been completed in South Korea that largely follows the clinical protocol of Foltynie and colleagues (13), and results are awaited. This trial, likewise, evaluates the contents of brain-enriched exosomes to define biomarkers of drug response. Additional clinical trials for exenatide and alike drugs in neurodegenerative disease treatment are currently underway (Table 2).

Although no clinical trials have yet been completed, semaglutide is also being investigated for treatment potential for AD and PD. Two phase 3 clinical trials are currently recruiting patients with early AD to test the effects of oral semaglutide treatment on dementia ratings and measures of various cognitive and behavioral symptoms of AD (283, 284). In the United Kingdom, a phase 2 clinical trial is recruiting to evaluate effects of oral semaglutide treatment on tau regulation in aged individuals (285). As concerns PD, a phase 2 trial has

been proposed to evaluate the effects of subcutaneous semaglutide treatment in improving motor function deficits in patients with PD (286).

The utilization of GLP-1R agonists to treat neurodegenerative diseases other than AD and PD, such as glaucoma and Friedreich ataxia (FRDA), has been investigated in very few clinical trials and requires further research. Glaucoma is a neurodegenerative disorder involving the deterioration and death of retinal ganglion cells (RGCs) and is, in large part, driven by neuroinflammation (287–289); thus, glaucoma has potential to be treated with incretin receptor agonists. In an observational retrospective study, the incidence of new glaucoma diagnoses in a cohort of approved GLP-1R agonist users was compared to that in a cohort of healthy control participants (11). The GLP-1R agonist user cohort exhibited a significantly lower incidence of new glaucoma diagnoses relative to the control cohort, suggesting a potential neuroprotective effect of GLP-1R stimulation in patients with glaucoma (11). FRDA is a heritable neurodegenerative movement disorder fueled and exacerbated by neuroinflammation (290–292), which could make it a candidate for GLP-1R agonist treatment. Exenatide treatment was found to re-elevate reduced levels of frataxin, a critical mitochondrial protein, in FRDA patients, which can enhance mitochondrial health and function and could, by extension, reduce neuroinflammation and neurodegeneration characteristic of the disease (293)—again, providing a potentially fruitful area of future basic and clinical research. Similarly, studies by Meissner and colleagues (178) demonstrated the presence of impaired insulin/IGF-1 and IR in vulnerable brain regions of multiple system atrophy patients and a related transgenic mouse model, and their mitigation in the latter by exendin-4, likewise suggesting a promising area of future research.

Finally, albeit it not a classical neurodegenerative disorder, studies by Sinclair and colleagues (294) demonstrated the efficacy of exenatide in reducing hypertension in a rat model of hydrocephalus, which has relevance to the human disorder of idiopathic intracranial hypertension for which effective pharmacological treatments are currently lacking (295). The choroid plexus expresses an abundance of GLP-1Rs and GLP-1R agonists reduce the activity of Na^+/K^+ ATPase, a marker of CSF secretion and, thereby, intracranial pressure (294). Whereas the primary pathogenesis of idiopathic intracranial hypertension remains to be identified, various mechanisms have been suggested to underpin the elevated CSF pressure that include heightened CSF generation, diminished CSF re-absorption, cerebral edema, and a raised cerebral venous pressure (296), and there is a proposed neuroinflammatory element (297). Early neuronal cell loss, later vision loss, and a host of sequela, such as severe chronic headache, ensue (298). A recent randomized, placebo-controlled, double-blind clinical trial of exenatide in women with idiopathic intracranial hypertension significantly decreased intracranial pressure, reduced headache frequency, and improved visual acuity in the treatment arm over the 12-week duration of the study (299). Following up on this, a 24-week randomized double-blind clinical trial of Presendin (which contains 2 mg of exenatide) versus a matching placebo group (once weekly) has just been initiated with a focus to evaluate 240 idiopathic intracranial hypertension patients (NCT05347147).

GLP-1R agonists may additionally have potential in treating neurological disorders that are not classified as neurodegenerative diseases, given the wealth of evidence for

neurotrophic, neuroprotective, and anti-inflammatory properties of GLP-1R signaling. Extensive preclinical studies using cellular and animal models of TBI have revealed that GLP-1R stimulation provides neurotrophic, anti-neuroinflammatory, anti-neurodegenerative, and anti-oxidative effects and not only mitigates cognitive and memory impairments but blocks TBI-initiated gene pathways leading to longer-term neurodegenerative diseases (100, 234, 251, 255, 300–305). In addition, GLP-1R agonists may protect against ischemic stroke (4) and ameliorate biological consequences of stroke, as indicated by aforementioned meta-analyses (3, 273). Furthermore, studies in animal and cellular models of ischemic stroke demonstrated that GLP-1R stimulation reduced neuroinflammation (2, 306), endothelial leakage (2), neural apoptosis (307), and ROS (308); protected the BBB (306, 308); and enhanced cerebral blood flow (309). MS, a disease in which the immune system attacks the CNS, demyelinates axons, and disrupts nervous system signaling, may also be treatable using GLP-1R agonism. Preclinical trials in rodent models of MS report that GLP-1R agonists were neuroprotective, improved myelination, and reduced neuroinflammation, oxidative stress, and reactive astrogliosis (102, 310–312). Clinical trials in these conditions should be considered in order to investigate the therapeutic potential of GLP-1R agonists across a broader range of neurological diseases.

