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Review

Antidiabetic agents as a novel treatment for Alzheimer's and Parkinson's disease

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ABSTRACT

Therapeutic strategies for neurodegenerative disorders have commonly targeted individual aspects of the disease pathogenesis to little success. Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by several pathological features. In AD and PD, there is an abnormal accumulation of toxic proteins, increased inflammation, decreased synaptic function, neuronal loss, increased astrocyte activation, and perhaps a state of insulin resistance. Epidemiological evidence has revealed a link between AD/PD and type 2 diabetes mellitus, with these disorders sharing some pathological commonalities. Such a link has opened up a promising avenue for repurposing antidiabetic agents in the treatment of neurodegenerative disorders. A successful therapeutic strategy for AD/PD would likely require a single or several agents which target the separate pathological processes in the disease. Targeting cerebral insulin signalling produces numerous neuroprotective effects in preclinical AD/PD brain models. Clinical trials have shown the promise of approved diabetic compounds in improving motor symptoms of PD and preventing neurodegenerative decline, with numerous further phase II trials and phase III trials underway in AD and PD populations. Alongside insulin signalling, targeting incretin receptors in the brain represents one of the most promising strategies for repurposing currently available agents for the treatment of AD/PD. Most notably, glucagon-like-peptide-1 (GLP-1) receptor agonists have displayed impressive clinical potential in preclinical and early clinical studies. In AD the GLP-1 receptor agonist, liraglutide, has been demonstrated to improve cerebral glucose metabolism and functional connectivity in small-scale pilot trials. Whilst in PD, the GLP-1 receptor agonist exenatide is effective in restoring motor function and cognition. Targeting brain incretin receptors reduces inflammation, inhibits apoptosis, prevents toxic protein aggregation, enhances long-term potentiation and autophagy as well as restores dysfunctional insulin signalling. Support is also increasing for the use of additional approved diabetic treatments, including intranasal insulin, metformin hydrochloride, peroxisome proliferator-activated nuclear receptor γ agonists, amylin analogs, and protein tyrosine phosphatase 1B inhibitors which are in the investigation for deployment in PD and AD treatment. As such, we provide a comprehensive review of several promising antidiabetic agents for the treatment of AD and PD.

1. Introduction

Neurodegenerative disease is a term for a range of debilitating conditions which primarily affect the neurons in the human central nervous system (CNS). Progressive degeneration and the death of nerve cells can result in movement impairment (ataxia), or mental dysfunction (dementia) (Gao and Hong, 2008). Alzheimer's disease (AD) and Parkinson's disease (PD), represent the most common neurodegenerative disorders (Aarsland et al., 2011). AD is responsible for roughly 60–70% of dementia cases internationally (World Health Organisation, 2020), with a global prevalence of around 50 million cases (Collaborators, 2019a). Increases in population ageing and growth have led to estimates that cases will triple by 2050, representing a huge economic burden (Alzheimer's Disease International, 2018). In 2016, 6.1 million individuals were estimated to have PD, more than double compared to 1990. Of all neurological disorders considered in the Global Burden

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Disease Study 2015, PD had the greatest increase in prevalence, disability, and deaths between 1990 and 2015 (Collaborators, 2019b; GBD, 2015). Similar to AD, the exact mechanisms of PD pathogenesis remain elusive, with both disorders characterized by the accumulation of toxic proteins. Current widely used treatment options for AD and PD only provide minimal symptomatic relief with no clinically effective disease-modifying strategy available (Van Bulck et al., 2019). Anti-amyloid therapy lecanemab recently received accelerated approval by the US Food and Drug Administration following the conditional approval of aducanumab in 2021. Both therapies effectively reduce the amyloid plaque burden (Knopman et al., 2021; van Dyck et al., 2022). However, the number of eligible patients could be relatively small due to the cost and issues with reimbursement.

There is a growing body of evidence recognizing the link between neurodegenerative disorders and metabolic disorders. Insulin signalling abnormalities are an established hallmark in older adults with pre-diabetes/type 2 diabetes mellitus (T2DM) and have also been observed in AD and PD (Banks et al., 2012; Hoyer, 2004). In a sample of patients from the Fremantle Diabetes Study, DM increased the risk of developing probable dementia by 11% (Bruce et al., 2001). Two separate cohort studies demonstrated a relative risk (RR) of AD development was 1.3 in individuals with DM (Luchsinger et al., 2001; MacKnight et al., 2002). Biological sex influences the risk of adults with DM developing AD, with an elevated risk in men (RR = 2.27) compared to women (RR = 1.37) (Leibson et al., 1997). Additionally, having both DM and the apolipoprotein E epsilon 4 (ApoE ε4) allele increases the risk of AD development in an additive manner (Irie et al., 2008; Peila et al., 2002). Epidemiological, preclinical, and clinical evidence has also established a possible connection between AD and T2DM (Li et al., 2015). Results from a scoping review totalling 38991 patients suggested that between 13% and 20% of people living with dementia are comorbid with diabetes (Bunn et al., 2016).

Similarly, epidemiological studies highlight an increased risk of PD in patients with T2DM (Hu et al., 2007). A meta-analysis of seven population-based cohort studies, representing 1761,632 individuals, suggested that diabetes is associated with an increased risk of developing PD by 38% (Yue et al., 2016). Furthermore, T2DM appears to have a detrimental effect on disease progression and symptom severity. For example, the onset of diabetes before PD increases the risk of developing more severe motor symptoms (depicted by the Unified Parkinson's Disease Rating Scale and Hoehn and Yahr Staging) and a greater detrimental effect on activities of daily living (Cereda et al., 2012). In PD subjects, worse performance on attention/working memory and frontal/executive function tasks compared to subjects without T2DM have also been observed in a large-scale case research series (Chung et al., 2019).

While the mechanistic link between the disorders remains to be fully elucidated, diabetes appears to share common pathological mechanisms with AD/PD, including inflammation, insulin resistance, and oxidative stress, which may explain the increased risk observed in patients with T2DM (Verdile et al., 2015). As such, this has provided a promising avenue of therapeutic strategies, with the potential to provide viable disease-modifying treatment in neurodegenerative diseases where there has been so little success. In this review, we focus on how anti-diabetic treatments could be repurposed for use in AD and PD.

2. Insulin signalling in the brain

Insulin was traditionally recognized for its crucial role in the regulation of glucose homeostasis in peripheral tissues, by stimulating glucose uptake into insulin-sensitive tissues such as skeletal muscle and adipose tissue, and by inhibiting glucose synthesis and release from the liver (Hoyer, 2004). Its primary role is as a key cell growth and repair factor. The discovery that insulin crosses the blood-brain barrier (BBB) via insulin transporters and acts on CNS insulin receptors led to the discovery that insulin signalling in the brain has many important functions (Rhea et al., 2018). Two functionally and structurally different isoforms of the insulin receptor exist, insulin receptor-A and insulin receptor-B, with both isoforms present in the brain (Garwood et al., 2015; Pomytkin et al., 2018). In vitro neurons have been shown to exclusively express the insulin receptor-A isoform (Garwood et al., 2015; Pomytkin et al., 2018), however, recent evidence has demonstrated that the insulin receptor-B isoform is present in mature neurons using in situ detection in human brain tissue (Spencer et al., 2018). Binding to the extracellular α-subunit of the insulin receptor results in autophosphorylation of the receptor-activating tyrosine kinases which mediate the cellular influence of insulin (Pomytkin et al., 2018). Receptor activation results in key second messenger cascades, namely the phosphatidylinositol 3-kinase (PI3K, a lipid kinase)/AKT (also known as PKB or protein kinase B) pathway and the Raf/MEK/mitogen activated protein kinase (MAPK) pathway (De Meyts, 2000). The major insulin receptor signalling networks are vital in promoting cell metabolism, neuronal growth and differentiation, synaptic plasticity, and neuroprotection (Blazquez et al., 2014) (See Fig. 1), with AKT phosphorylation associated with AD pathogenesis and cognitive dysfunction (Arvanitakis et al., 2020).

Cerebrospinal fluid (CSF) insulin concentration is significantly lower than plasma insulin levels, but they are closely related (Bromander et al., 2010; Wallum et al., 1987). Insulin in the brain is primarily derived from the blood (Banks, 2004) but has been explained to originate from both peripheral and central sources (Blazquez et al., 2014; Gray and Barrett, 2018). A reduction in the ratio between CSF and plasma occurs in individuals with a state of peripheral insulin resistance (Kern et al., 2006) and with age, potentially with the restricted transfer of insulin in the brain owing to impaired transport across the BBB (Sartorius et al., 2015). Local synthesis in the brain is shown by mRNA for insulin coding genes within the brain in rodents (Kuwabara et al., 2011; Mehran et al., 2012). Additional support is provided by the early observations that C-peptide, a by-product of local insulin synthesis, has been identified in the cytoplasm of neuronal cells (Dorn et al., 1982). Recently epithelial cells of the choroid plexus were demonstrated to produce insulin, with insulin secretion mediated by serotonin but not glucose (Mazucanti et al., 2019). Serotonin-mediated activation of the 5HT2C receptor was shown to initiate IP3-sensitive channel activation and the subsequent mobilization of $Ca2+$ from intracellular storage to induce insulin secretion (Mazucanti et al., 2019). Further research is essential to uncover the presence and identify the localization and function of insulin synthesis in the CNS, with the suggestion that synthesis within the CNS may have a functional role in local circuitry (Arnold et al., 2018). Insulin has been suggested to have numerous important and diverging roles in the brain owing to the wide distribution of insulin receptor expression throughout cortical and subcortical structures. Insulin receptors have a high expression within the hippocampus and cerebral cortex, suggesting that the insulin signaling pathway may play a crucial role in memory processing. This is supported by the fact that insulin itself can affect cognitive function by modulating activities of both excitatory and inhibitory receptors triggering signal transduction cascades, leading to long-term memory consolidation and learning (Zhao et al., 2004).

3. Insulin signalling in AD and PD

Insulin resistance can be defined as an absent or diminished response to insulin (Rhea et al., 2022). Dysregulation of brain insulin signalling has been proposed as a central feature in the pathogenesis of some neurodegenerative diseases, with AD being focused on more than others (Mittal and Katare, 2016). Whilst insulin resistance in the brain and periphery are both linked with cognitive decline (Rhea et al., 2022), brain insulin resistance can occur in absence of peripheral insulin resistance (Talbot et al., 2012a), demonstrating that CNS insulin resistance is not simply an extension of peripheral insulin resistance. In this section, we expand on the literature evaluating the existence of brain and peripheral insulin resistance in AD and PD.

