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Repurposing glucagon-like peptide-1 receptor agonists for the treatment of neurodegenerative disorders

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With therapeutic progress in Alzheimer's disease (AD), more molecular and mechanistic targets are coming into focus. Beyond amyloid, emerging targets include tau, neuroinflammation and neurotransmitters. Targeting neuroinflammation in neurodegenerative diseases has been explored using cyclooxygenase inhibitors, but it has mostly been unsuccessful. Among the drug classes under investigation for AD are the glucagon-like peptide-1 receptor agonists (GLP-1RAs), which are approved for the treatment of type 2 diabetes (T2D), obesity and cardiovascular disease. GLP-1RAs are candidate treatments for AD based on several concepts. First, epidemiological data reveal that patients with T2D and cardiovascular disease receiving GLP-1RAs have substantial reductions in the risk of developing all-cause dementia. Second, GLP-1RAs reduce neuroinflammatory changes in preclinical models. Clinical trials have not yet shown that GLP-1RAs can slow the rate of cognitive decline in mild cognitive impairment and mild dementia due to AD. Here, we summarize data supporting the use of GLP-1RAs for the treatment of neurodegenerative diseases, with a focus on AD.

Alzheimer's disease (AD) is the most common cause of dementia, accounting for about 70% of cases. AD affects approximately 35 million people worldwide, with cases projected to increase to around 105 million by 2050 (ref. 1). Key pathological hallmarks (Fig. 1) include the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau, as well as activation of the immune system[2]. Parkinson's disease (PD) is the most common movement disorder, affecting more than 1 million individuals[3]. Synucleinopathies (including dementia with Lewy bodies) are estimated to affect more than 2 million individuals in the USA alone. The third major neurodegenerative disease is amyotrophic lateral sclerosis (ALS), which is now linked to a TAR DNA-binding protein 43 (TDP-43) proteinopathy[4].

Substantial research is focused on understanding the pivotal role of neuroinflammation in disease progression, with evidence linking both innate and adaptive immune processes to the pathogenesis of AD, PD and ALS. Neuroimmune crosstalk between the brain and the periphery is critical for brain health and becomes dysregulated in neurodegenerative diseases like AD[5]. Here, we review the mechanisms and evidence supporting glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonists (GLP-1RAs) as novel therapies for neurodegenerative diseases, with a focus on AD.

Strategies and targets for the treatment of AD

Symptomatic treatments for AD include cholinesterase inhibitors and partial *N*-methyl-D-aspartate receptor antagonists[6]. These treatments improve memory loss but do not affect disease progression[7]. Multiple new targets and strategies have emerged, aiming to delay or reverse AD pathology (Fig. 1). These include amyloid-targeted therapies, such as monoclonal antibodies that target Aβ plaques and protofibrils in AD[8,9]. However, the requirement for greater efficacy, safety, convenience and accessibility of AD therapies necessitates the evaluation of alternative therapeutic targets beyond amyloid[10].

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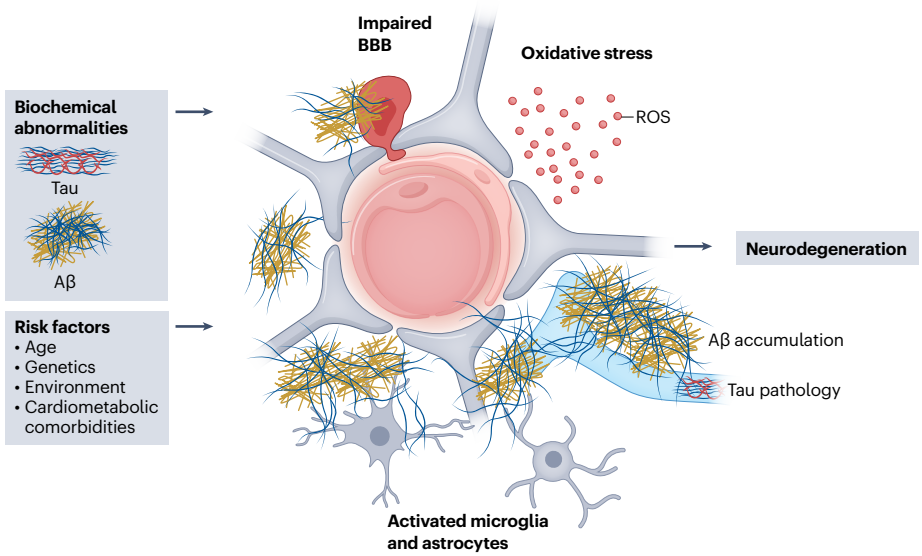

Fig. 1 | The complex pathophysiology of neurodegeneration. Multiple risk factors, along with both CNS and peripheral metabolic disorders, contribute to the development of neurodegenerative disorders such as AD. Changes in the structure and accumulation of key proteins, such as tau and Aβ, contribute to plaque formation and may disrupt the health, function and survival of neurons, collectively leading to a decline in cognitive function. ROS, reactive oxygen species.

Prominent among nonamyloid approaches are monoclonal antibodies or antisense oligonucleotides targeting tau isoforms, designed to block the spread of phosphorylated tau from neuron to neuron through prionosis. Additional strategies include tau aggregation inhibitors, gingipain inhibitors, antioxidants, tyrosine kinase inhibitors and metabolic approaches. There is also a renewed interest in targeting neuroinflammation[10]. GLP-1RAs reduce systemic inflammation in individuals with type 2 diabetes (T2D) or obesity, raising the possibility that they could be repurposed to reduce neuroinflammation[11] (Fig. 2).