4. Conclusion

An abundance of research in cellular and animal model systems highlights the potential for GLP-1R agonists in reducing neuroinflammation and treating neurodegenerative diseases. Many GLP-1R agonists have already been approved by the FDA for the treatment of diabetes and obesity and could be repurposed for the treatment of neuroinflammation and neurodegeneration. This repurposing will require additional research in human clinical trials to confirm the safety, tolerability, and efficacy of each drug in reducing neuroinflammation in the human brain, as well as reveal the implications for neurodegenerative disease treatment. Several clinical trials have been completed or are currently underway to investigate the utility of GLP-1R agonists in treating neurodegenerative diseases, and the use of exosomes to evaluate biomarkers of drug target engagement and biological cascades involved in disease progression would provide valuable insight into drug action. In future research on the development of effective incretin receptor-stimulating drugs for reducing neuroinflammation as well as mitigating disease progression via multiple potential neurotrophic/protective actions, important considerations should include BBB penetration and the demonstrated enhanced efficacy of multi-agonism relative to single agonism agents. Across preclinical studies, the introduction of pharmacokinetics can provide a valuable measure as to whether chosen drug doses have any translatable relevance to the human condition.

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Declaration of interests:

NHG is an inventor on patents related to incretin mimetics and has assigned them in entirety to the National Institute on Aging, NIH, US Government, and hence has no personal rights to these patents. The National Institute on Aging, NIH, has a Cooperative Research and Development Agreement with Peptron Inc. (S. Korea) to support the evaluation of GLP-1R agonists in neurodegenerative disorders. All other authors declare no conflict of interest.

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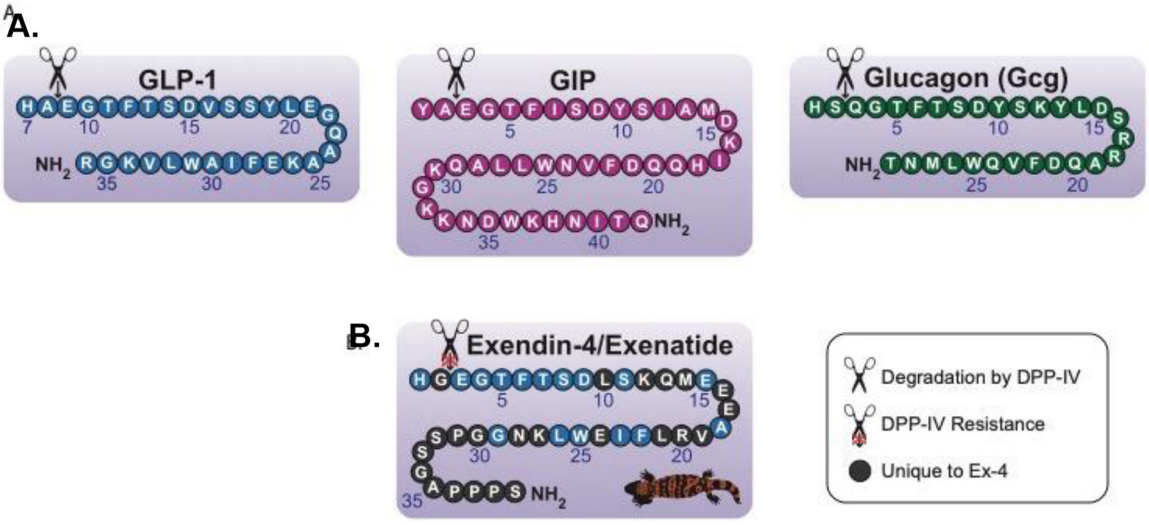

Figure 1.

(A) The endogenous secretins have similar amino acid sequences and structures, most notably their favorable cleavage sites for DPP-IV. This results in very short half-lives for these peptides. (B) Exendin-4 is a GLP-1 analog naturally occurring in Gila monster lizard venom. The unique glycine residue at the DPP-IV cleavage site renders the protein unrecognizable by DPP-IV and prolongs the half-life of the peptide. Thus, the exendin-4 backbone has been utilized in the creation of longer-acting synthetic GLP-1R agonists. Figure adapted from *Glotfelty et al. 2020* (5).