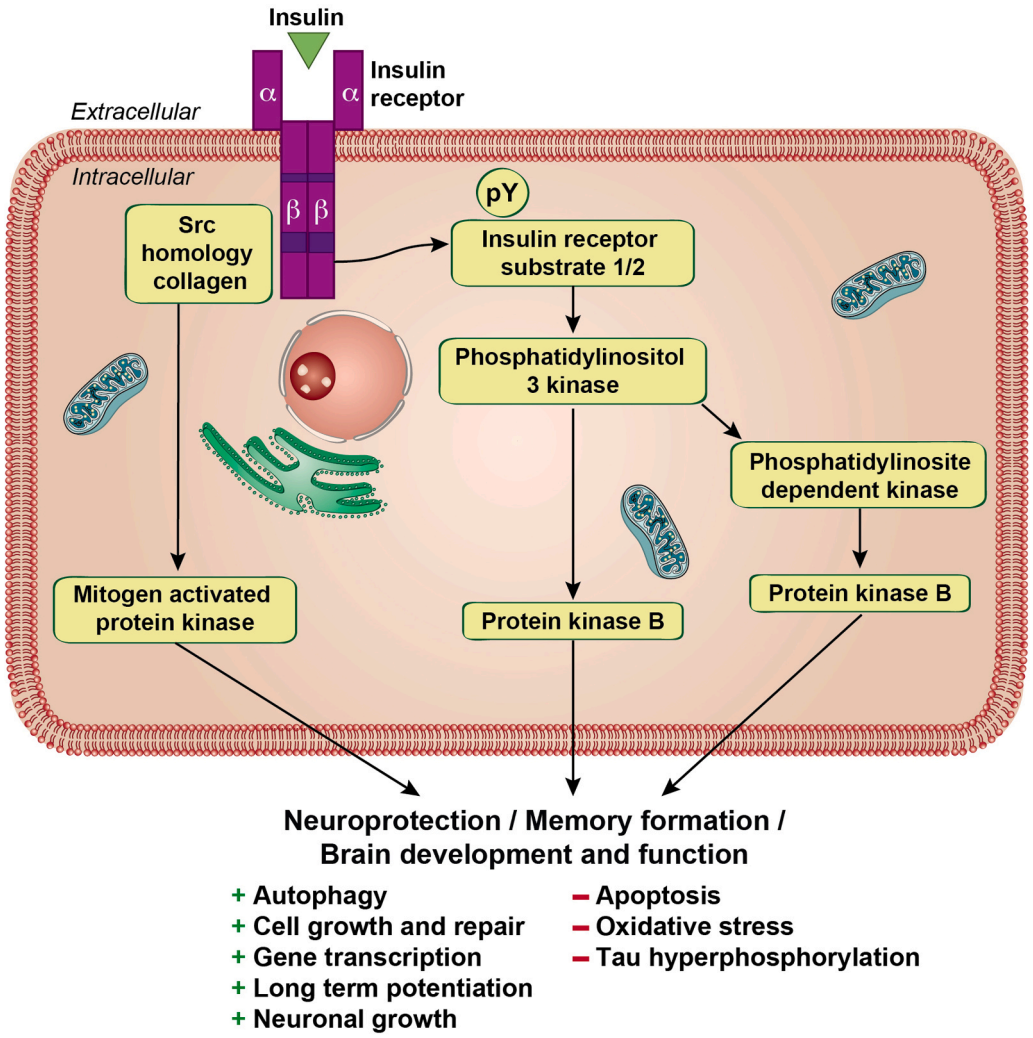

Fig. 1. Role of insulin signaling in neurons. Depiction of second messenger pathway activation.

Brain insulin resistance has been demonstrated in AD with an increased basal elevation of serine phosphorylation of insulin receptor substrate 1 (IRS-1) in the hippocampal formation and cerebral cortex tissue (Talbot et al., 2012b). Abnormal serine phosphorylation of IRS-1 in AD was confirmed by Yarchoan et al. (2014) and is associated with hyperphosphorylated tau and amyloid-β (Talbot et al., 2012b; Yarchoan et al., 2014). Analysis from neuronal-derived exosomes supports that brain insulin resistance occurs in AD (Kapogiannis et al., 2015) and that abnormal insulin signalling is associated with neurodegeneration (Mullins et al., 2017). Impaired insulin signalling in AD may arise from an increased inflammatory response. Several pro-inflammatory cytokines are implicated in suppressing IRS-1 via chronic upregulation of phosphorylated IRS-1 at serine residues including at sites 616 or 636 which attenuates insulin signalling in a feed-forward mechanism and via decreasing tyrosine phosphorylation of IRS-1 (Ferreira et al., 2018; Talbot et al., 2012b).

Insulin resistance itself is suggested to influence pathological hallmarks of AD including the aggregation of extracellular Aβ plaques and intracellular tau protein (Pivovarova et al., 2016). Insulin degrading enzyme (IDE) is an enzyme that is secreted by neuronal and microglial cells in the brain (Pivovarova et al., 2016). Central insulin resistance may reduce the levels of IDE, which has an important role as a principal regulator of Aβ levels in neuronal and microglial cells (Farris et al., 2003; Ohyagi et al., 2019). Several proteases are implicated in the degradation of Aβ with IDE, neprilysin, endothelin-converting enzymes, plasmin, and other Aβ-degrading proteases (e.g. matrix metalloproteases, cathepsin D) having important roles in determining cerebral Aβ levels (Chen et al., 2017; Saido and Leissring, 2012). Neprilysin and IDE represent the two proteases that significantly mediate both the intra- and extracellular degradation of Aβ (Kurochkin et al., 2018). Increased expression of IDE in insulin-cultured astrocytes facilitated Aβ plaque degradation, mediated via extracellular signal-regulated kinase (ERK) signalling (Yamamoto et al., 2018). Genetic variation of IDE is associated with the development of late-onset AD (Bjork et al., 2007). Insulin resistance in the brain may therefore inhibit the clearance of Aβ, promoting the formation of toxic plaques and neurodegeneration. Alongside Aβ, it is established that insulin resistance can induce tau pathology (Goncalves et al., 2019). Impaired insulin signalling leads to the reduction of Akt phosphorylation, which causes a subsequent increase in glycogen synthase kinase 3 beta (GSK3β) activity, inducing tau hyperphosphorylation (Zhang et al., 2018b).

To depict the relationship between insulin resistance, glucose hypometabolism, and neurodegenerative disease, in the Wisconsin Registry for Alzheimer's Prevention (WRAP) study, Willette and colleagues examined the association between peripheral insulin resistance and cerebral glucose uptake in middle-aged adults at risk for AD (Willette et al., 2015). In the WRAP study, 150 late middle-aged cognitively normal adults underwent neuropsychological testing, homeostatic model assessment of insulin resistance (HOMA-IR), and [^{18}F]-fluorodeoxyglucose positron emission tomography ([18 F]FDG). The researchers found that increased insulin resistance was associated with decreased glucose metabolism in several AD-vulnerable brain regions

including the left medial temporal lobe (MTL), which in turn may predict worse memory performance. Another study looked at the way insulin resistance affects hippocampal volume in women at risk for AD (Rasgon et al., 2011). Fifty postmenopausal women at risk for AD (50–65 years of age) underwent magnetic resonance imaging (MRI), cognitive testing, and HOMA-IR to investigate the association between insulin resistance and brain structure as well as functional changes. Results demonstrated a significant negative relationship between HOMA-IR and hippocampal volume, suggesting that insulin resistance in middle-aged individuals at risk is associated with AD degeneration.

Whilst the pathogenesis of PD remains unclear, there is emerging evidence that suggests that impaired insulin signalling may play a role. Insulin resistance may have a detrimental role on PD, accelerating development and exacerbating symptoms. 60% of nondiabetic patients with PD may have undiagnosed insulin resistance defined by HOMA-IR ≥ 2.0 and/or hemoglobin A1c (HbA_{1c}) ≥ 5.7 (Hogg et al., 2018), with increased insulin resistance in PD patients related to the severity of non-motor symptoms (Sanchez-Gomez et al., 2020). Insulin is effective in preventing cell death in a 1-Methyl-4-phenyl pyridinium-induced PD model (Ramalingam and Kim, 2016). Insulin also affects α-synuclein aggregation via the PI3K/Akt pathway (Fiory et al., 2019). In diabetic mice models and an ex vivo experimental design, insulin resistance was associated with increased α-synuclein expression (Hong et al., 2020). Similar to AD, brain insulin resistance may affect pathological hallmarks of PD mediated via the reduced expression of IDE. IDE is evidenced to prevent the formation of α-synuclein fibrils in vitro, perhaps protecting against the neurodegeneration of dopaminergic neurons (Sharma et al., 2015). In post-mortem brain tissue, PD patients show higher IRS-1 pS312 staining intensity in nigral dopaminergic neurons, further highlighting the possibility of brain insulin resistance in PD (Bassil et al.,

Table 1
Trial design and outcomes of clinical investigations of antidiabetic agents in AD and PD populations.

	Target /Drug name	Number of patients	Trial duration	Dosage	Outcomes
AD					
Gejl et al. (2016)	GLP-1 analog, liraglutide	38 patients with AD (N = 18 treatment, 20 placebo)	26 weeks	1.8 mg daily	Prevented decline in cerebral glucose metabolism No cognitive benefit (not powered to see cognitive change)
Watson et al. (2019)	GLP-1 analog, liraglutide	26 mid-aged participants with subjective cognitive complaints (N = 15 treatment, 11 placebo)	12 weeks	1.8 mg daily	Improved default mode network intrinsic connectivity No cognitive benefit (not powered to see cognitive change)
Mullins et al. (2019)	GLP-1 analog, exenatide	27 patients with probable AD (N = 13 Treatment, 14 placebo)	18 months	5 mcg twice daily	No cognitive benefit (not powered to see cognitive change)
Claxton et al. (2015)	Insulin, Intranasal insulin detemir	60 patients with MCI or mild to moderate AD (N = 21 insulin detemir 20 IU, 19 insulin detemir 40 IU, 20 placebo)	3 weeks	20 or 40 IU daily	40 IU insulin detemir improved memory composite
Craft et al. (2012)	Insulin, Intranasal regular insulin	104 patients with amnestic MCI or mild to moderate AD (N = 30 placebo, 36 insulin 20 IU, 38 insulin 40 IU	4 months	10 or 20 IU twice-daily	10 IU (twice-daily) improved delayed memory Both doses preserved caregiver-rated functional ability
Craft et al. (2017)	Insulin, Intranasal regular insulin or insulin detemir	36 patients with MCI or mild to moderate AD (N = 12 regular insulin, 12 insulin detemir, 12 placebo)	4 months	40 IU daily	Regular insulin improved memory and preserved MRI volume
Craft et al. (2020)	Insulin, Intranasal regular insulin	240 patients with amnestic MCI or AD	12 months	40 IU daily	No cognitive or functional benefit
Luchsinger et al. (2016)	Metformin	80 participants with amnestic MCI (N = 40 treatment, 40 placebo)	12 months	1000 mg twice daily	Treatment improved recall of the Selective Reminding Test of verbal memory No other cognitive or biomarker benefits
Koenig et al. (2017)	Metformin	20 patients MCI or mild dementia due to AD	16 weeks (crossover design)	1000 mg twice daily	Treatment improved executive functioning
Sato et al. (2011)	PPAR-γ agonist, pioglitazone	42 patients with mild AD (N = 21 treatment, 21 placebo)	6 months	15–30 mg daily	Treatment improved cognition and regional cerebral blood flow in the parietal lobe
Watson et al. (2005)	PPAR-γ agonist, rosiglitazone	36 patients with amnestic MCI or probable AD (N = 24 treatment, 12 placebo)	6 months	4 mg daily	Treatment preserved delayed-memory and selective attention
Risner et al. (2006)	PPAR-γ agonist, rosiglitazone	499 patients with probable AD (N = 127 treatment 2 mg, 130 treatment 4 mg, 132 treatment 8 mg, 122 placebo)	24 weeks	2, 4 or 8 mg daily	No cognitive benefit (primary analysis) ApoE ε4 non-carriers may have cognitive and functional benefit (exploratory)
Chamberlain et al. (2020)	PPAR δ/γ dual agonist, T3D-959	34 patients with mild to moderate AD (N = 9 treatment 3 mg, 9 treatment 10 mg, 10 treatment 30 mg, 8 treatment 90 mg)	2 weeks	3, 10, 30, or 90 mg daily	Treatment improved cognition and cerebral glucose metabolism
PD					
Aviles-Olmos et al. (2013)	GLP-1 analogue, exenatide	45 patients with moderate PD (N = 21 treatment, 24 control)	12 months	5-μg twice daily	Treatment improved motor and cognitive outcomes
Athauda et al. (2017)	GLP-1 analogue, exenatide	62 patients with moderate PD (N = 32 treatment, 30 placebo)	48 weeks	2 mg once weekly	Treatment improved motor outcomes No cognitive effects
Novak et al. (2019)	Insulin, Intranasal regular insulin	15 patients with a clinical diagnosis of PD or multiple system atrophy (N = 9 treatment, 6 placebo)	4 weeks	40 IU daily	Treatment improved motor performance and functionality

2021). Targeting central insulin signalling may therefore represent a promising strategy to alleviate cognitive and motor deficits in PD and provide neuroprotection (Sharma et al., 2021). Despite a possible role of insulin resistance in PD pathogenesis, the literature remains contentious, with newly diagnosed, unmedicated PD patients showing no change in peripheral insulin resistance compared to controls quantified with a hyperinsulinemic-euglycemic clamp (Aziz et al., 2020) highlighting the necessity for further research to elucidate the involvement of insulin resistance in PD.