Inflammation is a potential AD target

Historically, changes in glial cells were first described by Alois Alzheimer[12], and they were viewed as a bystander reaction to neurodegenerative processes. However, immune changes are now known to have an integral role in the pathogenesis of AD (Fig. 1). Microglia, the brain's resident immune cells, are a key source of complement factors, cytokines and chemokines[13]. When stimulated by Aβ, microglia-derived complement factor 3 can mark synapses, which are subsequently removed in excess[14]; in some cases, microglia can remove entire neurons[13]. The microglia become reactive and proliferate in response to Aβ plaques and neurofibrillary tangles. They are critical for the removal of aberrant proteins and are activated by therapeutic monoclonal antibodies to promote this process. They also activate destructive cytokine pathways that contribute to the formation of plaques and tangles through the release of ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) specks. This leads to the seeding of Aβ deposition[15], release of interleukin-1β (IL-1β) and subsequent tau phosphorylation[16]. This immune activation is present in both the symptomatic and presymptomatic phases of the disease. Early upregulation of the anti-inflammatory TAM (TYRO3, AXL and MERTK) receptor signaling correlates with neurocognitive preservation and reduced cortical brain atrophy[17], suggesting that initial immune responses exert a protective effect.

Biomarkers of neuroinflammation

Analyses of biofluids, including cerebrospinal fluid (CSF) and blood samples, have provided insights into the inflammatory landscape of AD[18]. Evaluation of C-reactive protein revealed inconsistent results in meta-analyses. Emerging biomarkers from CSF (for example, glial fibrillary acidic protein (GFAP), YKL-40 and triggering receptor expressed on myeloid cells 2 (TREM2)) and blood-based biomarkers may better delineate the inflammatory processes in AD. Inflammation is now represented in the ATN(X)—amyloid, tau, neurodegeneration and other—biomarker classification[19].

Cellular components facilitating neuroinflammation

Beyond microglia, astrocytes become reactive and produce inflammatory mediators that can either exacerbate or mitigate pathology[20,21]. Oligodendrocytes have a role, particularly in myelin damage associated with inflammation. Peripheral immune cells, including T lymphocytes and monocytes, can infiltrate the brain and influence disease progression[5,22,23]. When considering the infiltration of peripheral cells, the vascular system must be taken into account. Activated vascular cells contribute to blood–brain barrier (BBB) dysfunction (Fig. 1) in AD[24,25], leading to greater infiltration of peripheral immune cells into the central nervous system (CNS) and further exacerbating the inflammatory response. Therefore, investigating the role of peripheral immune cell dysfunction[26] may provide a more comprehensive assessment of neuroinflammation and the risk of neurodegeneration.

Genetics and neuroinflammation

The interplay between genetic predispositions and environmental factors shapes neuroinflammation in AD. Genetic risk factors, such as apolipoprotein E ε4, influence microglial function and overall immune responses within the brain[27]. Several genetic risk variants occur in genes encoding proteins that are important for immune function[28–30]. Environmental factors, ranging from traumatic brain injuries to diet, also modulate inflammation levels[31–34]. The gut microbiota also affects neuroinflammatory processes, highlighting areas for therapeutic intervention[35].

Anti-inflammatory and immunomodulatory drugs are being tested in clinical trials[10]. Inflammatory signaling pathways represent potential targets over the decade-long AD trajectory; activated pathways are likely to be dynamic and change with disease progression. Therefore, stage- and target-specific readouts must be identified to ensure optimal interventions for disease modification. Future observational and clinical trials should explore these pathways more comprehensively in a longitudinal manner. The identification of predementia stages, such as subjective cognitive impairment and mild cognitive impairment

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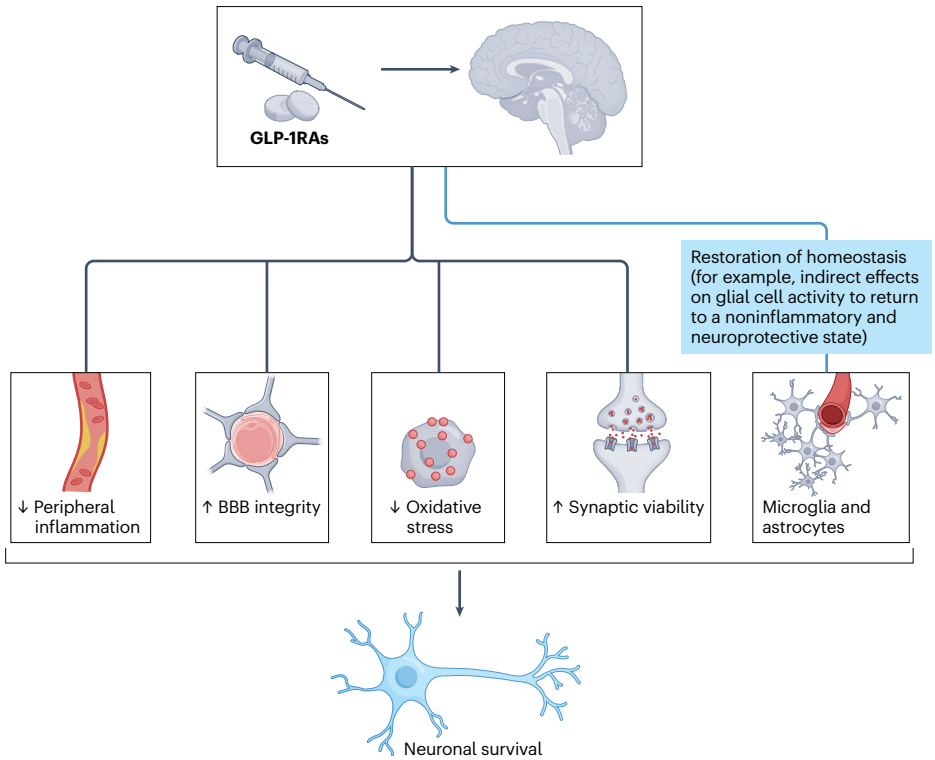

Fig. 2 | Mechanisms linking GLP-1RAs to the attenuation of neurodegeneration. GLP-1RAs may improve brain health indirectly by correcting glycemic dysregulation and reducing body weight or directly by acting on structures and cell types within the brain, thereby engaging actions that collectively attenuate neurodegeneration and maintain cognitive function.

(MCI), along with biomarker discovery, could enhance our ability to intervene before substantial cognitive decline occurs.

Translating findings from animal models to patients requires careful consideration of differences between species in terms of immune responses and disease manifestations[36]. As the complexities of central and peripheral immune processes involved in AD are revealed, there is growing enthusiasm for treatment strategies that could alter the course of the disease.