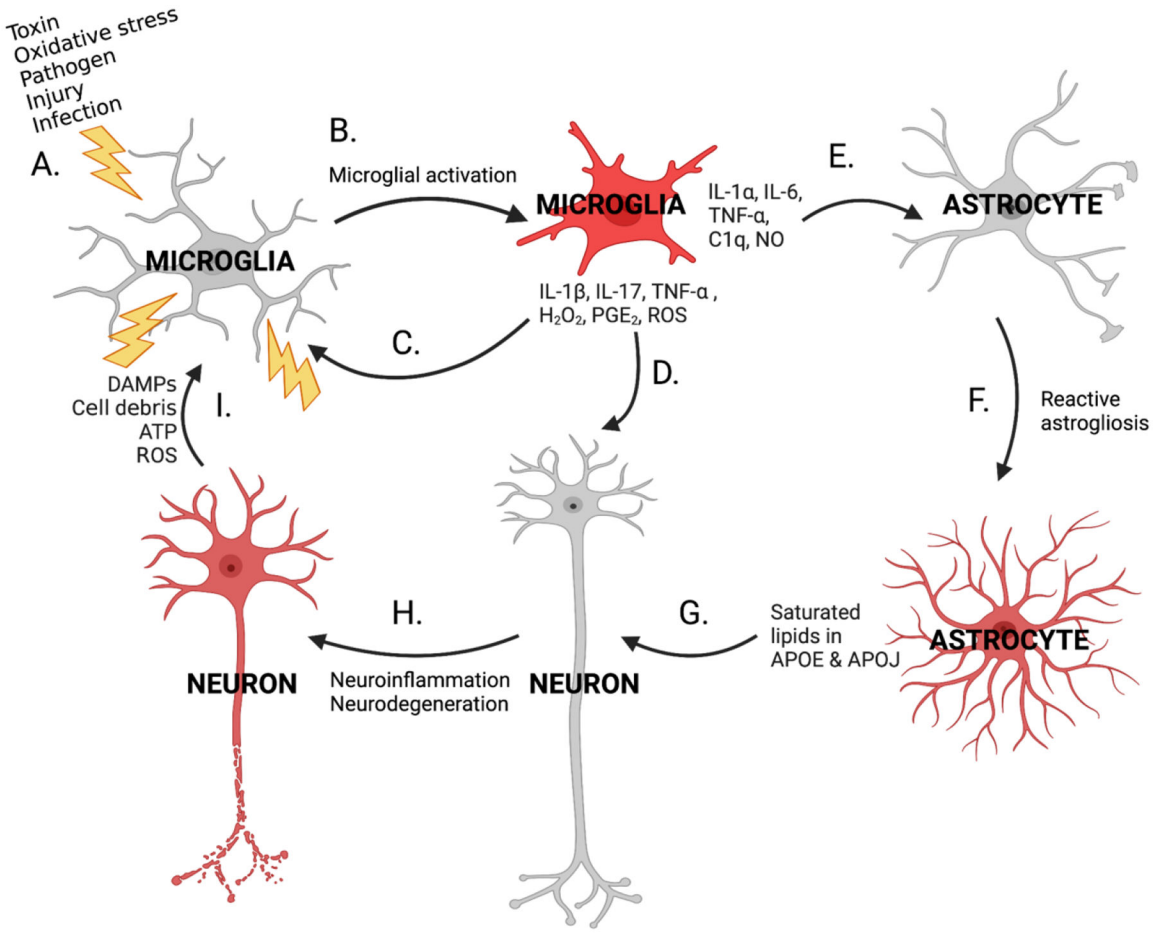

Figure 2.

Cycle of neuroinflammation. Various cellular stressors (A) can activate microglia (B), which release cytokines, chemokines, and other pro-inflammatory molecules onto neurons (D) and astrocytes (E). These pro-inflammatory molecules can also bind to microglia in an autocrine fashion, triggering activation of additional microglia and further inflammatory signaling (C). Intracellular neuroinflammatory pathways in astrocytes and neurons are stimulated in response. As a result, a subpopulation of astrocytes undergoes reactive astrogliosis and convert to their neurotoxic reactive form (F) and release APOE and APOJ particles containing harmful saturated lipids onto neurons (G), producing further neuroinflammation and neurodegeneration (H). Damaged neurons release DAMPs, cell debris, ATP, and ROS and activate additional microglia (I), recommencing and amplifying the cycle of neuroinflammation.