In conclusion, emerging evidence suggests that insulin resistance may be a part of AD and PD pathogenesis. Peripheral and central insulin resistance may both contribute to AD/PD; however, this is likely to be through separate pathways (Rhea et al., 2022) which future research should establish. Herein, we focus on antidiabetic agents for the treatment of AD/PD and indicate how targeting brain insulin resistance and incretin signalling are promising approaches.

4. Antidiabetic drugs for neurodegenerative disease

AD and PD are multifaceted disorders, involving numerous pathological processes such as abnormal accumulation of toxic proteins, inflammation, synaptic dysfunction, neuronal loss, astrocyte activation, and perhaps a state of insulin resistance. As described above, there are pathophysiological commonalities between DM and neurodegenerative diseases, and anti-diabetic agents have great potential as a therapeutic strategy for AD and PD.

(Refer to Table 1. for a summary of discussed clinical trials on antidiabetic treatments in AD and PD populations).

4.1. GLP-1 analogues in AD

Incretins are a class of peptide hormones that include glucagon-like-peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) (Yaribeygi et al., 2021). GLP-1 receptor agonists represent a class of drugs developed for the treatment of diabetes. GLP-1 produces insulinotropic effects, augmenting the release of insulin only in hyperglycaemic conditions; thus, GLP-1 does not induce hypoglycemia (Meier, 2012). Native GLP-1 has a short half-life of under 2 min owing to degradation via the enzyme dipeptidyl-peptidase IV (DPP IV) and rapid clearance (Muller et al., 2019). In the brain, GLP-1 receptors have been identified within the brainstem, hypothalamus, and some limbic areas (Daniels and Mietlicki-Baase, 2019).

GLP-1 receptor agonists have been modified to resist inactivation via DPP IV, generating an extended half-life compared to native GLP-1 (Gilbert and Pratley, 2020). Exenatide was the first synthetic GLP-1 receptor agonist approved for the treatment of T2DM (Aroda, 2018; Nauck, 2016). Liraglutide was the first long-acting, once-daily, GLP-1 receptor agonist with a half-life of over 13 h and sharing a 97% homology with native GLP-1 (Aroda, 2018; Nauck, 2016). Lixisenatide is a short-acting GLP-1 receptor agonist based on the structure exendin-4, with a half-life of 3 h (Aroda, 2018). Albiglutide is an approved once-weekly treatment for T2DM. Albiglutide is a protein generated through the genetic fusion of two copies of modified human GLP-1, with an extended half-life of 5 days (Aroda, 2018; Nauck, 2016). Another compound suitable for once-weekly injection is dulaglutide, produced with recombinant DNA technology (Nauck, 2016). A long-lasting agonist, semaglutide, is a newly available treatment administered as a once-weekly subcutaneous injection and the only GLP-1 receptor agonist available as an oral compound. (See Fig. 2 for the structure of GIP and GLP-1 receptor agonists).

4.1.1. Possible neuroprotective mechanism

It is possible that within the brain GLP-1 receptor activation can compensate for dysregulated insulin signalling in the brain (Gault and Holscher, 2018). GLP-1 exerts its action via the GLP-1 receptor, part of the G protein-coupled receptor family. GLP-1 signalling is best characterized within pancreatic β cells, where receptor activation enhances insulin secretion (Smith et al., 2019). Besides influencing insulin signalling, it has been postulated that GLP-1 activity can stimulate synaptic neurotransmitter release and induce long-term potentiation (LTP) in neurons (Calsolaro and Edison, 2015). Ligand binding stimulates the intracellular accumulation of cyclic adenosine monophosphate (cAMP) (Grieco et al., 2019; Smith et al., 2019). An increase in cAMP results in PKA/CREB pathway activation as well as exchange protein directly activated by cAMP (EPAC) dependent processes (Grieco et al., 2019). Together this triggers the opening of L-type voltage-gated Ca^{2+} channels. Several additional pathways are enhanced following receptor stimulation including Akt/PKB and PI3K/MAPK (Grieco et al., 2019). GLP-1 signalling is implicated to produce several protective effects, inducing anti-inflammatory signalling, reducing oxidative stress, enhancing gene transcription, and regulating autophagy (Calsolaro and Edison, 2015; Grieco et al., 2019; Smith et al., 2019). Further research is required to identify subtle differences in the intracellular signalling pathways, which may depend on multiple factors including the region of the brain (Calsolaro and Edison, 2015; Grieco et al., 2019; Smith et al., 2019). Refer to Fig. 3 for GLP-1 signalling in the brain.

4.1.2. The influence of GLP-1 in several other tissues

GLP-1 receptors are expressed in islet α and β cells and peripheral tissues, including the pancreas, heart, gastrointestinal tract, adipose tissue, kidney, and muscles. Owing to such a widespread expression, GLP-1 is implicated in a variety of systems and processes (Ceccarelli et al., 2013; Lund et al., 2014) (Fig. 4). Regulation of glucagon secretion by pancreatic α-cells β cells whilst increasing insulin biosynthesis and pancreatic β cell proliferation, in a glucose-dependent manner, are additional effects of this drug class shown in rodents (Zhang et al., 2019). GLP-1 exerts influence on lipogenic and lipolytic activity and improves glucose uptake in the adipose tissue (Ejarque et al., 2019), reduces albumin excretion and natriuresis in the kidney, and upregulates glycogen synthesis and glucose oxidation in the muscle. GLP-1 promotes cardioprotection through its influence on the heart, whereby it generates a decrease in systolic blood pressure, whilst increasing heart rate. GLP-1 receptor agonists have been identified to target liver inflammation and fibrosis, with potential utility in the treatment of non-alcoholic fatty liver disease (Seghieri et al., 2018). In blood vessels, GLP-1 signalling suppresses pro-atherosclerotic factors and promotes vasodilation which has been suggested to improve blood vessel wall abnormalities (Kimura et al., 2018). Activation of the GLP-1 receptor protects against cardiovascular complications by reducing vascular inflammation (Helmstadter et al., 2020).

4.1.3. Preclinical evidence

Preclinical evidence has revealed that there is a strong promise for GLP-1 receptor agonists to protect against progressive neurodegeneration. In 7-month-old APP/PS1 mice, 8 weeks of daily liraglutide treatment prevented memory loss, an effect that was accompanied by a reduction in synaptic loss and protection of synaptic plasticity within the hippocampus (McClean et al., 2011). Liraglutide treatment was also effective in reducing the accumulation of β-amyloid and attenuating the inflammatory response, reducing the number of activated microglia (McClean et al., 2011). In a follow-up study in aged 14-month-old APP/PS1 mice, the neuroprotective effects of liraglutide were maintained suggesting that GLP-1 receptor agonists are not only protective in the early stages of AD development but can reverse key pathological features of the disease (McClean and Holscher, 2014). In SAMP8 mice, liraglutide successfully prevented memory decline and neuronal loss in the hippocampus in comparison to vehicle-dosed mice (Hansen et al., 2015). Liraglutide has been demonstrated to reduce the level of cortical β-amyloid and inflammation as well as normalize oxidative stress and mitochondrial function in 3xTg-AD female mice. The neuroprotective effects of liraglutide were accompanied by the normalization of brain GLP-1 signalling, with restored levels of PKA

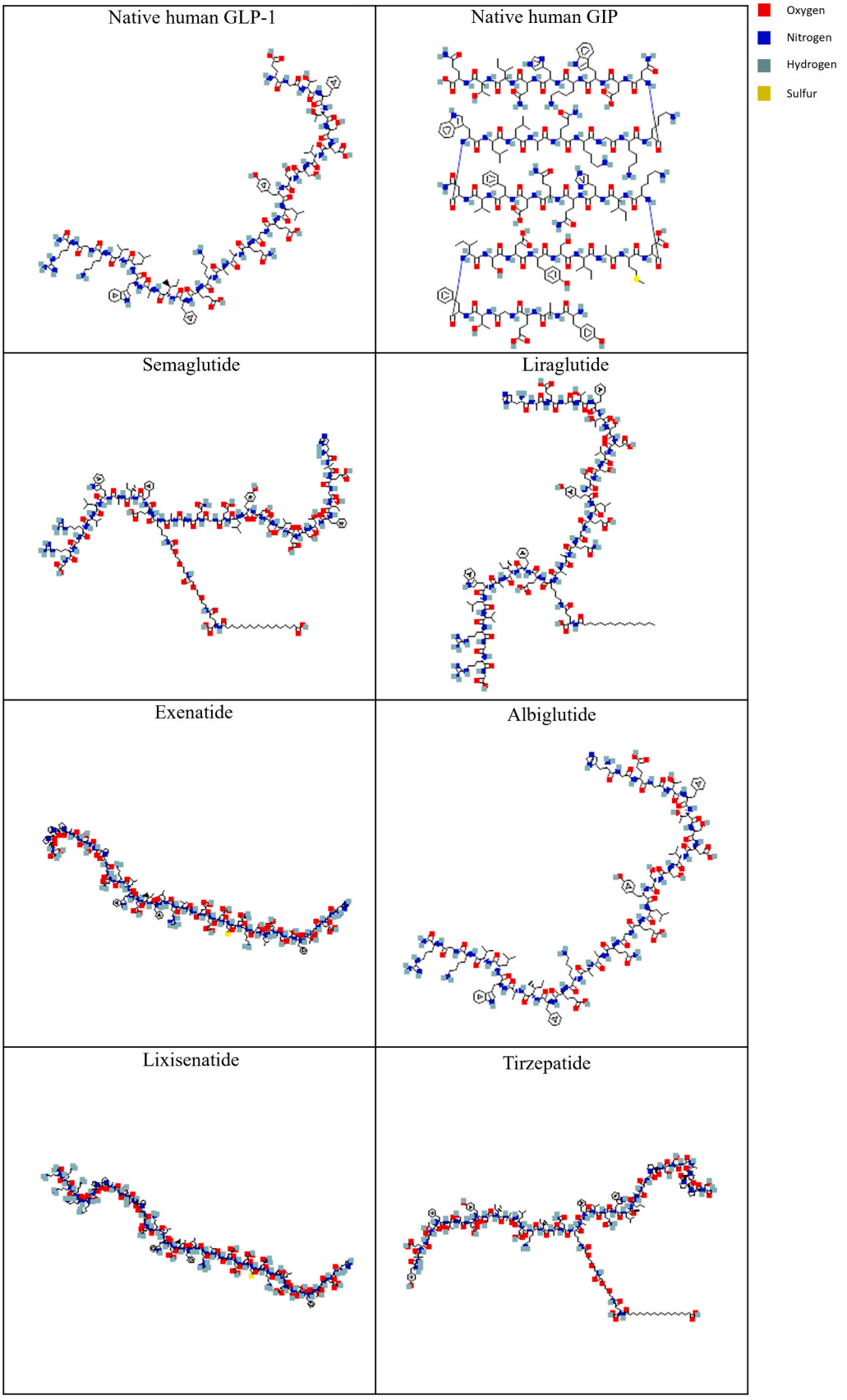

Fig. 2. Structure of native human GLP-1, GIP and GLP-1 analogues exenatide, lixisenatide, liraglutide, albiglutide, semaglutide, dulaglutide, and dual GLP-1/GIP receptor agonist, tirzepatide. Abbreviations: GIP Gastric inhibitory polypeptide, GLP-1 glucagon-like peptide-1. Structure references: GLP-1 CID 90488821 URL https://pubchem.ncbi.nlm.nih.gov/compound/90488821. GIP CID 131954558 URL https://pubchem.ncbi.nlm.nih.gov/compound/GIP-_human. Semaglutide CID 56843331 URL https://pubchem.ncbi.nlm.nih.gov/compound/Semaglutide. Liraglutide CID 16134956 URL https://pubchem.ncbi.nlm.nih.gov/compound/Liraglutide. Exenatide CID 45588096 URL https://pubchem.ncbi.nlm.nih.gov/compound/Byetta. Albiglutide CID 145994868 URL https://pubchem.ncbi.nlm.nih.gov/compound/Albiglutide. Lixisenatide CID 90472060 URL https://pubchem.ncbi.nlm.nih.gov/substance/135267128. Tirzepatide CID 163285897 URL https://pubchem.ncbi.nlm.nih.gov/compound/Tirzepatide.