GLP-1, GLP-1R and GLP-1RAs

Structure, synthesis, secretion and metabolic actions of GLP-1

GLP-1 is a peptide hormone encoded by the glucagon (*GCG*) gene[37]. GLP-1 is released from the gut and from neurons in the hindbrain, and it is transported to and acts on multiple regions in the CNS. The full-length GLP-1(1–37) undergoes N-terminal monobasic cleavage to yield two shorter yet equally bioactive peptides: GLP-1(7–36)amide and GLP-1(7–37)[37].

The majority of GLP-1-producing enteroendocrine cells are located in the ileum and colon, and circulating GLP-1 is derived from endocrine L cells[38]. GLP-1 promotes the secretion of insulin following meal ingestion[37], increases somatostatin release, inhibits glucagon secretion and impedes gastric emptying, thereby reducing glycemia in both the fasted and postprandial state.

GLP-1 is also a neurotransmitter with an independent yet modest physiological effect on energy intake[39]. GLP-1R is widely expressed in the brain (Fig. 3), and some neurons in the hypothalamus and hindbrain are accessible and targeted by circulating GLP-1 (ref. 40). Other neuronal populations, including the septal nucleus, are targets of GLP-1 originating from hindbrain neurons[41–43]. Analysis of GLP-1R expression can be challenging due to limitations in the sensitivity and specificity of multiple antibodies and is ideally complemented by the use of ligand-binding approaches, as well as single-cell RNA sequencing or in situ hybridization to localize GLP-1R mRNA transcripts to the same regions and cell types[44]. GLP-1R activation could address dysfunction in neurons and other CNS cell types affected in AD through indirect mechanisms to restore metabolic function and directly by reducing reactive oxygen species, neuroinflammation and cytotoxicity (Figs. 2 and 3).

Pharmaceutical development of GLP-1RAs

The first GLP-1RA approved for clinical use in individuals with T2D was exenatide, administered twice daily. The structurally related exendin 4 derivative lixisenatide was subsequently approved for once-daily administration[45]. The first two long-acting GLP-1RAs developed for T2D, liraglutide once daily and exenatide once weekly, provided 24-h activation of GLP-1R, enabling improved glucose control[46]. Newer GLP-1RAs exhibit longer circulating half-lives, including dulaglutide and semaglutide, which both require once-weekly administration and are now widely used for the treatment of T2D[47,48]. The long-acting GLP-1RAs also reduce the rates of myocardial infarction, stroke, cardiovascular death and all-cause mortality in individuals with T2D and obesity[49,50].

The two most widely used GLP-1 medicines are semaglutide, which activates GLP-1R, and tirzepatide, which activates both GLP-1R and the glucose-dependent insulinotropic polypeptide receptor (GIPR). Both medicines are approved for the treatment of T2D and obesity[51]. Semaglutide is cardioprotective in individuals with T2D and those with a history of atherosclerotic cardiovascular disease who are living with overweight or obesity and weight-related risk factors[52], while tirzepatide was shown to be non-inferior to dulaglutide, a GLP-1 medicine with proven cardioprotective benefits[11] in patients with T2D randomized to trizepatide versus dulaglutide in the SURPASS-CVOT trial.

GLP-1 and GLP-1R expression and action in the brain

Considerable evidence links peripheral and brain insulin resistance to AD[53]. Acute infusion of GLP-1 does not improve insulin sensitivity in healthy human participants[54]. Nevertheless, GLP-1RAs improve insulin sensitivity, either by reducing glucose toxicity or, secondarily,

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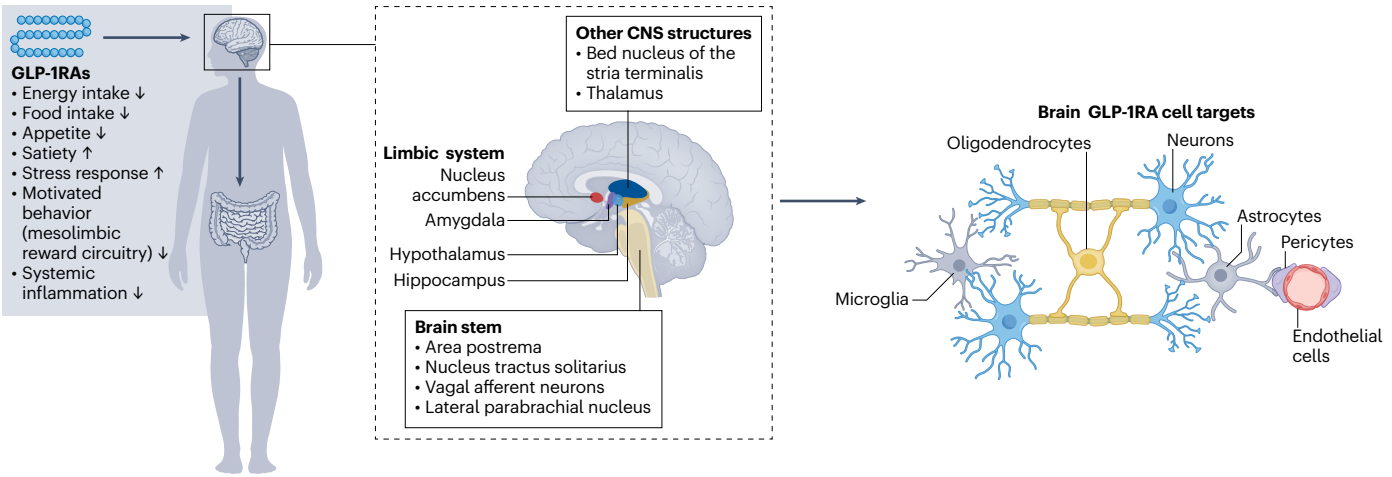

Fig. 3 | GLP-1RAs improve metabolism and target multiple cell types and regions in the brain. GLP-1 medicines may improve brain function indirectly by enhancing metabolism, reducing glucotoxicity and lipotoxicity, and decreasing systemic inflammation and insulin resistance. GLP-1R has been localized to multiple cell types in the CNS, both in mice and humans, enabling the engagement of multiple brain regions susceptible to AD pathophysiology.

through improved blood flow and weight loss, thereby indirectly causing a reduction in liver fat and ectopic fat in other tissues. This leads to decreased low-grade inflammation and increased insulin sensitivity in both animals and humans. Notably, the canonical GLP-1R is not expressed in skeletal muscle myocytes, white or brown adipocytes, or hepatocytes[55], all of which are tissues that control insulin sensitivity in the periphery. Native GLP-1 enhances microvascular blood flow in some regional vascular beds within skeletal muscle, cardiac muscle and adipose tissue, thereby indirectly contributing to improved insulin action[56]. Acute or sustained administration of GLP-1RAs stimulates insulin secretion under hyperglycemic conditions, further enhancing insulin action in insulin-sensitive tissues.