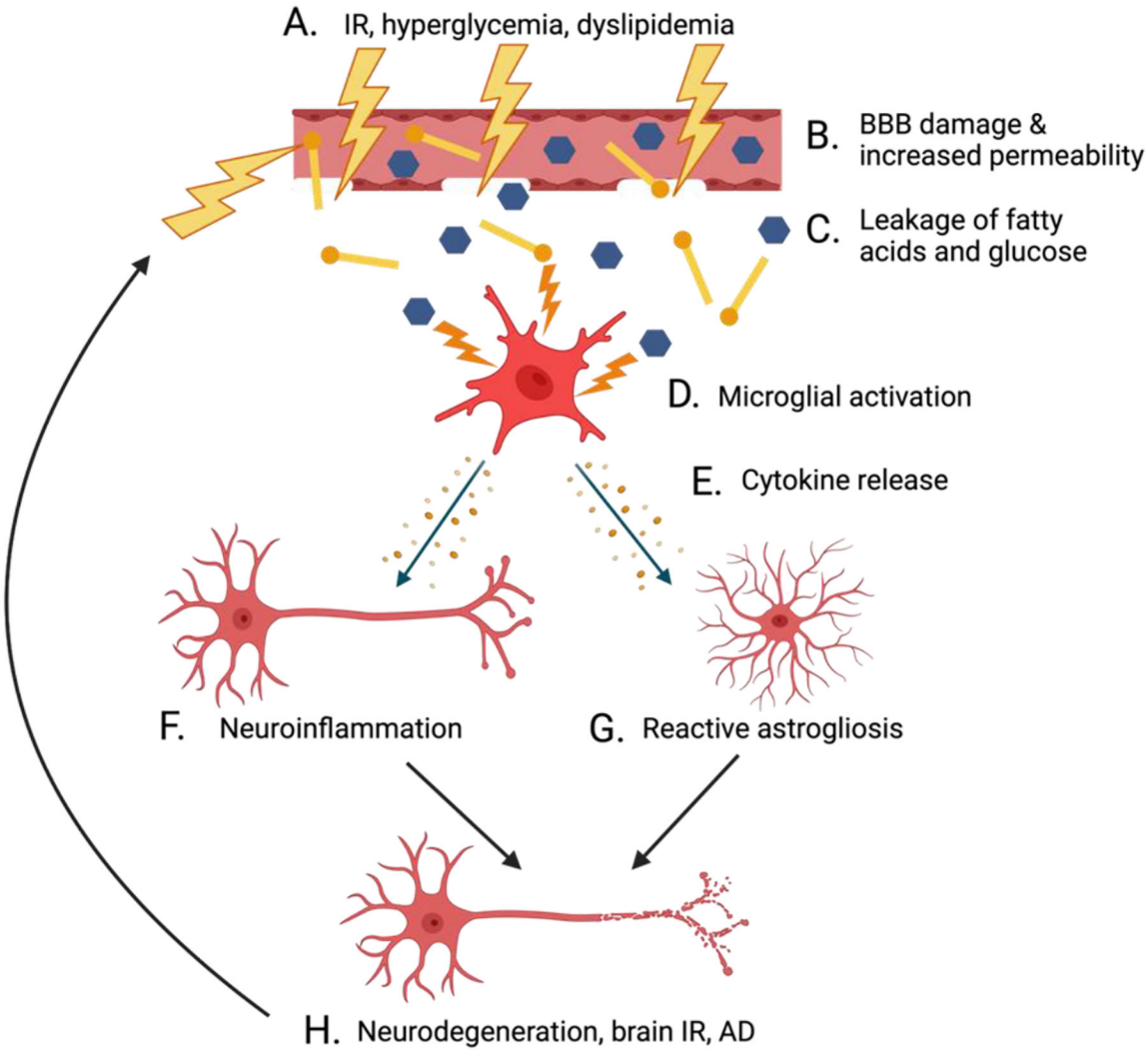

Figure 3.

Interactions between IR, neuroinflammation, and neurodegenerative disease. Elevated blood sugar levels and dyslipidemia in the blood are consequences of IR (A) that can damage and increase permeability of the BBB (B). BBB damage results in the infiltration of the brain with free fatty acids and excessive glucose (C), thus activating microglia into a pro-inflammatory state (D). These activated microglia release cytokines (E) that stimulate neuroinflammation (F) and reactive astrogliosis (G). Chronic neuroinflammation fuels the development of brain IR, neurodegeneration, and the progression of AD (H).

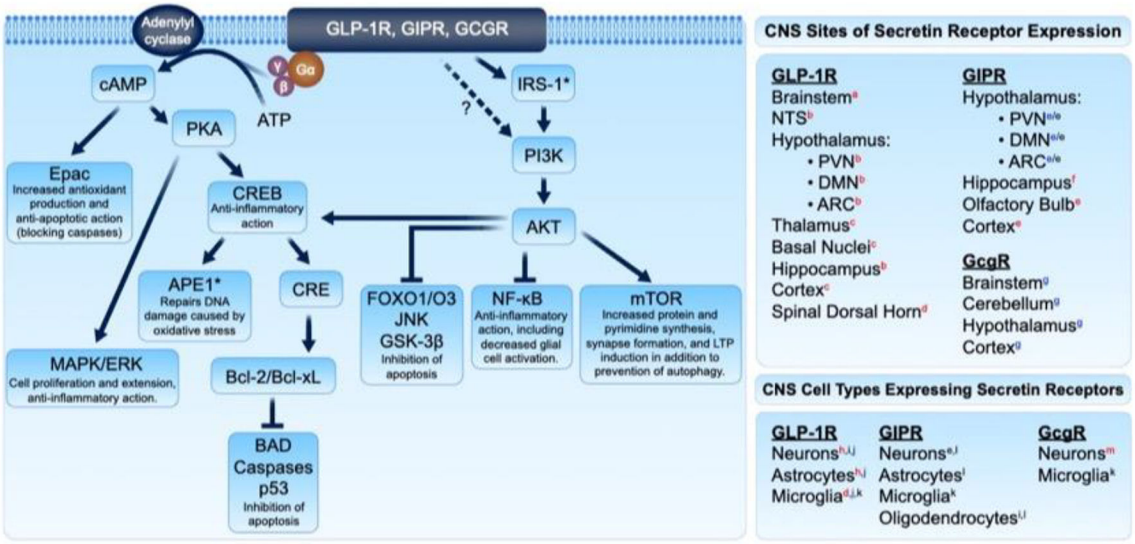

Figure 4.

Anti-inflammatory mechanisms of GLP-1R/GIPR/GcgR signaling, and sites of receptor expression as evidenced in rats (red superscript), mice (blue superscript), and humans (black superscript). Signaling pathways downstream of secretin receptor activation minimize neuroinflammation, oxidative stress, and apoptosis and provide cytoprotective effects. Sources: (a.) ref(208); (b.) ref(77); (c.) ref(209); (d.) ref(210); (e.) ref(78); (f.) ref(81); (g.) ref(211); (h.) ref(212); (i.) ref(213); (j.) ref(214); (k.) ref(215); (l.) ref(216); (m.) ref(217). Figure adapted from *Glotfelty et al. 2019* (12).