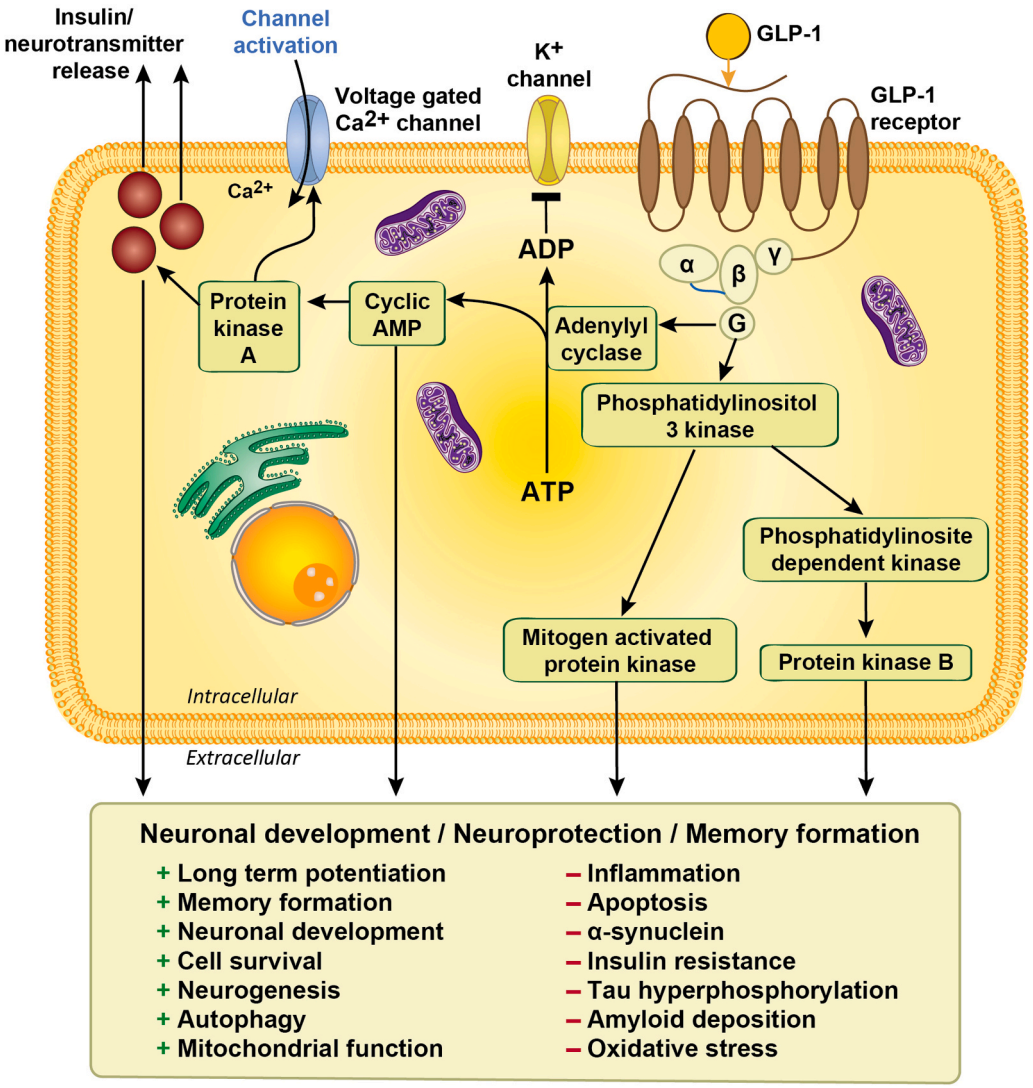

Fig. 3. GLP-1 signaling in the brain. Neuroprotective influence of downstream signaling cascades. Abbreviations: ADP adenosine diphosphate, ATP adenosine triphosphate GLP-1 glucagon-like peptide-1, GLP-1R glucagon-like peptide-1 receptor.

(Duarte et al., 2020). In Aβ-treated astrocytes, liraglutide effectively ameliorated mitochondrial dysfunction as well as neuronal loss via the cAMP/PKA pathway (Xie et al., 2021). Cognitive benefits have reliably been shown following liraglutide treatment, with mice displaying improved performance on the Morris water maze. The benefits of this GLP-1 receptor agonist also included improved astrocytic glycolysis, with enhanced PI3K/Akt signalling evidenced to underlie these promising results (Zheng et al., 2021).

An additional mechanism underlying the effectiveness of liraglutide treatment may be through restored brain insulin signalling. Liraglutide prevents insulin receptor loss in both mice and non-human primate β-amyloid oligomer-induced models (Batista et al., 2018). Furthermore, alongside the prevention of brain insulin receptor pathology, treatment attenuated synaptic loss with the beneficial influence of liraglutide mediated via cAMP/PKA signalling (Batista et al., 2018). Two months of liraglutide treatment has also been demonstrated to effectively restore IRS-1/PI3K/Akt signalling in APP/PS1 mice (Talbot et al., 2011). Liraglutide was also identified to increase the levels of IDE, phosphorylated insulin receptors, and GSK3β, suggesting the restoration of cerebral insulin signalling may in part mediate the neuroprotective influence of this GLP-1 receptor agonist (Paladugu et al., 2021).

Several GLP-1 receptor agonists in addition to liraglutide have displayed promise in preclinical models of AD. Exenatide effectively ameliorated memory deficits and reduced β-amyloid in the prefrontal cortex and hippocampus of male rats. Furthermore, exenatide prevented mitochondrial toxicity and increased Akt (Garabadu and Verma, 2019). A protective influence of exenatide on mitochondrial function was demonstrated with treatment effective in preventing synaptic damage in the hippocampus in 5 ×FAD mice (An et al., 2019). Semaglutide also displays efficacy against β-amyloid pathology via inhibiting apoptosis and enhancing autophagy in SH-SY5Y cells (Chang et al., 2020). A novel GLP-1 receptor agonist, CJC-1131, with a long half-life of up to 353 h, was effective in enhancing LTP, restoring levels of PKA, and protecting against cognitive decline (Zhang et al., 2017). Salameh et al., suggest that out of several GLP-1 receptor agonists, exenatide deserves special consideration for the treatment of neurodegenerative conditions owing to its favourable pharmacokinetics. Exenatide showed a greater ability to cross the BBB in comparison to liraglutide, lixisenatide, and semaglutide (Salameh et al., 2020). Whilst liraglutide and semaglutide were not shown to measurably cross the BBB (Salameh et al., 2020), liraglutide and semaglutide have been shown to access parts of the septal nucleus, brainstem, and hypothalamus (Gabery et al., 2020). Alternatively, these agents may influence brain function indirectly by affecting another substance that can cross the BBB (Salameh et al., 2020).

Together preclinical models demonstrate that GLP-1 receptor agonists have the potential to influence several critical pathological features

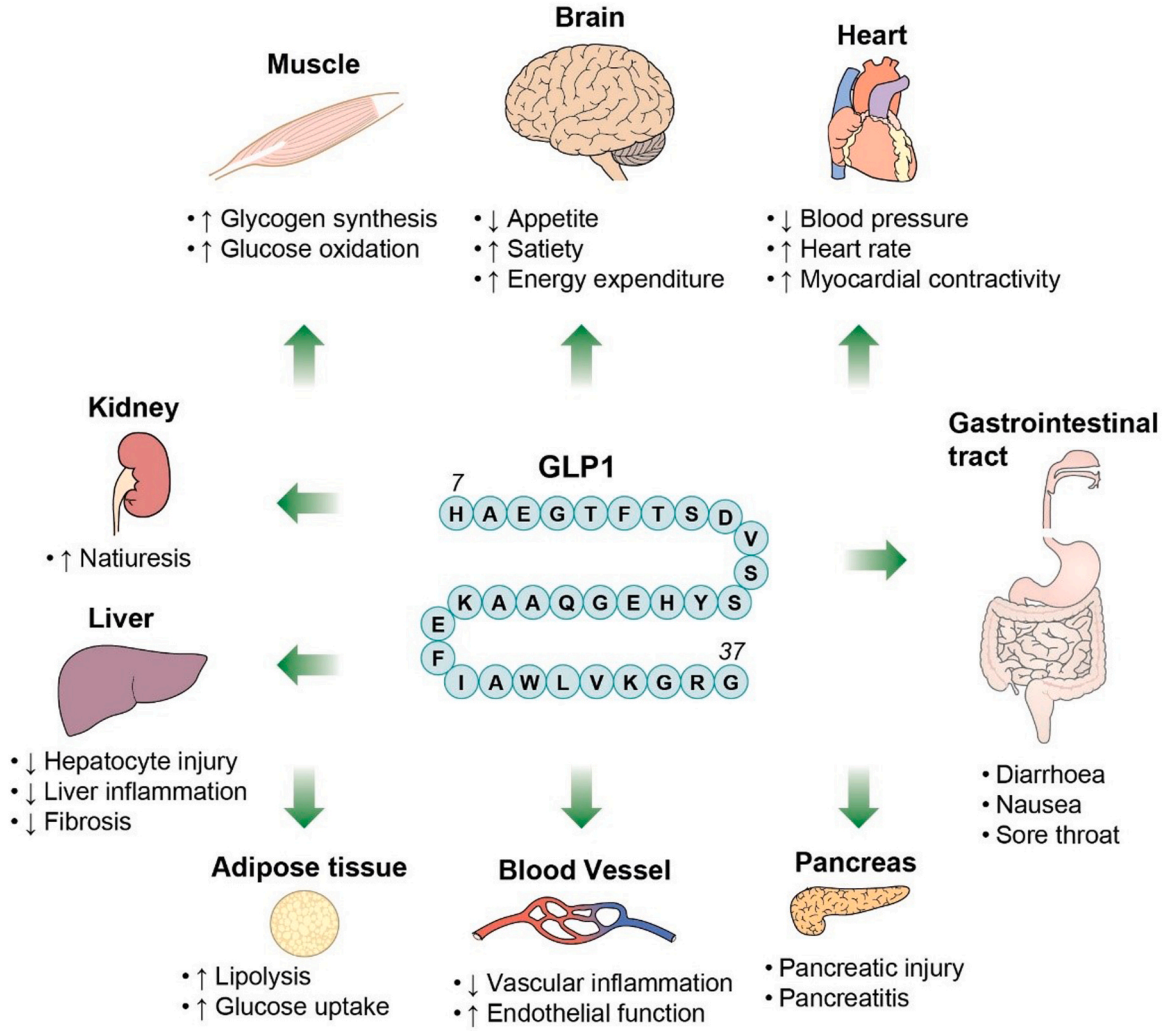

Fig. 4. Role of GLP-1 and GLP-1 analogues in different organs in the body. Abbreviations: GLP-1 glucagon-like peptide-1.

of AD including preventing amyloid plaque formation, reducing inflammation, improving cognition, and enhancing neurogenesis. Promisingly, increasing evidence suggests GLP-1 receptor agonists can also affect tau pathology. Exenatide injections were demonstrated to reduce tau hyperphosphorylation in a high-fat diet rodent T2DM rodent model (Yang et al., 2016). In a hTauP301L mouse tauopathy model, 6 months of liraglutide treatment successfully decreased the levels of phosphorylated tau and significantly increased survival rates (Hansen et al., 2016). Dulaglutide similarly showed efficacy against AD tauopathy, reducing tau hyperphosphorylation in streptozotocin-treated mice via improved PI3K/AKT/GSK3β signalling (Zhou et al., 2019). These findings are supported in non-human primates in which liraglutide prevents the abnormal phosphorylation of tau (Batista et al., 2018).