Within the mammalian brain, GLP-1 originates from hindbrain neurons within the nucleus tractus solitarius[42]. These neurons project widely to multiple populations of GLP-1Rs throughout the CNS. The CNS GLP-1R exhibits a predominantly neuronal pattern of expression but is also expressed in multiple non-neuronal cell types, including astrocytes and some glial cells, predominantly oligodendrocytes, as well as endothelial cells, vascular smooth muscle cells and some pericytes[57–60]. Subsets of T cells also express the receptor[61]. Although the GLP-1R expression patterns in neurons may translate from mice to higher-order species[62,63], the distribution of GLP-1R in other human non-neuronal cell types is relatively poorly described. Human single-cell data identify GLP-1R expression in smooth muscle cells, astrocytes, ependymal cells and some oligodendrocyte precursors in the hippocampus of individuals with AD[64].

Brain insulin resistance, including enhanced serine phosphorylation and reduced function of insulin receptor substrate 1, is evident in preclinical animal models of neurodegeneration and in sections of human brains from patients with AD studied ex vivo[65]. Whether the putative actions of GLP-1RAs to reduce brain insulin resistance reflect direct engagement of CNS GLP-1Rs or are indirect (due to reductions in glycemia, body weight and inflammation; Fig. 2) remains to be determined.

GLP-1 and the BBB

The BBB has an integral role in the defense against neuroinflammation. GLP-1RAs preserve the integrity of the BBB in animals with experimental brain injury secondary to trauma or ischemic stroke[66]. Rats with experimental diabetes induced by streptozotocin exhibited improved BBB function following treatment with exendin 4 for 28 days, as evidenced by reduced extravasation of Evans blue dye and preservation of the BBB-associated proteins occludin and aquaporin 4 (ref. 67). In mice with experimental diabetes, treatment with exendin 4 for 28 days preserved the CNS expression of the tight junction and BBB protein occludin[68]. Daily administration of semaglutide for 5 days to mice with experimental stroke (transient middle cerebral artery occlusion) attenuated the disruption of the BBB[69]. Exendin 4 also reduced Evans blue dye extravasation in the brains of rats after transient middle cerebral artery occlusion, which was associated with the relative preservation of the expression of occludin, zonulin 1 and claudin 5 (refs. 70,71).

Uptake of GLP-1RAs, such as liraglutide, in the mouse brain requires a functional GLP-1R[40]; however, the uptake is limited to circumventricular areas and regions near blood circulation. A potential role for GLP-1R in transporting GLP-1-related peptides across the BBB was identified in murine tanycytes, specialized ependymal cells that contribute to the integrity of the BBB. Silencing of tanycyte *Glp1r* expression impaired liraglutide transport into the brain, diminished liraglutide-activated hypothalamic gene expression, reduced food intake and decreased body weight[72].

Minute levels of liraglutide were detected in the CSF of patients with T2D who were treated with and responsive to liraglutide, as assessed by weight loss. However, the low levels of liraglutide in CSF did not correlate with its levels in plasma[73]. In mice, both liraglutide and semaglutide signal to secondarily activated neurons in deeper parts of the brain, including the parabrachial nucleus, the bed nucleus of the stria terminalis and the amygdala[43]. Preclinical studies suggest that liraglutide, semaglutide and exenatide cross the BBB[74,75]. Dulaglutide and tirzepatide cross the BBB at different rates[76]. Nevertheless, GLP-1Rs may be accessible in circumventricular organs that are not fully protected by the BBB, and liraglutide and semaglutide rapidly activate FOS expression in multiple regions of the CNS that are not directly engaged by the peptide receptor agonists[40,43]. Notably, even much larger GLP-1 medicines, such as the bispecific antibody with glucose-dependent insulinotropic polypeptide receptor antagonist and GLP-1RA activity, maridebart cafraglutide, as well as the albumin-based GLP-1RA albiglutide, produce robust acute FOS activation in the CNS, despite limited CNS penetration[77,78]. Hence, accessible CNS GLP-1Rs rapidly relay signals to multiple regions of the CNS through incompletely defined intercellular communication pathways.

Modes of action of GLP-1RAs in the brain and in disease models

Role in neuronal function, survival and experimental models of neurodegeneration

GLP-1RAs are neuroprotective in preclinical models of experimental brain injury. Semaglutide and dulaglutide also reduce the rates

of incident stroke in cardiovascular outcome trials, driven by their effect on small vessel disease[79,80]. GLP-1R agonism reduces experimental neuronal apoptosis, whereas enhanced susceptibility to seizures and neuronal injury is observed in *Glp1r*$^{-/-}$ mice[81]. The GLP-1RA NLY01 attenuates microglia-mediated reactive astrocyte conversion and preserves neuronal viability in 5xFAD and 3xTG-AD mice[82]. The neuronal and non-neuronal actions of GLP-1 medicines may be mediated in part through AMP-activated protein kinase (AMPK) activation, and these actions are associated with the induction of microglial phagocytosis and the attenuation of inflammation in cells challenged with Aβ oligomers[83]. Similarly, treatment of APP23/PS45 mice with exendin 4 for 8 weeks increased brain AMPK phosphorylation and reduced BACE1 cleavage of amyloid precursor protein and Aβ production[83]. GLP-1R agonism in cultured mouse astrocytes inhibited glucose uptake and promoted β-oxidation, whereas deletion of the astrocyte GLP-1R impaired mitochondrial activity, which was associated with a generalized reduction in stress responses in vulnerable astrocytes[59].