Table 1.

Comprehensive list of incretin receptor-targeting drugs for metabolic disease treatment. Numerous incretin receptor-targeting treatments have been approved (red if in the United States, green if abroad) or are currently in clinical trials or being developed (blue) for metabolic diseases, namely T2DM and obesity, and/or promoting weight loss. Highlighted drugs are in clinical trials for the treatment of AD or PD. While DPP-IV inhibitors do not directly stimulate incretin receptors, they increase levels of endogenous incretins and, thereby, promote incretin receptor signaling, and thus are included in the table. Only Victoza®, Bydureon®, and Byetta® have completed clinical trials for incretin analog treatment for neurodegenerative diseases; Ozempic®, Rybelsus®, Adlyxin®/Lyxumia®, PT320, and NLY01 are currently in clinical trials for neurodegenerative disease treatment.

Mechanism of Action	Company	Drug Name		Administration	Uses	Other Notes
GLP-1R Agonist	AstraZeneca	Exenatide	***Bydureon BCise*** ® ™	Once weekly SC	T2DM	Latest formulation of *Bydureon*®.
			Bydureon ®	Once weekly SC	T2DM	2 mg injection once each week, extended release formulation. Completed clinical trial in severely obese adolescents in 2020 (#NCT02496611). Phase 2 clinical trial (#NCT01971242) for PD patients completed in 2016 (see (a.) *Athauda et al. 2017*). Additional clinical trials for PD patients ongoing.
			Byetta ®	Twice daily SC	T2DM	Used any time within 1 hour before morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). In clinical trial (#NCT02442791), neuroprotective effects of Byetta® administration following cardiac arrest showed no significant outcomes (see (b.) *Wiberg et al. 2016*). Phase 2 clinical trial (#NCT02838589) completed investigating effects on cerebral blood flow. Clinical trials in AD (#NCT01255163; see (c.) *Mullins et al. 2019*) and PD (*EUCTR2009-018137-37-GB; see (d.) *Aviles-Olmos et al. 2013*) completed in 2016 and 2013, respectively.
	Sanofi-Aventis	Lixisenatide + insulin glargine	***Soliqua*** ®	Once daily SC	T2DM	Approved for adults with T2DM to lower A1C. 15–60 units of Soliqua® 100/33 per injection. Each unit of Solique 100/33 contains 0.33 mcg lixisenatide and 1 unit of Lantus.
		Lixisenatide	***Adlyxin***®/ ***Lyxumia***®	Once daily SC	T2DM	10 mcg once daily injection for 14 days. On Day 15, dosage increased to 20 mcg once daily. Administered within one hour before the first meal of the day. Currently in phase 2 clinical

Mechanism of Action	Company	Drug Name		Administration	Uses	Other Notes
						trial (#NCT03439943) for PD treatment.
	Sanofi-Aventis/ Hanmi Pharmaceuticals	Efpeglenatide	*HM 11260C*	Once weekly SC	T2DM	Completed Phase 3 clinical trial for T2DM treatment (#NCT03353350).
	Novo Nordisk	Liraglutide	*Victoza* ®	Once daily SC	T2DM	Used at any time of day, independent of meals. Use 0.6 mg per day for one week then increase to 1.2 mg, which can be increased to 1.8 mg for additional glycemic control. Clinical trial in AD patients (#NCT01469351) completed in 2013 (see (e.) *Gejl et al. 2016*). Additional clinical trials for AD and PD patients ongoing.
			Saxenda ®	Once daily SC	Weight Loss	3 mg daily SC injection.
		Liraglutide + insulin degludec	*Xultophy* ®	Once daily SC	T2DM	10 units Xultophy® 100/3.6 (10 units insulin degludec, 0.36 mg liraglutide) once daily SC. In patients converting from basal insulin or GLP 1R agonist: 16 units Xultophy® 100/3.6 (16 units insulin degludec, 0.58 mg liraglutide).
		Semaglutide	*Ozempic* ®	Once weekly SC	T2DM	0.25 mg (with or without meals). After 4 weeks, dose increased to 0.5 mg once weekly. Can be increased to 1 mg once weekly if needed. Phase 2 clinical trial (#NCT03659682) not yet recruiting in PD patients.
			Rybelsus ®	Oral once daily	T2DM	7 mg or 14 mg tablets. Approved to lower A1C, may help with weight loss. Currently recruiting for phase 3 clinical trials (#NCT04777409, #NCT04777396) in early AD patients.
			Wegovy ®	Once weekly SC	Obesity	2.4 mg weekly SC injection.
			IcoSema	Once weekly SC	T2DM	Semaglutide + insulin icodec. Phase 3 clinical trial (#NCT05259033) currently recruiting.
			NASH	Daily SC	NASH/ NAFLD	Phase 2 clinical trial (#NCT02970942) completed. NASH measurements are primary outcome with NAFLD as secondary outcome measure.
		----------	*NN9926, NN9927*	Oral	T2DM	Long acting, new molecular entities currently in development.
	Eli Lilly	Dulaglutide	*Trulicity* ®	Once weekly SC	T2DM	0.75 or 1.5 mg SC injection once weekly from single dose pen.
	Beijing Dongfang Biotech Co., Ltd.	Exendin-4	*JY09*	Once dailly SC	T2DM	Phase 1 clinical trial (#NCT04354090) completed.