4.1.4. Clinical evidence

In a pilot trial of liraglutide, 38 patients diagnosed with AD were randomly allocated to receive active treatment (n = 18) or placebo (n = 20) (Gejl et al., 2016). All subjects completed [18 F]FDG and [11 C]PIB scans at baseline and after 6 months of treatment to evaluate the regional cerebral glucose metabolic rate (CMRGlc) and deposition of amyloid respectively. Liraglutide prevented a reduction in cerebral glucose metabolism, whilst no effect was found on cognitive scores or amyloid load. A recent 12-week placebo-controlled trial enrolled 43 patients with subjective memory complaints to examine the neural effects of liraglutide (Watson et al., 2019). Out of the 26 subjects who completed the trial, 15 were allocated liraglutide, and 11 were assigned placebo treatment. Using seed-based resting state functional MRI, patients receiving liraglutide showed improved intrinsic connectivity within default-mode network structures compared to placebo. A recent large-scale 12-month phase II b trial Evaluating Liraglutide in Alzheimer's Disease (ELAD) is awaiting publication (Femminella et al., 2019).

In an 18-month pilot trial evaluating the influence of exenatide in AD, 11 patients were randomly assigned to receive exenatide, and 10 were assigned to placebo twice daily (Mullins et al., 2019). Exenatide treatment was safe and well-tolerated. Neuropsychological and MRI outcomes were similar between patients treated with exenatide or placebo. However, exenatide treatment was demonstrated to reduce the level of $A\beta_{42}$ in extracellular vesicles at 18 months compared to baseline and placebo-treated participants. Thus, perhaps exenatide can reduce brain amyloidosis which warrants further investigation in AD. The trial was terminated prematurely limiting the statistical power to reach the predefined outcomes.

In a large multicenter trial, the efficacy of weekly dulaglutide treatment on cardiovascular endpoints in patients with T2DM was evaluated. Dulaglutide was well tolerated and treatment reduced cardiovascular outcomes, lowered weight, HbA_{1c}, low-density lipoprotein cholesterol, systolic blood pressure, and modestly increased heart rate (Gerstein et al., 2019). An exploratory analysis of REWIND which assessed cognitive function at baseline and follow-up time points

identified that the risk of developing substantive cognitive impairment was reduced by 14% in the dulaglutide-treated patients (Cukierman-Yaffe et al., 2020). Additionally, a pooled post hoc analysis from three cardiovascular outcome trials: LEADER (Marso et al., 2016b), SUSTAIN 6 (Marso et al., 2016a), and PIONEER 6 (Husain et al., 2019), aimed to ascertain the hazard ratio for dementia diagnosis in 15,820 T2DM patients treated with liraglutide or semaglutide (Ballard et al., 2020). Promisingly, the risk of a dementia diagnosis was halved in patients receiving liraglutide/semaglutide compared to placebo. However, as only 13–20% of patients with dementia are comorbid for diabetes (Bunn et al., 2016), it is debatable whether these findings will translate to the wider population of AD cases.

Together preclinical and early clinical evaluation for repurposing GLP-1 receptor agonists for AD is promising, with semaglutide entering a large-scale phase 3 evaluation in people with early AD (NCT04777396). It is important to note key limitations when comparing preclinical and clinical research in AD which evaluate the therapeutic efficacy of antidiabetic agents. The majority of preclinical research utilizes transgenic mice models based on mutations that cause the familial form of AD (Elder et al., 2010), despite over 99% of people living with AD suffering from the sporadic form of the disease (Yokoyama et al., 2022). The development and onset of brain insulin resistance in animal models of familiar AD used in pharma industry may differ from that in AD patients enrolled in clinical trials with a predominantly sporadic form, which brings into question the translational value of animal to human data when evaluating the therapeutic potential of antidiabetic agents in AD populations with over 99% patients suffering from its sporadic form.

4.2. GLP-1 analogues in PD

Even though symptomatic treatment for PD is available, there is still a lack of an effective disease-modifying agent and it remains imperative to identify better therapies (Stoker and Barker, 2020). In repurposing anti-diabetic treatments for PD, GLP-1 receptor agonists are one of the most promising candidates (Victorino et al., 2021). Postprandial plasma levels of GLP-1 are diminished in patients with PD compared to controls (Manfready et al., 2021). In a large cohort-based study in patients with diabetes, the incidence ratio rate of PD for participants treated with a DPP-4 inhibitor or a GLP-1 receptor agonist was 36% and 62% lower, respectively (Brauer et al., 2020). This supports that targeting GLP-1 signalling represents a promising neuroprotective and potentially disease-modifying strategy for PD (Brauer et al., 2020).

4.2.1. Possible mechanism

The neuroprotective effects of GLP-1 on PD may be via modulation of the PI3K-AKT signalling pathway (Victorino et al., 2021). Several major downstream targets of this pathway may exert protection such as forkhead box protein O (FoxO), mechanistic target of rapamycin (mTOR), glycogen synthase kinase 3β (GSK3β), and nuclear factor kappa beta (NF-κB) (Victorino et al., 2021). Binding to the GLP-1 receptor activates Akt which can inhibit GSK3β and decrease the aggregation of toxic proteins including α-synuclein (Victorino et al., 2021). Activation of mTOR can regenerate nigrostriatal axons and prevent neurodegeneration (Victorino et al., 2021). NF-κB signalling has been proposed to reduce inflammation by downregulating pro-inflammatory cytokines (Victorino et al., 2021). Upregulation of cAMP following GLP-1 receptor activation may further underlie the positive effects against PD pathology (Glotfelty et al., 2020). cAMP stimulates several downstream pathways which reduce inflammation, oxidative stress, and apoptosis (Glotfelty et al., 2020). Similar to AD, GLP-1 may exert further protection through the restoration of insulin signalling in PD (Glotfelty et al., 2020). Furthermore, it has been postulated that a protective influence of GLP-1 may have a role in the maintenance of the BBB (Glotfelty et al., 2020; Liu et al., 2017; Victorino et al., 2021).

4.2.2. Preclinical evidence

Exenatide treatment provides neuroprotection in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD. Administration of exenatide is demonstrated to protect against dopaminergic neuronal damage and improve motor functioning (Li et al., 2009). In addition, treatment with exenatide successfully attenuates the loss of substantia nigra pars compacta neurons and the striatal dopaminergic fibers in MPTP mice (Kim et al., 2009). In vivo and in vitro models of PD display the therapeutic benefit of exenatide in promoting neurogenesis and restoring dopaminergic neurotransmission (Bertilsson et al., 2008). Exenatide is limited by a short half-life; however, an extended-release exendin-4 formulation, PT302, displays efficacy in reducing motor impairments and neurodegeneration in a 6-hydroxydopamine rat model of PD (Chen et al., 2018). Semaglutide was also effective in alleviating motor deficits and inflammation, whilst restoring levels of tyrosine hydroxylase. Furthermore, treatment reduced apoptosis and increased autophagy with semaglutide displaying superior neuroprotective properties than liraglutide (Zhang et al., 2018a). A long-acting GLP-1 receptor agonist, NLY01, was effective in preventing dopaminergic loss and behavioural deficits in an α-synuclein preformed fibril model of sporadic PD. Promisingly, NLY01 prevented the conversion of astrocytes to the toxic A1 phenotype, an important finding since inflammation is evidenced as one of the principal contributors to PD (Yun et al., 2018).

4.2.3. Clinical evidence

In a proof-of-concept, single-blind trial 45 patients with moderate PD were randomly assigned to receive exenatide (n = 20 completed trial) for 12 months or act as controls (n = 24 completed trial) (Aviles-Olmos et al., 2013). In general, exenatide was safe and well tolerated by participants. Participants treated with exenatide displayed improved motor performance at 12 months with a mean increase of 2.7 points on the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), compared to a mean 2.2-point decrease in controls. Improvements in motor function were maintained in an off-medication state 2 months following treatment cessation. Additionally, cognitive performance was improved in exenatide-treated participants compared to controls as measured by the Mattis dementia rating scale–2 (MDRS). In a follow-up evaluation, it was observed that motor and cognitive benefits persisted 12 months post-treatment (Aviles-Olmos et al., 2014). Despite encouraging results, the findings from Aviles-Olmos et al. should not be treated as evidence of a disease-modifying effect owing to the single-blind design and small sample size. In a larger phase II trial, Athauda et al. enrolled 62 patients with idiopathic PD to evaluate the effects of exenatide (Athauda et al., 2017). Participants were randomly assigned exenatide (N = 30) or placebo (N = 32) once weekly for 48 weeks with a 12-week washout period. At 48 weeks and 60 weeks, in the off-medication phase, exenatide-treated patients demonstrated a significant improvement on part 3 of the MDS-UPDRS compared to placebo-treated patients. Exenatide treatment did not significantly improve MDRS scores, or quality of life compared to placebo. Whilst treatment effects on motor function may simply represent a symptomatic benefit, the positive effect of exenatide beyond the period of exposure is perhaps evidence that GLP-1 can influence the underlying PD pathophysiology (Athauda et al., 2017). A post hoc analysis of the main trial results revealed that younger patients with lower disease severity tended to respond better, highlighting the importance of early intervention (Athauda et al., 2019b). Of note, the authors further identified that patients with higher insulin resistance or obesity at baseline had improved cognitive outcomes following exenatide. Whilst speculative, this is in support of the possible influence of GLP-1 on dysfunctional brain insulin signalling pathways.

To uncover the mechanism of action of exenatide, secondary analysis from the most recent RCT was conducted using neuronal-derived extracellular vesicles to explore the influence within the CNS (Athauda et al., 2019a). In vivo assessment of neuronal-derived

extracellular vesicles has increasingly been recognized as a promising method to reveal the mechanism of centrally acting drugs. Exenatide treatment was demonstrated to increase tyrosine phosphorylation of IRS-1, an effect that was associated with changes in the downstream effectors, Akt, and mTOR. Furthermore, levels of mTOR were demonstrated to associate with the level of clinical benefit. Thus, augmentation of insulin signalling may underlie the neuroprotective effects of exenatide. Engagement of AKT and mTOR pathways may prevent α-synuclein aggregation, protect dopaminergic neurons, reduce inflammation, and enhance cell survival. Results failed to suggest that the beneficial effects of exenatide were through the engagement of the MAPK pathway.

Results from RCTs show a potential clinical utility for GLP-1 receptor agonists in the treatment of motor symptoms for PD. In two meta-analyses (Mulvaney et al., 2020; Wang et al., 2020b) of GLP-1 receptor agonists, only the two previously discussed trials met the inclusion criteria (Athauda et al., 2017; Aviles-Olmos et al., 2013). In combination, the trials show exenatide treatment displays promise in treating motor symptoms of PD, an effect that appears to persist even in off-medication states. Exenatide was effective in improving scores on the Unified Parkinson's Disease Rating Scale Part I (UPDRS-I), UPDRS Part IV (UPDRS-IV), and the MDRS. Also, exenatide demonstrates a good safety profile in PD with treatment unlikely to be related to serious adverse events reported in either trial. However, it remains inconclusive whether treatment can improve quality of life, activities of daily living, and psychological outcomes.