GLP-1RAs reduce amyloid plaque deposition in some but not all mouse models of AD. Liraglutide decreased the rate of memory loss and preserved the number of hippocampal CA1 neurons in SAMP8 (senescence-accelerated mouse prone 8) mice before the detection of amyloid plaques or phosphorylated tau in 10-month-old animals[84]. Treatment of hTauP301L mice with liraglutide once daily for 6 months, starting at 3 months of age, reduced clasping-associated lethality, along with a decreased burden of neuronal phosphorylated tau in multiple brain regions[85]. By contrast, liraglutide, semaglutide and tirzepatide had minimal therapeutic benefits in two different transgenic mouse models with genetic mutations in amyloid precursor protein and presenilin 1, with no effect on biomarkers of neuroinflammation or amyloid plaque burden[86,87].

GLP-1RAs attenuate neuroinflammation

Preclinical studies[88–90] have shown that GLP-1RAs attenuate neuroinflammation (Fig. 2), and they accomplish this by targeting neurons, astrocytes and microglia[82]. These actions of GLP-1RAs have been shown in experimental brain injury and stroke[69]; in mouse and rat models of AD[91,92], PD[93], high-fat diet-induced obesity[94] and encephalitis[95]; and in glial and astrocyte cultures treated with lipopolysaccharide[96]. GLP-1 degradation products, such as GLP-1(9–36)amide, also reduce stroke-related neuroinflammation and attenuate the expression of tumor necrosis factor (TNF), IL-1β and IL-6 in astrocytes ex vivo, independent of the known GLP-1R[97]. Nevertheless, exendin 4, which does not lead to the formation of a similar metabolite, attenuated cognitive dysfunction and suppressed the expression of multiple inflammation-related proteins, including Toll-like receptor 4, cyclooxygenases 1 and 2, nuclear factor-κB (NF-κB), CD45 and inducible nitric oxide synthase, in the hippocampus of mice treated with intrahippocampal CA1 injection of lipopolysaccharide[98].

Pretreatment of primary microglia cultures with the GLP-1RA NLY01 suppressed the expression of oligomeric Aβ(1–42)-induced cytokine RNA and protein, actions dependent on the canonical GLP-1R[82]. Expression of GLP-1R in human microglia has not been confirmed, although GLP-1RAs orchestrate the activities of a variety of brain cell types (Figs. 2 and 3), collectively contributing to dampened neuroinflammation.

The anti-inflammatory effects of GLP-1RAs result in the inhibition of NF-κB and a reduction in the levels of proinflammatory cytokines, including IL-1β, IL-6, TNF and interferon-γ[99]. Peripheral inflammation leads to dysfunction of the BBB and activation of microglial cells and astroglia[100]. These effects may be diminished by the anti-inflammatory effects of GLP-1RAs, actions mediated in part by GLP-1R signaling in CNS neurons[101].

Mechanisms beyond neuroinflammation

GLP-1 medicines improve cardiometabolic health, partly by reducing glycemia and body weight, as well as through weight loss-independent mechanisms[102]. GLP-1 medicines reduce blood pressure, intestinal lipoprotein secretion, systemic inflammation and platelet aggregation through weight loss-independent mechanisms[103]. Collectively, these mechanisms underlie consistent reductions in the risk of nonfatal myocardial infarction, stroke, cardiovascular death and all-cause mortality[50,52] and may potentially contribute to the preservation of cognitive function in humans.

Clinical evidence supporting the repurposing of GLP-1RAs for AD, PD and ALS

Real-world evidence reveals a reduced risk of dementia or AD with GLP-1RAs

Several lines of clinical evidence support a potentially beneficial role for GLP-1RAs in reducing incident dementia in patients with T2D. Registry data from individuals with diabetes have been queried to assess the real-world evidence of the risk of AD or dementia in patients taking GLP-1RAs. A systematic review assessed data from more than 800,000 individuals with T2D, examining the effect of diabetes treatment on incident dementia[104], including five studies that investigated the potential benefits of GLP-1RAs[105–108]. These studies reported a lower incidence of dementia in patients with T2D who were receiving GLP-1RAs, with the relative risk varying from 0.47 to 0.90. A meta-analysis suggested a risk reduction of incident dementia by 28% (relative risk 0.72; 95% confidence interval (CI) 0.54–0.97)[104]. Analysis of UK primary care data, which included about 18,000 individuals with T2D, confirmed the reduction in incident dementia among those receiving GLP-1RAs[109].

The association of GLP-1RAs with AD was assessed using a large US Food and Drug Administration database. Treatment with exenatide (adjusted reporting odds ratio (aROR) 0.22; 95% CI 0.11–0.37; $P < 0.001$), liraglutide (aROR 0.36; 95% CI 0.19–0.62; $P < 0.001$), dulaglutide (aROR 0.39; 95% CI 0.17–0.77; $P = 0.014$) and the dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin (aROR 0.75; 95% CI 0.60–0.93; $P = 0.011$) was associated with a significantly lower risk of AD than treatment with metformin[110]. Exposure to GLP-1RAs was assessed in patients with T2D and a subsequent diagnosis of dementia in (1) two large data sources with long-term follow-up; (2) a pooled analysis of three randomized, double-blind, placebo-controlled cardiovascular outcome trials (combined total of 15,820 patients); and (3) a nationwide Danish registry-based cohort (120,054 patients). Treatment with liraglutide or semaglutide was associated with a reduction in the diagnosis of all-cause dementia compared to placebo[106]. The study by Nørgaard et al.[106] included participants with a first prescription of a second-line treatment for T2D, ensuring that the treatments were well matched from a diabetes management perspective, and required a treatment duration of at least 5 years before the onset of dementia. A significant reduction in dementia incidence (OR 0.89) was observed in participants treated with GLP-1RAs in a Danish registry[106]. Dementia rates were also lower in patients randomized to receive GLP-1RAs than in those who received placebo (hazard ratio (HR) 0.47; 95% CI 0.25–0.86)[106]. Although the results were encouraging, the number of individuals who developed incident dementia was small, and there was also a reduction in stroke, which is a potential mediating factor. In a different analysis from a Danish registry (1995–2012) involving 176,250 patients with T2D, an evaluation of 11,619 patients with dementia and 46,476 controls revealed that patients exposed to GLP-1RAs had a 42% lower risk of developing dementia[107].