Mechanism of Action	Company	Drug Name		Administration	Uses	Other Notes
						Exendin-4 + human Immunoglobulin G2 (IgG2) Fc fragment.
	Peptron	Exenatide SR	***PT320***	Biweekly SC	T2DM/ Obesity/ PD	Formerly PT302. Proprietary formulation allows for injection with smaller needle to reduce injection pain. Phase 1 clinical trial (#NCT00964262) completed for treatment of T2DM. Phase 2 clinical trials completed in South Korea for T2DM. Phase 2 clinical tral in PD patients in progress (#NCT04269642).
	Intarcia	Exenatide	***ITCA 650***	Long term implant	T2DM	Implant with potential to offer 6 month exenatide delivery with 1 year delivery options in development. Phase 3 clinical trials have been completed with New Drug Application (NDA) submitted to the Food and Drug Administration (FDA) (pending approval).
	vTv Therapeutics	----------	***TTP273***	Oral once or twice daily	T2DM	Non-peptide GLP-1R agonist. Completed phase 2 clinical trial (#NCT02653599) for T2DM treatment.
	CSPC ZhongQi Pharmaceutical Technology Co., Ltd.	Recombinant Exenatide	***rExenatide-4***	SC twice daily	T2DM	Phase 3 clinical trial (#NCT03239119) in Chinese T2DM patients initiated, but not yet recruiting.
	Oramed	Exenatide Oral	***ORMD-0901***	Oral	T2DM	US FDA cleared Investigational New Drug (IND) application for trials in humans as of September 2018.
	Shanghai Biolaxy	Exenatide	***Nodexen***	Oral	T2DM	Nanoparticle oral delivery. Clinical trials ongoing in China.
	Jiangsu Hengrui Medicine Co. Ltd.	Loxenatide	***PEX168***	Once weekly SC	T2DM	Phase 3 clinical trial in progress (#NCT02477969). This is a PEGylated formulation.
	Shanghai Benemae Pharmaceutical	----------	***Beinaglutide***	3x daily SC	T2DM/ Obesity	Phase 4 clinical trial recruiting (#NCT05005741). Approved for use in China in 2016.
	Zydus Lifesciences Ltd.	----------	***ZYD1***	Oral and SC	T2DM	Phase 1 clinical trial completed (#NCT01972893).
	PegBio Co., Ltd.	----------	***PB-119***	Once weekly SC	T2DM	Phase 3 clinical trial (#NCT04504396) recruiting. This is a PEGylated exenatide formulation.
	Regor Pharmaceuticals Inc.	----------	***RGT001-075***	Oral once daily	T2DM	Phase 2 clinical trial (#NCT05297045) in progress.
	CSPC Baike (Shandong) Biopharmaceutical Co., Ltd.	----------	***TG103***	Once weekly SC	Obesity	Phase 2 clinical trial (#NCT05299697) recruiting.

Mechanism of Action	Company	Drug Name		Administration	Uses	Other Notes
	Hansoh Pharmaceuticals	Polyethylene Glycol Loxenatide	***Fu Laimei*** ®	Once weekly SC	T2DM	Approved in China for adults with poor blood glucose control. Recommended dose 0.1–0.2 mg/week.
	Neuraly Inc.	Exenatide	***NLY01***	Once weekly SC	PD/AD	This is a PEGylated formulation. Phase 1 clinical trial completed in 2019 (#NCT03672604; see (f.) *Yun et al. 2018*). Phase 2 clinical trial ongoing in patients with PD (#NCT04154072).
GIPR Agonist	----------	GIP Peptide	----------	----------	T1DM	GIP peptide completed clinical trial (#NCT03556098) investigating its efficacy as a safeguard against hypoglycemia in patients with Type-1 diabetes mellitus (T1DM).
	Zealand Pharmaceuticals	----------	***ZP4165***	Intra Venous (I.V.) or SC	T2DM	DPP-IV resistance and potentiates GLP-1 mediated weight loss and improved glycemic control in rats (see (g.) *Nørregaard et al. 2018*).
GLP-1R/ GcgR Dual Agonist	Hamni Pharmaceuticals/ Janssen Research & Development, LLC	----------	***HM12525A/ JNJ-64565111***	Once weekly SC	T2DM/ Obesity	Phase 2 clinical trial completed (#NCT03586830).
	Zealand Pharmaceuticals/ Boehringer Ingelheim	----------	***BI 456906***	Once weekly SC	Obesity	Long lasting analogue of amylin and partially builds on the effects of oxyntomodulin. Completed phase 1 clinical tral (#NCT03175211) to assess safety, tolerability, and pharmacokinetics/ pharmacodynamics. Phase 1 trials in Germany for obesity initiated.
	Astra Zeneca/ MedImmune	----------	***MEDI0382***	Daily SC	T2DM	Completed phase 2a (see (h.) *Ambery et al. 2018)* and phase 2b clinical trials (#NCT03235050).
	Sanofi-Aventis	----------	***SAR425899***	Daily SC	T2DM/ Obesity	Completed phase 1 clinical trial (#NCT03414736; see (i.) *Goebel et al. 2018*).
	Janssen Pharmaceuticals	----------	***JNJ-54728518***	----------	T2DM/ Obesity	Phase 1 clinical trials initiated for obesity and T2DM in 2016. Pre-clinical trials for obesity also initiated in 2016.
	Novo Nordisk	----------	***NNC9204-1177***	Once weekly SC	Obesity	Completed phase 1 clinical trial (#NCT03308721).
	Prolor/OPKO Biological	----------	***OPK-88003***	Once weekly SC	T2DM	Completed phase 2 clinical trial (#NCT03406377).
	Spitfire Pharma	----------	***SP-1373***	Once daily SC	NASH/ T2DM/ Obesity	Clinical trial for T2DM and obesity planned for 2019.
	Boehringer Ingelheim	----------	***BI 456906***	----------	Obesity	Completed phase 1 clinical trial (#NCT03591718) in patients with obesity.