GLP-1 receptor agonists represent a hopeful strategy to alleviate cognitive, motor, and non-motor symptoms associated with PD, however, larger trials and research assessing promising GLP-1 receptor agonists including dulaglutide are still required. Phase II trials of GLP-1 agonists, lixisenatide (NCT03439943), liraglutide (NCT02953665), and semaglutide (NCT03659682) are currently ongoing. Exenatide is undergoing a multicenter phase III trial for PD (NCT04232969).

4.3. GIP-GLP receptor Co-agonists

Another primary incretin hormone is GIP, which displays a similar physiological role to GLP-1 and is metabolized by DPP-IV. Activation of the GIP receptor, also a seven-transmembrane G protein-coupled receptor, enhances cAMP secretion (Holscher, 2020). In addition to its insulinotropic effects, GIP influences several targets with receptors in pancreatic β-cells, the cardiovascular system, bone, gastrointestinal tract, and brain (McIntosh et al., 2009). In different tissues and organs, GIP displays some opposing functions to GLP-1, including stimulating postprandial glucagon response and bone formation which are, in contrast, suppressed by GLP-1 (Seino et al., 2010). GIP has been identified in all major brain regions, including within the hippocampus, amygdala, and brainstem including dopaminergic neurons in the substantia nigra (Zhang and Holscher, 2020). The GIP receptor is expressed in neuronal and non-neuronal cells in the hypothalamus, a key feeding center of the brain (Adriaenssens et al., 2019). Little is known regarding the differences in signalling events downstream of GIP and GLP-1 receptors, although it is known that GIP receptor signalling involves an increase in cAMP concentration and activation of PKA similar to GLP-1 (Mathiesen et al., 2019). Of note GIP induces weight gain, whereas GLP-1 induces weight loss, as such, a dual GIP/GLP-1 agonist has a much more balanced influence on weight (Ji et al., 2016a). Currently, there is limited data evaluating incretin levels in the AD condition, and plasma GIP levels in PD.

Analogs of GIP display neuroprotective and anti-inflammatory properties, presenting a novel candidate for the treatment of neurodegenerative conditions including AD and PD. GIP displays efficacy in protecting against microglial degeneration and promoting microglial secretion of essential growth factors including brain-derived neurotrophic factor (BDNF), glial cell-line derived neurotrophic factor (GDNF), and nerve growth factor (NGF) (Spielman et al., 2017). In the APP/PS1 mouse model of AD, the GIP receptor agonist D-Ala2GIP reduced amyloid plaque load, chronic oxidative stress, and inflammation as measured via lowered astrocyte activation in the hippocampus and cortex (Duffy and Hölscher, 2013). Furthermore, this incretin mimetic successfully facilitated synaptic plasticity in aged mice in the CA1 region of the hippocampus, suggesting potential utility in the later stages of AD progression (Faivre and Hölscher, 2013). A novel long-lasting GIP receptor agonist, D-Ala2-GIP-glu-PAL improved motor function, restored tyrosine hydroxylase expression in dopaminergic neurons, reduced inflammation, and normalized cAMP/PKA/CREB signalling (Li et al., 2016). Therefore, targeting the incretin GIP represents a promising strategy alongside GLP-1 in the search for new treatments for AD and PD.

Novel dual GLP-1/GIP receptor agonists have been created for the treatment of diabetes and obesity with tirzepatide receiving recent FDA approval (Jastreboff et al., 2022). Owing to the promise of repurposing incretin mimetics for neurodegenerative disorders, research is underway investigating the additional benefit of co-agonism. A dual receptor agonist nicknamed 'twincretin' demonstrated a strong neuroprotective potential increasing cAMP levels to higher levels than single incretin receptor agonists in SH-SY5Y cells (Tamargo et al., 2017). DA3-CH, a dual GLP-1/GIP receptor agonist, displays promising neuroprotective effects in the APP/PS1 mouse model of AD. This dual agonist reduced amyloid plaque load and rescued memory impairments whilst also improving endoplasmic-reticulum stress and autophagy (Panagaki et al., 2018). Another novel dual agonist, DA4-JC, shows a dose-dependent effect on inflammation and amyloid plaque load in APP/PS1 mice. At equal doses, DA4-JC was superior to liraglutide in reversing memory impairments, enhancing hippocampal LTP as well as lowering amyloid plaque and pro-inflammatory cytokine levels (Maskery et al., 2020). Recently, the promising influence of this dual GIP/GLP-1 agonist was further demonstrated in APP/PS1 mice. Neuroprotective effects of DA4-JC included increasing synaptic and dendritic spine numbers, and restoring mitochondrial numbers, whilst alleviating pathological hallmarks of AD (Cai et al., 2021). Another dual GIP-GLP receptor agonist, DA5-CH, was recently developed to treat AD or PD. In APP/PS1 mice, DA5-CH is effective in improving memory impairments, reducing toxic protein aggregation including amyloid plaque load and levels of phosphorylated tau, as well as LTP. Treatment with DA5-CH restored PI3K/Akt/GSK3β signalling (Cao et al., 2018).

A dual agonist DA-JC1 displays efficacy in MPTP mouse models of PD, reversing motor impairments, normalizing the number of tyrosine hydroxylase positive neurons in the substantia nigra, attenuating the chronic inflammatory response, and increasing BDNF expression (Cao et al., 2016; Ji et al., 2016b). The effectiveness of DA-JC1 remained consistent in a 6-OHDA rat model of PD, with several neuroprotective effects including protecting against neuronal loss within the substantia nigra (Jalewa et al., 2017). DA3-CH reversed motor deficits, enhanced dopamine synthesis, reduced inflammation, and increased GDNF expression, a key growth factor supporting dopaminergic neurons, in MPTP mice. The effects of dual GIP/GLP-1 agonism were superior to that of liraglutide (Yuan et al., 2017). DA4-JC similarly displays neuroprotective effects in a rat PD model. As well as restoring motor functioning, DA4-JC treatment protected dopaminergic neurons, an effect associated with attenuated mitochondrial stress and inhibited apoptosis. This protective influence was dependent on Akt/JNK signalling (Li et al., 2020b). Recently, a novel dual agonist DA-CH5 showed greater brain penetration than other dual and single receptor agonists. Furthermore, DA-CH5 was more effective than both exenatide and liraglutide in MPTP mice, highlighting its potential as a treatment for PD (Zhang et al., 2020). However, there remains uncertainty about the ability of DA-CH5 to cross the BBB, with rigorous studies controlling for labelled drug trapping in capillaries and sequestration required (Girges et al., 2021). In a separate study, both dual agonists DA4-JC and DA5-CH treatment demonstrated higher efficacy than liraglutide or DA1-JC (Feng et al., 2018). The highly promising effects of DA5-CH were further supported in MPTP mice when compared to NLY01. DA5-CH shows more potent

effects on motor performance, whilst also showing greater efficacy in improving tyrosine hydroxylase expression. DA5-CH was also effective in reducing inflammatory markers and normalizing the levels of growth factors, while NLY01 showed no significant effects (Lv et al., 2021).

Additionally, preclinical investigations on GLP-1/GIP/glucagon triple agonists are currently underway. Triple agonists have been demonstrated to ameliorate cognitive deficits and pathological changes in the hippocampus in AD mouse models (Li et al., 2018; Tai et al., 2018). In 3xTg-AD mice, a triple agonist effectively improved memory formation and synaptic activity in pyramidal neurons in hippocampal slices (Li et al., 2020a). Neuroprotective effects of the triple agonist also included reduced neuronal excitability and maintaining Ca^{2+} balance (Li et al., 2020a). A novel triple agonist, HM15211, has demonstrated efficacy in the chronic MPTP PD mouse model (WONKI et al., 2019). HM15211 effectively protected dopaminergic neurons, reduced striatal α-synuclein, and improved motor function (WONKI et al., 2019). Whether triple agonists will offer a clear therapeutic benefit than dual agonists is unclear; however, the addition of glucagon agonism demonstrated superior effects against glutamate toxicity in SH-SY5Y cells (Li et al., 2020c).

In summary, preliminary findings suggest that dual or tri agonists may provide an added clinical benefit to targeting GLP-1 or GIP individually. Future studies should expand on these early findings and conduct clinical trials in patients with neurodegenerative disease.

4.4. DPP-IV

The enzyme DPP-IV degrades numerous peptides including both GIP and GLP-1, which represents an alternative therapeutic target for AD/PD. DPP-IV inactivates endogenous GLP-1 rapidly, leading to a short half-life of GLP-1 in circulation of under 2 min (Angelopoulou and Piperi, 2018). Inhibition of DPP-IV can increase insulin stimulation owing to an extended half-life of incretins and has been shown to benefit cognitive functioning in diabetic patients with or without AD (Wu et al., 2020). A Swedish nationwide case-control study also identified that previous DPP-IV usage lowers the incidence rate of PD development (Svenningsson et al., 2016).

In vitro evidence identified that linagliptin, a DPP-IV inhibitor, reduces Aβ-mediated cytotoxicity and mitochondrial dysfunction, restoring impaired insulin signalling in cultured SK-N-MC human neuronal cells (Kornelius et al., 2015). Restoration of insulin signalling prevented GSK3β activation and tau hyperphosphorylation. In vivo, linagliptin improved cognitive function in a 3xTg-AD mouse model and demonstrated neuroprotective properties, with mice showing enhanced brain incretin levels and attenuated levels of amyloid-beta, tau phosphorylation as well as neuroinflammation (Kosaraju et al., 2017). As linagliptin does not cross the BBB, it has been suggested that the neuroprotective effect is generated, at least to some extent, through an increase in incretin bioavailability (Angelopoulou and Piperi, 2018). In a rodent rotenone model of PD, rats treated with a DPP-IV inhibitor exhibited normalized motor function and suppression of cerebral inflammation and apoptosis (Abdelsalam and Safar, 2015). Furthermore, simultaneous inhibition of DPP-IV and P2X7 purinoceptors was also identified to provide mid-brain and striatal neuronal protection in a 6-hydroxydopamine rodent model of PD (Jamali-Raeufy et al., 2020).

DPP-IV inhibitors have demonstrated efficacy in protecting cognitive function in elderly patients with mild cognitive impairment (Rizzo et al., 2014) and AD (Isik et al., 2017). Rizzo et al., evaluated the use of DPP-IV inhibitors and metformin or metformin with sulfonylureas over two years in 240 older patients DM affected by mild cognitive impairment (MCI). Patients treated with a DPP-IV inhibitor demonstrated improved cognitive functioning, particularly in attentional and executive function domains (Rizzo et al., 2014). A separate retrospective longitudinal study explored the influence of the DPP-4 inhibitor, sitagliptin, in 52 elderly DM patients diagnosed with AD (Isik et al., 2017). Sitagliptin treatment for 6-months improved MMSE scores in comparison to those receiving metformin in patients with AD (Isik et al., 2017). Future studies should evaluate the benefit of DPP-IV inhibitors in non-diabetic AD patients.

These findings collectively indicate that DPP-IV inhibition shows promise in preclinical models for treating neurodegenerative disorders. Whether utilizing novel DPP-IV resistant treatments as a stand-alone therapeutic strategy or co-administering DPP-IV inhibitors with existing treatments requires further evaluation.

4.5. Intranasal insulin

Commonly used in treating T2DM, insulin functions as a non-invasive, rapid method of regulating blood glucose levels. Direct delivery of drugs to the brain is an ideal concept for CNS-related diseases such as AD and PD, with intranasal delivery offering a solution to bypassing the blood-brain barrier via paracellular transport for better brain-targeted drug delivery (Tashima, 2020). Intranasal delivery of short-acting (regular) insulin shows favourable pharmacokinetics, achieving therapeutically relevant concentrations in the brain without causing hypoglycaemia (Nedelcovych et al., 2018; Roque et al., 2021). Preclinical data suggest that intranasal delivery of recombinant human insulin can reach deep brain structures including the hippocampus and nigrostriatal pathways (Fan et al., 2019).