Seven target trial emulation analyses involving 1,094,761 eligible patients with T2D who did not have a prior AD diagnosis compared semaglutide to seven other glucose-lowering medications. First-ever diagnosis of AD occurred within a 3-year follow-up period and was examined using Cox proportional hazards and Kaplan–Meier survival analyses. Semaglutide was associated with a 40–70% reduced risk of a first-time AD diagnosis in patients with T2D compared to other medications, including other GLP-1RAs[111].

A separate study used target trial emulation methodology and data from 1.7 million patients with T2D to compare semaglutide to other glucose-lowering medications. Semaglutide use was associated with a reduced risk of overall AD and a decreased incidence of AD-related dementias (HR 0.54; 95% CI 0.49–0.59) compared to insulin[112].

A meta-analysis examined 26 randomized controlled trials that collected data on cognition and dementia diagnosis. Overall, there was no observed effect of diabetes treatment on dementia incidence. Within classes of glucose-lowering agents, GLP-1RAs were associated with a decreased occurrence of dementia, suggesting that glucose control is not the sole explanation for the differential benefit of GLP-1RAs on dementia incidence[113].

The cardiovascular actions of GLP-1RAs may reduce both large[114] and small vessel disease, which contribute to vascular cognitive impairment and AD. Circulating proteomic signatures observed in participants of a clinical trial examining liraglutide's effects on AD revealed changes in vascular and inflammatory proteins, consistent with observations in nonclinical models[115].

Clinical evidence for potential therapeutic benefit in AD from studies of T2D and obesity

Obesity and T2D are risk factors for AD and PD and are associated with inflammation, compromised immune response, oxidative stress, and endothelial and mitochondrial dysfunction[116]. GLP-1RAs reduce the incidence of AD and dementia associated with these risk states[117].

Forty metformin-treated participants with obesity who had prediabetes or newly diagnosed T2D were randomized to receive liraglutide (1.8 mg per day; $n = 20$) or lifestyle counseling (dietary intervention and exercise training; $n = 20$). All participants underwent neuropsychological assessments. After comparable weight loss and similar glycemic control and insulin sensitivity, significant improvements in short-term cognitive performance (mean digit span z score from −0.06 to 0.80, $P = 0.024$) and memory composite z score (mean memory z score from −0.67 to 0.032, $P = 0.0065$) were observed in liraglutide-exposed participants (between-group $P = 0.041$ and $P = 0.033$, respectively)[118].

In a large cardiovascular outcome trial involving patients with T2D, nearly 10,000 participants were randomly assigned to receive either dulaglutide ($n = 4{,}949$) or placebo ($n = 4{,}952$). During a median follow-up of 5.4 years (interquartile range 5.1–5.9 years), 8,828 participants provided baseline and one or more follow-up scores in MoCA (Montreal Cognitive Assessment) or the Digit Symbol Substitution Test. After post hoc adjustment for individual standardized baseline scores, the readjusted HR of substantive cognitive impairment was reduced by 14% in those assigned to dulaglutide treatment (HR 0.86; 95% CI 0.79–0.95; $P = 0.0018$)[119]. A smaller study of 50 patients with T2D treated for 12 weeks found that liraglutide improved cognitive function, and this beneficial outcome was independent of its glucose-lowering and weight loss effects[120]. Similar benefits have been identified with other T2D treatments, such as sodium–glucose cotransporter 2 inhibitors and DPP-4 inhibitors[104,109].

Some of these findings are based on post hoc analyses, but they are consistent with a role for GLP-1RA treatment in preventing or lowering the risk of developing dementia in individuals with T2D. The cause of dementia in these studies and the proportion of patients with AD are unknown. A key question is whether these benefits also extend to individuals with, or at risk of developing, AD in the absence of T2D.

Clinical trial data supporting the use of GLP-1RAs for AD

A placebo-controlled randomized controlled trial was conducted in 38 patients with AD, with [^{18}F]fluorodeoxyglucose positron emission tomography results as the primary outcome measure. Treatment with liraglutide (1.8 mg per day) for 6 months resulted in a relative preservation of brain glucose metabolism as a marker of brain activity[121]. Limitations include the use of clinical criteria to diagnose AD (with no biomarker confirmation) and the small sample size.

A small placebo-controlled randomized trial studied 21 participants who were treated with exenatide twice daily over 18 months[122]. Exenatide did not confer any benefits on cognitive, neuroimaging or CSF endpoints. The Evaluating liraglutide in Alzheimer's disease (ELAD) study was a 12-month randomized trial of liraglutide in 204 participants with mild to moderate AD without T2D. Although there was no significant benefit on the primary outcome measure (cerebral glucose metabolism as assessed using [^{18}F]fluorodeoxyglucose positron emission tomography), liraglutide conferred significant benefits on cognitive function (as measured by the AD Assessment Scale (ADAS)-EXEC (ADAS cognitive subscale with executive domains of the Neuropsychological Test Battery)) and showed significant advantages with respect to temporal lobe and whole-cortical volumes on magnetic resonance imaging. The benefits were similar in patients with and without concurrent vascular pathology[123]. No significant differences were observed in the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL) (−0.58; 95% CI: −3.13 to 1.97; $P = 0.65$) or Clinical Dementia Rating Scale (CDR)-Sum of Boxes (−0.06; 95% CI: −0.57 to 0.44; unadjusted $P = 0.81$) scores assessing different domains of functional activity and cognitive function.