Mechanism of Action	Company	Drug Name		Administration	Uses	Other Notes
GLP-1R/ GLP-2R Dual Agonist	Zealand Pharmaceuticals	----------	*Dapiglutide*	----------	T2DM	Early phase 1 clinical trials completed (#NCT03994549, #NCT04612517).
GLP-1R/ GIPR Dual Agonist	Eli Lilly	Tirzepatide	*Mounjaro* ™	Once weekly SC	T2DM	Approved for adults with T2DM. Available in 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg doses through auto-injector pen.
	Novo Nordisk	----------	*RG 7697/ NNC0090-2746/ MAR709*	Once daily SC	T2DM	Completed phase 2 clinical trial (#NCT02205528; see (j.) *Frias et al. 2017*).
	Kariya Pharmaceuticals	----------	*KP405*	Info not available	PD/AD	Ready for phase 1 clinical trials. Toxicology studies completed.
	Sanofi	----------	*SAR438335*	Info not available	T2DM	Currently in phase 1 clinical trals in France.
GLP-1R/ GIPR/ GcgR Triagonist	Novo Nordisk	----------	*NNC9204-1706*	Once daily SC	Obesity	Completed phase 1 clinical trial (#NCT03661879).
	Hanmi Pharmaceutical Co. Lmtd.	----------	*HM15211*	SC	Obesity	Long acting formulation. Current phase 1 clinical trial (#NCT03374241) recruiting (see (k.) *Kim et al. 2018* for latest research on compound).
	Sanofi	----------	*SAR441255*	SC	T2DM/ Obesity/ NASH	Preclinical.
DPP-IV Inhibition	Astra Zeneca	Saxagliptin	*Onglyza* ™	Once daily oral	T2DM	2.5 or 5 mg regardless of meals.
		Saxagliptin + metformin HCl	*Kombiglyze* ® *XR*	Once daily oral	T2DM	Take once daily with evening meal. Available in 5 mg saxagliptin/500 mg metformin HCl, 5 mg saxagliptin/1000 mg metformin HCl, or 2.5 mg saxagliptin/1000 mg metformin HCl doses.
	Merck	Sitagliptin	*Januvia* ®	Once daily oral	T2DM	25, 50, or 100 mg with or without food.
		Sitagliptin phosphate + metformin HCl	*Janumet* ® / *Janumet* ® *XR*	Oral twice daily/ Once daily (XR formula)	T2DM	Combination drug therapy with metformin. XR formulation is an extended release version. Max dosage 100 mg Sitagliptin and 2000 mg metformin HCl.
		Omarigliptin	*Marizev* ®	Oral once weekly	T2DM	Available in Japan. See (l.) *Goldenberg et al. 2017* for phase 3 clinical trial information (#NCT01703221). Possible repositioning of drug for intran asal delivery for PD (see (m.) *Ayoub et al. 2018*).
	Takeda	Trelagliptin	*Zafatek* ®	Oral once weekly	T2DM	Approved for use in Japan. Phase 2 clinical trials abandoned in the USA because of costs.
		Alogliptin	*Nesina* ®	Oral once daily	T2DM	25 mg with or without food.
		Alogliptin + metformin HCl	*Kazano* ®	Oral twice daily	T2DM	Take oral twce daily with food. Available in 12.5 mg alogliptin/500 mg metformin HCl or 12.5 mg alogliptin/1000

Mechanism of Action	Company	Drug Name		Administration	Uses	Other Notes
						mg metformin HCl doses. Max dosage 25 mg alogliptin/2000 mg metformin HCl per day.
		Alogliptin + pioglitazone	***Oseni*** ®	Oral once daily.	T2DM	Take with or without food. Available in 12.5 or 25 mg alogliptin doses.
	Boehringer Ingelheim	Linagliptin	***Tradjenta*** ®	Oral once daily	T2DM	5 mg once daily.
		Linagliptin + empagliflozin	***Glyxambi*** ®	Oral once daily	T2DM	Take once daily in the morning with or without food. Available in 10 mg empagliflozin/5 mg linagliptin and 25 mg empagliflozin/5 mg linagliptin doses.
		Linagliptin + metformin HCl	***Jentadueto*** ® / ***Jentadueto*** ® ***XR***	Oral twice daily/ Once daily (XR formula)	T2DM	Combination drug therapy with metformin. XR formulation is an extended release version. Max dosage 2.5 mg linagliptin and 1000 mg metformin HCl.
	Dong-A ST	Evogliptin	***Suganon*** ®	Oral once daily	T2DM	5 mg once daily. Approved for use in South Korea in 2015. Sold with extended release metformin.
	SatRx LLC	Gosogliptin	***SatRx*** ®	Oral	T2DM	Approved for use in Russia. Completed phase 3 clinical trial of safety alone or with metformin compared to Vildagliptin alone or with metformin (#NCT03088670).
	LG Life Sciences/ Sanofi	Gemigliptin	***Zemiglo*** ™	Oral once daily	T2DM	Long acting DPP-IV inhibitor. See (n.) *Kim et al. 2016* for characterization.
	Zealand Pharmaceuticals	Vildagliptin	***Galvus*** ®	Oral once daily	T2DM	50 mg in combination with metformin (see (o.) *Mathieu & Degrande 2008*).
	Mitsubishi Tanabe Pharma and Daiichi Sankyo	Tenegliptin	***Tenelia*** ®	Oral twice daily	T2DM	20 mg twice daily. See (p.) *Kishimoto 2013*.
	Zealand Pharmaceuticals	Anagliptin	***Suiny*** ®	Oral twice daily	T2DM	Approved for use in Japan, 200 mg daily. See (q.) *Nishio et al. 2015*