Initial small-scale studies highlighted the potential benefits of intranasal insulin in treating MCI and AD. Pilot research indicated that short-acting (regular) insulin facilitates recall of verbal memory in ApoE ε4 non-carriers (Reger et al., 2006). ApoE ε4 is the major known genetic risk factor in sporadic AD development. Intriguingly, the administration of intranasal short-acting (regular) insulin was detrimental to memory performance in ApoE ε4 carriers (Reger et al., 2006). A follow-up study with 33 MCI/AD patients and controls reiterated the benefits of intranasal short-acting (regular) insulin in memory-impaired non-ApoE ε4 carriers, but conversely, depicted a decline in verbal memory in ApoE ε4 carriers (Reger et al., 2008a). Cognitive improvements beyond verbal memory in orientation, social interaction, home activities, and general attentional/functional status have also been observed in participants with mild AD or MCI when compared with placebo (Reger et al., 2008b).

This initial pilot research has led to larger randomized controlled trials (RCT). Craft and colleagues conducted an RCT in 104 subjects in which intranasal short-acting (regular) insulin (20 or 40 IU) was administered to amnestic MCI and AD (mild or moderate) subjects over four months (Craft et al., 2012). Both doses preserved caregiver-rated functional ability and stabilized general cognition; however, memory improvements were made in the 20 IU group which were sustained 2 months after cessation. Hypometabolism progression was minimized by intranasal short-acting (regular) insulin, as assessed by [18 F]FDG. This indicates that intranasal short-acting (regular) insulin had halted the degeneration of brain activity and glucose utilization. Post-hoc research analyzed plasma samples to investigate whether intranasal short-acting (regular) insulin engaged the insulin signalling cascade and therefore whether changes to insulin resistance had occurred (Mustapic et al., 2019). In neuronal-enriched extracellular vesicles, pS312-IRS-1 and pY-IRS-1 were correlated with changes in ADAS-Cog scores in ApoE ε4 non-carriers, in line with modulatory effects on cognitive outcomes in the original trial. Thus, engagement of the insulin cascade by intranasal insulin is probably strongest in ApoE ε4 non-carriers. A systematic review of seven RCTs for AD/MCI showed that, while verbal memory improved, the effect was restricted to ApoE ε4 non-carriers (Avgerinos et al., 2018). No clear effect on other cognitive domains such as everyday functioning, visuospatial or attentional ability, executive function, or response inhibition was established.

A follow-up pilot clinical trial compared intranasal short-acting (regular) insulin, placebo, and intranasal administration of a long-acting insulin analog detemir (Craft et al., 2017). Reaffirming prior research, intranasal short-acting (regular) insulin improved memory after 2 and 4 months of treatment, which was associated with preserved brain volume and a reduction in CSF tau P181 and Aβ levels. No effects

on cognition were observed in the detemir-treated group, nor were there improvements in daily functioning or CSF ratio of tau p181 in any group. The detemir-treated group showed decreased volume in the right cuneus and hippocampus, whilst left anterior and middle cingulum volumes were preserved relative to placebo-treated participants. Therefore, intranasal short-acting (regular) insulin appeared to have both pathophysiological and cognitive benefits in AD, whilst outperforming its long-acting analog. Intriguingly, in contrast to acute treatment, Claxton et al. demonstrate that the benefits of insulin detemir are limited to ApoE ε4 carriers, with participants in the 40 IU treatment group showing improved memory composite scores compared to placebo (Claxton et al., 2015). Greater insulin resistance at baseline predicted an improved response to treatment within this group. In contrast, ApoE ε4-non carriers showed worsening scores on the composite memory measure compared to placebo-treated participants.

In a recent randomized, 12-month clinical trial of intranasal short-acting (regular) insulin in 289 MCI or AD patients, no significant cognitive or functional benefits were observed (Craft et al., 2020). Such results must be carefully interpreted, as problems with the delivery device resulted in a change of device midway through the trial, to a device that had not been tested in AD populations. The authors suggest that further evaluation of delivery devices is required, including an assessment of the utility of devices to deliver the compound to the CNS to evaluate the efficacy of intranasal insulin in AD.

The potential use of intranasal insulin is not restricted to AD but has potential in other neurodegenerative diseases such as Parkinson's and multiple system atrophy (MSA). A proof-of-concept RCT evaluated the effect of 40 IU intranasal short-acting (regular) insulin, administered daily over four weeks on cognitive and functional performance in Parkinson's disease and one case of MSA (Novak et al., 2019). Verbal fluency score increased in the intranasal short-acting (regular) insulin-treated group but decreased in participants treated with placebo; paired comparisons between baseline and post-treatment between groups were not significant. Thus, the results from Novak et al. were inconclusive due to the variance in the small number of cases studied. Intranasal short-acting (regular) insulin treatment improved motor performance and function with a lower disability score (HY scale) compared to placebo and improvements in the UPDRS-motor score compared to baseline. For the one MSA case, the patient remained stable over the four weeks with post-treatment scores suggesting an upwards trend toward improvement. Besides motor and cognitive improvements, there were no significant implications regarding patient safety with the absence of serious adverse events, hypoglycemic episodes, and a change in serum glucose.

In summary, intranasal insulin requires further testing with reliable delivery devices in an attempt to treat cognitive and motor deficits in neurodegenerative disorders, with treatment effects modulated by ApoE genotype. ApoE4 has been shown to inhibit neuronal insulin signalling as it binds to the insulin receptor, trapping the receptor in endosomes (Zhao et al., 2017). In comparison with ApoE3, ApoE4 may block insulin binding to its cognate receptor more effectively (Zhao et al., 2017). Zhao et al., therefore, provide a mechanistic basis underlying the discrepancies between ApoE genotypes. Perhaps as ApoE4 impairs insulin signalling, acute intranasal treatment is insufficient to provide functional benefits in ApoE ε4 carriers. Conversely, chronic treatment with insulin detemir may induce cerebral insulin resistance in ApoE ε4-non carriers (Zhao et al., 2017). In future investigations, the effect of intranasal insulin on cognition must be ascertained when controlling for ApoE ε4 status.

4.6. Metformin hydrochloride

Metformin hydrochloride is an approved prescription drug used to treat T2DM, which can effectively control blood sugar and insulin sensitivity (Rena et al., 2017). Most commonly metformin treatment has been evidenced to reduce AD risk (Gupta et al., 2011; Kickstein et al., 2010), but the literature is conflicting with a recent meta-analysis indicating that metformin use failed to reduce the risk of AD development and increased PD risk (Ping et al., 2020). Further, some literature indicates that metformin treatment enhances the risk of cognitive impairment (Imfeld et al., 2012; Moore et al., 2013). It has been suggested that metformin exacerbates vitamin B12 deficiency, which may underlie the conflicting results (Campbell et al., 2017). In a national case-control study, there was no evidence that long-term metformin treatment increased the risk of AD development, in fact, older users with diabetes treatment significantly reduced the incidence of AD (Sluggett et al., 2020). In 5528 patients with T2DM, long-term metformin use (> 2 years) significantly reduced the risk of developing neurodegenerative disorders including dementia, AD, PD, Huntington's disease, and MCI with a median follow-up period of 5.2 years (Shi et al., 2019). Thus, whilst short-term use has no reliable effect, long-term treatment is effective in reducing the risk of cognitive decline in T2DM cases. Discrepancies in results may stem from methodological issues with several studies failing to account for diabetes duration, severity, or how well diabetes is controlled.

Preclinical evidence suggests that metformin can improve cognitive function through a reduction of phosphorylated tau in a SAMP8 AD mouse model (Farr et al., 2019). Metformin improved learning and memory in APP/PS1 via enhanced neurogenesis and reduced inflammation (Ou et al., 2018; Saffari et al., 2020). A recent investigation expanded on previous trials which reported that metformin in APP/PS1 transgenic mice could ameliorate learning and memory deficits. The key mechanism behind the neuroprotective effect of metformin may be through enhanced IDE, which was demonstrated to reduce the brain Aβ burden (Lu et al., 2020). In PD, metformin is indicated to prevent L-dopa-induced dyskinesia via normalizing GSK3β activity, whilst preserving the therapeutic benefits of L-dopa (Ryu et al., 2018). Metformin has also been shown to protect dopaminergic neurons by reducing endoplasmic reticulum stress and inflammation in a rotenone PD model (Wang et al., 2020a). Additional neuroprotective properties of metformin were indicated in a 6-hydroxydopamine-induced C. elegans model, in which, dopaminergic neuronal loss and α-synuclein aggregation was attenuated (Saewanee et al., 2021). Long-term metformin treatment was beneficial in restoring motor function in MTTP mice (Patil et al., 2014).

Minimal research has been conducted in AD populations to assess the efficacy of using metformin to reduce pathophysiological or cognitive changes. A 12-month pilot trial in 80 overweight, amnestic MCI patients without T2DM revealed marginally significant improvements in recall of the Selective Reminding Test of verbal memory (Luchsinger et al., 2016). There was no change in other cognitive or biomarker outcomes. Tolerance of metformin dose varied, with only 10% tolerating the maximum dose, although no adverse events were reported.

Furthermore, a small-scale, phase 2, placebo-controlled, cross-over design exposed 20 non-T2DM, MCI, or mild AD participants to metformin or placebo for 8 weeks (Koenig et al., 2017). AD CSF biomarkers were not altered as a result of metformin, although metformin was shown to cross the BBB. Post-hoc analysis of cerebral blood flow, measured using arterial spin labelling, identified an increase in superior and middle orbitofrontal regions. Decreases in regional metabolism in such areas have been encountered in AD individuals, accounting for information-encoding deficits (Dai et al., 2009). Cognitive improvements were seen in executive functioning measured by trail tests; statistical trends suggest improvement in learning, memory, and attention through the use of PAL and DMS percent correct simultaneous tasks. Nonetheless, further research is warranted to assess the true effect of metformin, as there was no wash-out period in the design, nor has the research assessed metformin on a more severe presentation of AD.

Clinical studies into the use of metformin in PD are scarce, with existing research comparing or combining metformin with oral hyperglycaemic agents. Clinical data is weak as there is a lack of evidence that metformin reduces PD risk in T2DM populations and any evidence that it has a therapeutic effect in such cases (Rotermund et al., 2018).

4.7. PPAR-gamma agonists (PPAR-γ)

Peroxisome proliferator-activated nuclear receptor γ (PPARγ) is a ligand-activated transcription factor regulating lipid metabolism and inflammation (Landreth, 2007). Agonists such as thiazolidinediones (TZDs) have been approved for use in T2DM since 1997, functioning by regulating blood sugar and triglyceride levels, whilst boosting insulin sensitivity. An increased expression of PPARγ in AD brains has been observed and it is suggested that activators may inhibit inflammatory events and be beneficial in the treatment of AD (Kitamura et al., 1999).

In animal models of AD, pioglitazone has been shown to reduce Aβ plaque burden, $A\beta_{42}$ levels in the brain, and numbers of activated microglia and inflammatory markers, although to what extent is contested (Heneka et al., 2005; Yan et al., 2003). In a small-scale 6-month open controlled trial of 42 mild AD patients with DM, patients were randomly assigned to receive 15–30 mg pioglitazone daily (n = 21) or not (n = 21). Pioglitazone use enhanced insulin sensitivity, through a decrease in fasting plasma insulin levels. Pioglitazone-treated participants also demonstrated improved cognition on several neuropsychological evaluations including MMSE and increased regional cerebral blood flow in the parietal lobe (Sato et al., 2011). When analyzing the association of pioglitazone and incidence of dementia, determined by at least two outpatient visits or one inpatient care visit for dementia, in a study of 145,928 participants free of dementia and T2DM, long-term use appears promising in lowering dementia incidence in T2DM (Chou et al., 2017). A large clinical trial was therefore needed to assess its effectiveness in non-DM AD patients or those at risk. The 'TOMMORROW' phase 3 trial aimed to close the gap in the literature, by investigating pioglitazone as a way to delay the onset of MCI due to AD biomarker risk (Burns et al., 2019). 3500 participants were enrolled worldwide, but unfortunately, an inadequate treatment effect was observed during an interim futility analysis, and subsequently, the trial was deemed unsuccessful.