The evoke and evoke+ studies

Given the totality of evidence from preclinical and clinical studies, as well as real-world evidence, the evoke and evoke+ trials were initiated and enrolled 3,808 participants each to study the effects of semaglutide[124]. The trials enrolled participants aged 55–85 years across 40 countries who had biomarker-confirmed MCI or mild AD dementia (positive for amyloid or with abnormal CSF amyloid levels). The primary outcome was the effect on progression, as measured by the CDR-Sum of Boxes, between participants taking oral semaglutide (14 mg daily) and those who received placebo for 104 weeks[124]. The evoke+ study has an identical design but allowed participants with established small vessel ischemic cerebrovascular disease[124]. The baseline data from the evoke and evoke+ studies[125] revealed that the mean (s.d.) participant ages were 71.8 (7.1) and 72.6 (7.1) years; 53.0% and 51.8% of the participants were women; most (76.6%) were white; and 59.7% and 54.5% were receiving AD medication, respectively. In the evoke and evoke+ trials, the mean baseline (s.d.) CDR-Sum of Boxes score was 3.7 (1.5) and 3.7 (1.6); the ADCS-ADL-MCI (ADCS-ADL for use in MCI) score was 39.4 (7.3) and 38.9 (7.5); and 72.5% and 68.7% of the participants had a CDR global score of 0.5 (ref. 125), respectively. Notably, the putative dose–response relationship for the presumed neuroprotective actions of GLP-1RAs has not yet been established. Topline data from the two evoke trials indicate that participantts randomized to oral semaglutide did not demonstrate a reduction of progression of AD, as measured by the change in Clinical Dementia Rating–Sum of Boxes score compared to baseline, despite evidence for reduction in levels of biomarkers reflective of disease activity[126]. Potential reasons for failure to achieve benefit include potentially suboptimal circulating levels of semaglutide achieved with oral semaglutide and the limited penetration of semaglutide into brain regions such as the hippocampus, an important site for intervention in AD pathophysiology. Real-world data suggesting a benefit of reduced rates of cognitive decline in healthier populations treated with GLP-1 medicines raise the possibility that individuals studied in the evoke trial were already too far advanced in their disease progression to benefit from oral semaglutide. Evidence for favorable effects of semaglutide on biomarkers of disease activity in a substudy highlight the need to better understand the utility of these various biomarkers as potentially reliable readouts that might be associated with preservation of cognitive function in future studies. Finally the evoke trial results remind us that we have a limited understanding of the optimal time for the initiation, and duration, of therapy with GLP-1 medicines that might be helpful to attenuate cognitive decline in patients at risk for progressive AD.

Safety concerns have been raised regarding GLP-1RA-induced weight loss in older individuals. In a pooled analysis of trials assessing

injectable or oral semaglutide for T2D, obesity and other conditions that included 3,529 participants aged ≥65 years, those receiving semaglutide had an estimated weight loss of 3.8% at week 52 without new safety concerns, suggesting that semaglutide can be safely administered to an aging population[127].

GLP-1RAs in the treatment of PD

In PD, along with α-synuclein accumulation, there is associated inflammation, synaptic dysfunction and dopaminergic neuronal loss, with some data also suggesting insulin resistance[128]. Preclinical studies show that GLP-1RAs restore dopamine levels, inhibit dopaminergic loss, attenuate neuronal degeneration, and alleviate both motor and nonmotor features of PD[129]. Exendin 4 improved autophagy and protected against mitochondrial stress induced by rotenone in dopaminergic cell cultures, thereby increasing SH-SY5Y cell survival[130]. Peripheral administration of GLP-1RAs increased the expression of tyrosine hydroxylase (TH)-containing neurons[131], and exendin 4 alleviated TH-positive neuronal loss in a PD rat model[132]. Motor dysfunction, glial activation and dopaminergic neuronal death were reversed by exendin 4 in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) PD mouse model[133]. Once-weekly administration of semaglutide restored TH levels in MPTP-treated mice[93,134]. Overall, preclinical studies show that GLP-1RAs can restore dopamine levels, inhibit dopaminergic loss, attenuate neuronal degeneration, and alleviate both motor and nonmotor features of PD[129].

Several GLP-1RAs have been tested as potential treatments in patients with PD[135]. A pilot study of exenatide showed positive effects on motor function in patients with PD in the 'off state', but no effects were observed in patients taking concomitant PD medications[136]. In a double-blind, placebo-controlled trial of lixisenatide involving 156 patients with PD, lixisenatide improved MDS-UPDRS (Movement Disorder Society-sponsored revision of the Unified PD Rating Scale) scores compared to placebo[137]. Although the treatment effect of GLP-1RAs may be mediated through neuroprotective effects and changes in dopamine, the mitigation of neuroinflammation may also contribute. Nevertheless, the largest and longest randomized trial (194 participants, 96 weeks) of GLP-1RAs in PD evaluating once-weekly exenatide failed to show a benefit[138].

GLP-1RAs in the treatment of ALS

ALS is a devastating neurodegenerative disease characterized by the progressive loss of motor neurons. The pathogenesis of ALS includes oxidative stress, mitochondrial dysfunction, neuroinflammation and glutamate excitotoxicity[139]. In preclinical models of ALS (SOD1 and TDP-43), liraglutide-treated animals showed no significant differences in disease progression or motor decline compared to vehicle-dosed animals[140].

Clinical studies align with these animal data. One case report demonstrated an accelerated progression of ALS symptoms in a patient treated with semaglutide[141]. In a case-controlled study of ALS and T2D, patients treated with GLP-1RAs had significantly lower tracheostomy-free survival, suggesting an acceleration of patient decline[141]. Thus, GLP-1RAs are unlikely to emerge as a treatment for ALS.

Conclusions

Interest in GLP-1RAs continues to expand across multiple therapeutic areas. In an observational study of more than 1,400,000 veterans, researchers examined data from patients treated with a GLP-1RA between 2017 and 2023. GLP-1RA use was associated with a reduced risk of substance use and psychotic disorders, seizures, coagulation disorders, cardiometabolic disorders, infectious illnesses and several respiratory conditions. A 12% reduction in the risk of an AD diagnosis was also reported[142].

The interest in using GLP-1RAs for AD and PD stems from the multiple targets for GLP-1 modulation, including peripheral immune cells and the vasculature (Fig. 2). GLP-1 medications reduce inflammation in the heart, vascular system, brain, liver and other organ systems. GLP-1RAs also reduce glucotoxicity, oxidative stress, immune cell recruitment and cytokine production through indirect pathways involving interorgan communication and through direct mechanisms affecting GLP-1R$^+$ immune cells[143]. GLP-1 medicines may also indirectly improve brain health by enhancing glucose control and reducing the deleterious metabolic consequences of obesity[144], as well as directly by improving BBB integrity. Collectively, these actions promote cell survival, maintain mitochondrial integrity and function, augment cellular metabolic processes, and attenuate astrocyte and glial activation, contributing to the preservation of CNS health and cognitive function[60].