#: Visit https://clinicaltrials.gov to locate clinical trials registered in the United States.

*: Visit https://trialsearch.who.int to locate clinical trials registered internationally.

NASH = nonalcoholic steatohepatitis; NAFLD = nonalcoholic fatty liver disease; SC = subcutaneous injection; T1DM = Type 1 Diabetes Mellitus. Sources: (a) ref(13); (b) ref(256); (c) ref(257); (d) ref(258); (e) ref(259); (f) ref(103); (g) ref(260); (h) ref(261); (i) ref(262); (j) ref(263); (k) ref(264); (l) ref(265); (m) ref(266); (n) ref(267); (o) ref(268); (p) ref(269); (q) ref(270). Table updated from *Glotfelty et al., 2019* (12).

Table 2.

GLP-1R agonists in clinical trials for repurposing to treat neurodegenerative diseases. Drugs in red (approved in the United States) or green (approved abroad) have been approved for metabolic disease treatment, and those in blue are in clinical trials for metabolic disease treatment. Only Bydureon®, Byetta®, and Victoza® have completed interventional clinical studies and demonstrated efficacy in treating a neurodegenerative disease.

Company	Drug Name		Use	Clinical Trial	Phase	Status	Outcomes
AstraZeneca	Exenatide	***Bydureon*** ®	PD	#NCT03456687	1	Ongoing	N/A
				#NCT01971242	2	Completed (2020)	Treatment improved off-medication motor scores. See (a.) *Athauda et al., 2017.*
				#NCT04305002	2	Recruiting	N/A
				*EUCTR2019-000732-26-SE	2	Ongoing	N/A
				#NCT04232969	3	Ongoing	N/A
				*ISRCTN14552789	3	Ongoing	N/A
				*ACTRN12620000627954	4	Recruiting	N/A
		Byetta ®	AD	#NCT01255163	2	Completed (2016)	Treatment reduced amyloid-β-42 concentration in extracellular vesicles. See (b.) *Mullins et al., 2019.*
			PD	#NCT01174810	2	Completed (2013)	Treatment improved motor abilities and cognition. See (c.) *Aviles-Olmos et al., 2013.*
			FRDA	*EUCTR2014-003598-41-BE	Pilot	Completed (2019)	Treatment improved frataxin levels in FRDA patients. See (d.) *Igoillo-Esteve et al., 2020.*
Novo Nordisk	Liraglutide	***Victoza*** ®	AD	#NCT01469351	2	Completed (2013)	Treatment maintained healthy brain glucose metabolism. See (e.) *Gejl et al., 2016.*
				#NCT01843075	2	Ongoing	N/A
			PD	#NCT02953665	2	Completed (2022)	Treatment improved non-motor symptoms, quality of life, and mobility. See (f.) *Hogg et al., 2022.*
	Semaglutide	***Ozempic*** ®	PD	#NCT03659682	2	Not yet recruiting	N/A

Company	Drug Name		Use	Clinical Trial	Phase	Status	Outcomes
		Rybelsus ®	AD	*ISRCTN71283871	2	Recruiting	N/A
				#NCT04777409	3	Recruiting	N/A
				#NCT04777396	3	Recruiting	N/A
Neuraly Inc.	Exenatide	***NLY01***	PD	#NCT03672604	1	Ongoing	N/A
				#NCT04154072	2	Ongoing	N/A
Peptron	Exenatide	***PT320***	PD	#NCT04269642	2	Ongoing	N/A
Sanofi-Aventis	Lixisenatide	***Adlyxin***®/ ***Lyxumia***®	PD	#NCT03439943	2	Ongoing	N/A
Various	Any GLP-1R agonist approved for metabolic disease treatment	***Various***	Glaucoma	N/A	N/A	Completed (2021)	GLP-1R agonist treatment cohort had reduced risk of developing glaucoma. See (g.) *Sterling et al., 2021.*

#: Visit https://clinicaltrials.gov to locate clinical trials registered in the United States.

*: Visit https://trialsearch.who.int to locate clinical trials registered internationally.

FRDA = Friedreich ataxia. Sources: (a) ref(13); (b) ref(257); (c) ref(258); (d) ref(293); (e) ref(259); (f) ref(276); (g) ref(11).