Pilot trials showed the promise of rosiglitazone treatment for AD and MCI, which provided improvements in delayed recall, attention (Watson et al., 2005), and ADAS-Cog change from baseline in ApoE ε4 non-carrier AD patients (Risner et al., 2006). The cognitive benefits observed were dose-dependent, only in mild to moderate populations, and may be reliant on ApoE ε4 status. The utility of rosiglitazone is further limited by safety concerns, as it is not approved for use in DM, nor has significant improvement been observed in AD populations in a large phase clinical trial (Harrington et al., 2011).

Dual PPAR agonists may demonstrate an advantage over single agonists, as PPAR δ is predominant in the brain followed by PPAR γ. Although the neuroprotective effects of PPAR δ/γ are similar, they both target separate downstream insulin-responsive targets (Reich et al., 2018). A proof of mechanism study highlighted the potential benefits of a two-week course of T3D-959 in mild to moderate AD. Cognitive improvements were seen in both ApoE ε4 carriers and non-carriers, although ApoE ε4 positive participants required a higher dose. Furthermore, [18 F]FDG signal increased (Chamberlain et al., 2020). As a result of promising findings, PIONEER, a phase 2, 24-week, randomized, placebo-controlled, parallel-group trial started enrolment of 252 patients with mild to moderate AD in 2020.

4.8. Amylin analogs

Islet amyloid polypeptide, or amylin, is a hormone co-secreted with insulin to maintain and regulate glucose homeostasis. It functions by inhibiting glucagon secretion and slowing gastric emptying (Gedulin et al., 2006). Amylin analogs, such as pramlintide (PRAM), are clinically available in the US and have been investigated in a series of randomized controlled trials for the treatment of type 1 (Ratner et al., 2004; Whitehouse et al., 2002) and type 2 diabetes (Hollander et al., 2003; Ratner et al., 2002; Riddle et al., 2007). Synthetic amylin analogs aim to replace lost native amylin signalling, without instigating amylin accumulation. PRAM effectively does so, owing to an absence of three amino acids in human amylin (Grizzanti et al., 2018).

Conflicting evidence exists regarding the changes to the amylin system as a result of AD. When compared with normal controls, amylin oligomers, and plaques were observed in the brain amongst amyloid- β plaques and mixed plaques (amylin and amyloid-β) (Jackson et al., 2013). There is a propensity for amylin receptors to be upregulated in regions with elevated amyloid burden, with blockage of amylin receptors effective in reducing amyloid-β toxicity (Jhamandas et al., 2011). Alternative research indicates that it is loss of amylin signalling, rather than misfolding and aggregation, which contributes to T2DM and AD cognitive dysfunction (Ly and Despa, 2015). For example, lower mean plasma amylin levels in AD and MCI compared with non-cognitively impaired subjects have been observed, even when adjusting for amyloid or diabetes status (Adler et al., 2014).

Mouse models suggest that amylin analogs, such as pramlintide, can ameliorate pathophysiological and cognitive symptoms of AD. For example, in the SAMP8 mouse model of sporadic AD, pramlintide administration improved recognition learning and memory in object recognition tasks, whilst synapse loss and oxidative stress/inflammation were eased (Adler et al., 2014). Similarly, in 5XFAD mice (APP/PS1 double transgenic mice with five familial AD mutations), both intraperitoneal amylin and pramlintide improved memory and learning in the Y maze and Morris water maze tests (Zhu et al., 2015). Behavioural findings were coupled with a marked reduction in dense-core plaque burden, Aβ plaque size, and soluble $A\beta_{1-42}$. Conversely, in TgSwDI mouse brains, pramlintide was shown to increase Aβ levels, associated with apoptosis, synapse loss, and inflammatory response (Mousa et al., 2020). Therefore, whether pramlintide increases risk or mediates AD-associated pathology is controversial.

In clinical populations, pramlintide has been proven safe in non-diabetic, AD populations (Zhu et al., 2017). In an attempt to assess the role of pramlintide as an AD diagnostic test, amylin and pramlintide were shown to potentially regulate lipid metabolism (Tao et al., 2018), and therefore further research to ascertain its therapeutic potential in neurodegeneration is required. At present, the role of pramlintide has only been assessed for diagnostic purposes, and not for treatment.

4.9. PTP1B inhibitors

Protein tyrosine phosphatases (PTPs) are enzymes that control cellular protein tyrosine phosphorylation underlying vital cellular processes in a coordinated and reversible manner (He et al., 2014). Specifically, PTP1B has a direct role in insulin and leptin signal transduction by dephosphorylating insulin receptors, its substrates, JAK2, and subsequently STAT3 (Vieira et al., 2018). Leptin is a hormone and growth factor involved in the regularization of energy utilization, which can interact with the insulin receptor and resensitize insulin signalling activating IRS, PI3K, and Akt (Holscher, 2019). Consequently, PTP1B inhibitors have been effectively utilized in reducing heightened PTP1B activity in clinical trials involving participants with T2DM (Eleftheriou et al., 2019; Hussain et al., 2019; Nguyen et al., 2013).

Neuronal insulin and leptin signalling dysfunction have been associated with increased PTP1B activity (Vieira et al., 2017). PTP1B inhibition could also be beneficial in AD treatment as a means of sensitizing defective neuronal insulin and leptin signalling pathways (Bomfim et al., 2012; Bonda et al., 2014). Moreover, PTP1B plays a vital role in modulating additional signalling pathways, such as those involved in learning and memory, endoplasmic reticulum stress, microglia-mediated neuroinflammation, and synapse regulation (Vieira et al., 2017). For example, leptin signalling in the hippocampus is imperative in cognition and memory (Gomes et al., 2014). It modifies Aβ levels and reduces tau phosphorylation in neuronal cells, therefore preventing or minimizing synaptic disruption and neuronal death induced by such AD pathology (Doherty et al., 2013; Fewlass et al., 2004; Greco et al., 2009).

Recent research in AD mouse models indicates that using trodusquemine, a PTP1B inhibitor, could prevent both physiological and cognitive symptoms of familial AD. Ricke and colleagues (Ricke et al., 2020) noted that trodusquemine use in hAPP-J20 mice resulted in the prevention of hippocampal neuronal loss, attenuated inflammation in the hippocampus, and cognitive decline (measured by spatial memory in the Morris Water Maze). Moreover, the insulin response was rescued through restoring pIRS1 levels and similarly, basal phosphorylation of cerebral GSK3β was restored. However, owing to a paucity of research into the role of PTP1B in neurodegeneration, it is unknown whether PTP1B inhibition delays, prevents, or temporarily ameliorates AD symptoms (Vieira et al., 2017).

Inhibitors designed to bind to the active site of PTP1B often exhibit off-target binding effects to other PTPs and therefore, it would be difficult to inhibit PTP1B alone if assessed in human populations (Tamrakar et al., 2014). Subsequently, further investigation is needed.

4.10. Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are an approved class of medications for T2DM that lower blood sugar by inhibiting glucose reabsorption via the SGLT2 in the kidney (Lin et al., 2021). SGLT2 inhibitors reduce reactive oxygen species production, protect mitochondrial integrity and reduce inflammation, thus, this class of medication represents a promising strategy for neurodegenerative disease, with authors highlighting their possible utility for disease modification of AD (Esterline et al., 2020) and PD (Lin et al., 2021).

In the ovariectomized/D-galactose rat model of AD, dapagliflozin restored spatial memory, reduced pathological features of AD, and regulated autophagy (Ibrahim et al., 2022). Moreover, Hierro-Bujalance et al., investigated the effect of 22-week empagliflozin treatment in a mixed AD-T2DM mouse model (APP/PS1xdb/db mice) (Hierro-Bujalance et al., 2020). The authors demonstrated that SGLT2 inhibitor treatment could reduce brain atrophy and amyloid pathology whilst improving memory and learning (Hierro-Bujalance et al., 2020). Whilst preclinical data on the effect of SGLT2 inhibitors in PD models are scarce, empagliflozin improved motor function, reduced neuroinflammation, augmented autophagy, protected dopaminergic neurons, and enhanced neuroplasticity in the rotenone-induced mouse model of PD (Motawi et al., 2022; Mousa et al., 2023).

In a population-based cohort, patients prescribed SGLT2 inhibitors showed an 11% reduced risk of dementia incidence compared to non-users (Siao et al., 2022). Furthermore, among 106,903 participants with DM, those dispensed an SGLT2 inhibitor demonstrated a 20% lower association with dementia risk than DPP-IV inhibitors (Wu et al., 2022). Out of the SGLT2 inhibitors examined, dapagliflozin users exhibited the lowest dementia risk (adjusted hazard ratio = 0.67), followed by empagliflozin (adjusted hazard ratio = 0.78), whilst canagliflozin users showed no significant risk reduction (adjusted hazard ratio = 0.96) (Wu et al., 2022). In 21 non-diabetics aged 55 or older, 14 days of empagliflozin treatment enhanced brain insulin signalling pathways (IRS-1/Akt) and reduced glutamate concentrations (Avgerinos et al., 2022). Thus, SGLT2 inhibitors are a promising candidate to alleviate brain insulin signalling deficits and glutamate excitotoxicity observed in AD. Clinical investigation is underway evaluating the efficacy of combining intranasal regular insulin and empagliflozin in patients with amnestic MCI or early AD (NCT05081219).

5. Future therapeutic opportunities in neurodegenerative diseases

Antidiabetic agents are promising candidates for repurposing in the treatment of AD and PD. Numerous promising candidates are entering late-stage clinical evaluation, which target pathways such as GLP-1, GIP, and insulin signalling and may produce neuroprotective effects. By enhancing autophagy, increasing neuronal survival, reducing apoptosis and oxidative stress, as well as alleviating neuroinflammation and insulin resistance, anti-diabetic agents offer general neuroprotective effects against shared features of AD/PD progression. The different pathological hallmarks of AD (amyloid plaques, tau tangles) and PD (dopaminergic neuronal loss, α-synuclein), may be targeted via similar signalling cascades, such as engagement of PI3K/Akt and GSK3β. Antidiabetic agents may also offer disease-specific benefits, for example through the influence of proteases (e.g. IDE degradation of amyloid plaques for AD) and their efficacy could depend on the ability of the agent to access the regions typically affected by AD (hippocampus) and PD (striatum, substantia nigra).

Additionally, targeting GLP-1 signalling displays efficacy in preclinical trials in targeting several critical aspects which underlie AD and PD development. GLP-1 receptor agonists are demonstrated to reduce inflammation and oxidative stress, prevent the accumulation of the characteristic toxic proteins as well as influence impaired insulin signalling. Consequently, positive results of antidiabetic agents such as GLP-1 receptor agonists which exert their effect on multiple aspects of neurodegeneration in AD and PD are encouraging and would need confirmatory Phase 3 trials to fully evaluate their clinical efficacy. GLP-1/GIP dual agonists have great potential and warrant evaluation in human trials. Other agents available for the treatment of diabetes including metformin, PPARγ agonists, amylin analogs, and PTP1B inhibitors have shown promise in the initial stages of evaluation for AD and/or PD and future trials should aim to establish their efficacy. Together, antidiabetic agents show impressive potential in the treatment of AD/PD and may have disease-modifying effects, not only in pathophysiology but also in cognitive and behavioural symptoms.

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Consent to participate

Not applicable.

Consent for publication

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Code availability

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Paul Edison was responsible for the concept and design of the manuscript. Joseph Nowell, Eleanor Blunt, Dhruv Gupta and Paul Edison drafted the manuscript and reviewed the manuscript. Joseph Nowell and Eleanor Blunt contributed equally to the manuscript preparation.

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Data Availability

Not applicable.

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