Several key questions remain. Are the benefits of reducing incident dementia evident only in individuals with T2D? Are benefits detected in individuals with cognitive impairment related to cerebrovascular disease? Is the dose response established for successful treatment of T2D or obesity analogous to the dosing of GLP-1 medicines required to reduce neuroinflammation, preserve cognitive function and achieve neuroprotection in at-risk individuals?

Common adverse effects of GLP-1 medicines include nausea, vomiting, diarrhea and, if not desired, weight loss[145]. In contrast to antibodies targeting amyloid plaques, the absence of an absolute requirement for amyloid-related imaging abnormalities and the ease of administration of GLP-1RAs represent potential advantages over current disease-modifying therapies. The widespread benefits of GLP-1 medicines, which include the reduction of cardiovascular, liver and kidney diseases, coupled with their emerging therapeutic potential in neurodegenerative disorders[146], raise the possibility that GLP-1 medicines may be broadly useful in older populations to extend healthspan and reduce the development of a broad range of age-related comorbidities. Notably, the results of the ELAD and evoke trials indicate that it is possible to treat older individuals with cognitive impairment with normal or lower BMIs with liraglutide and semaglutide without introduction of new serious events. Nevertheless, the available clinical trial data do not yet support the use of oral semaglutide up to 14 mg daily for the treatment of established AD, highlighting the need to identify more suitable patient populations, appropriate dosing, optimal timepoints and durations for intervention, and perhaps next-generation GLP-1 medicines that are optimized for CNS penetration and neuroprotection, in future studies.

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Competing interests

M.N.S. discloses ownership interest (stock or stock options) in Lighthouse Pharmaceuticals; he consults for Eisai, Lilly, NeuroTherapia, Signant Health, Novo Nordisk, Anavex Life Sciences, Alzheon, Cognito Therapeutics, GSK and AbbVie. M.N.S. is supported by the National Institutes of Health grants R01AG059008, R01AG073212 and P30AG072980, as well as by the Barrow Neurological Foundation. J.L.C. has provided consultation to Acadia Pharmaceuticals, Acumen Pharmaceuticals, ALZpath, Annovis, Aprinoia Therapeutics, Artery Therapeutics, Biogen, Biohaven, BioXcel, Bristol Myers Squibb, Eisai, Fosun, GAP Foundation, Green Valley, Janssen, Karuna, Kinoxis Therapeutics, Lighthouse Pharmaceuticals, Lilly, Lundbeck, LSP/EQT Life Sciences, Mangrove Therapeutics, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, OptoCeutics, Otsuka, Oxford Brain Diagnostics, Praxis, Prothena, reMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, Sinaptica, T-Neuro, TrueBinding and Vaxxinity pharmaceutical, assessment and investment companies. J.L.C. is supported by the National Institute of General Medical Sciences (NIGMS) grant P20GM109025, National Institute on Aging (NIA) grants R35AG71476 and R25AG083721-01, National Institute of Neurological Disorders and Stroke (NINDS) grant RO1NS139383, the Alzheimer's Drug Discovery Foundation (ADDF), Ted and Maria Quirk Endowment, and Joy Chambers-Grundy Endowment. C.B. has received contract grant funding from Acadia Pharmaceuticals, Lundbeck, Takeda and Axovant pharmaceutical companies, as well as honoraria from Lundbeck, Lilly, Otsuka and Orion pharmaceutical companies. W.M.v.d.F. declares having research programs that have been funded by ZonMw, NWO, EU-JPND, EU-IHI, Alzheimer Nederland, Hersenstichting CardioVascular Onderzoek Nederland, Health~Holland (Topsector Life Sciences & Health), Stichting Dioraphte, Gieskes-Strijbis Fonds, Stichting Equilibrio, Edwin Bouw Fonds, Pasman Stichting, Stichting Alzheimer & Neuropsychiatrie Foundation, Philips, Biogen MA Inc., Novartis-NL, Life-MI, AVID, Roche BV, Eli Lilly-NL, Fujifilm, Eisai and Combinostics. W.M.v.d.F. holds the Pasman chair. W.M.v.d.F. is a recipient of ABOARD, which is a public–private partnership receiving funding from ZonMw (#73305095007) and Health~Holland (Topsector Life Sciences & Health) (public–private partnership allowance; #LSHM20106). W.M.v.d.F. is a recipient of TAP-dementia (www.tap-dementia.nl), which receives funding from ZonMw (#10510032120003). TAP-dementia receives cofinancing from Avid Radiopharmaceuticals and Amprion. All funding is paid to her institution. W.M.v.d.F. has been an invited speaker at Biogen MA Inc., Danone, Eisai, WebMD Neurology (Medscape), Novo Nordisk, Springer Healthcare and European Brain Council. All funding is paid to her institution. W.M.v.d.F. is a consultant to Oxford Health Policy Forum CIC, Roche, Biogen MA Inc. and Eisai. All funding is paid to her institution. W.M.v.d.F. participated in the advisory boards of Biogen MA Inc., Roche and Eli Lilly. W.M.v.d.F. is a member of the steering committee of evoke/evoke+ (Novo Nordisk). All funding is paid to her institution. W.M.v.d.F. is a member of the steering committee of PAVE and Think Brain Health. W.M.v.d.F. was an associate editor of *Alzheimer's Research & Therapy* in 2020/2021 and is an associate editor at *Brain*. M.T.H. serves on the science advisory board of the UK Dementia Research Institute at Imperial College London, Life and Health Sciences Research Institute of the University of Minho School of Medicine, the Lyon Neuroscience Research Center, Alector, Muna Therapeutics and T3D Therapeutics. He has received speaking honoraria from Novo Nordisk, Novartis, Biogen and Eli Lilly. J.J.H. consults for Novo Nordisk and is the founder of Antag Pharmaceuticals. L.B.K. is an employee and a minor employee related shareholder of Novo Nordisk A/S. L.B.K. is an inventor on several patents related to GLP-1-based medicines and various uses of them. S.S. has provided

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