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Antidiabetic Drugs A New Setback To Cure Neurodegenerative Disorders

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Abstract :

During recent years, diabetes, especially type 2 diabetes mellitus (T2DM), has been recognized as an important risk factor for progressive changes in the brain, characterized by biochemical, cellular and structural alterations, loss of brain function, and ultimately an increased likelihood of dementia. Notably, clinical studies have shown that patients with T2DM were predisposed to neurodegenerative diseases like AD and PD . This predisposition is associated with common patholog-ical features, such as oxidative stress, hyperglycemia and mitochondrial dysfunction.

Keyword's :

Alzheimer's disease, Parkinson's disease, diabetes mellitus, antidiabetic drug's, insulin, oxidation stress, neurodegenerative disorder, antidiabetic drug's.

Introduction :

Neurodegenerative diseases, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD), cause significant impairment by affecting neurons in the central nervous system (CNS). These conditions lead to progressive nerve cell degeneration and death, resulting in movement disorders like ataxia and cognitive impairments such as dementia. AD alone accounts for 60-70% of dementia cases worldwide.A growing body of research highlights a link between neurodegenerative and metabolic disorders. Insulin signaling abnormalities, common in older adults with pre-diabetes or type 2 diabetes mellitus (T2DM), are also observed in AD and PD. Although the exact mechanisms connecting these disorders remain unclear, shared pathological features such as inflammation, insulin resistance, and oxidative stress suggest a common link. This overlap has spurred interest in repurposing antidiabetic drugs for treating neurodegenerative diseases.Antidiabetic medications,

particularly those targeting insulin resistance and inflammation, offer potential as disease-modifying treatments for AD and PD. Despite the challenges in developing effective therapies for these neurodegenerative conditions, exploring the use of antidiabetic drugs presents a promising avenue for future research and therapeutic strategies. This review focuses on the potential of repurposing antidiabetic treatments to manage and possibly alter the course of AD and PD.

Insulin's Role in Brain Functioning:

Traditionally, insulin is known for regulating glucose homeostasis in peripheral tissues, facilitating glucose uptake in muscle and fat tissues, and inhibiting glucose production in the liver. It is also a key factor in cell growth and repair. The discovery that insulin crosses the blood-brain barrier (BBB) and interacts with central nervous system (CNS) insulin receptors revealed its significant role in brain functions.There are two isoforms of the insulin receptor in the brain: insulin receptor-A and insulin receptor-B. Initially, neurons were believed to express only the insulin receptor-A isoform, but recent evidence shows that mature neurons also have the insulin receptor-B isoform. When insulin binds to these receptors, it activates tyrosine kinases through autophosphorylation, initiating major signaling pathways like the phosphatidylinositol 3-kinase/AKT pathway and the Raf/MEK/mitogen-activated protein kinase (MAPK) pathway. These pathways are crucial for cell metabolism, neuronal growth, synaptic plasticity, and neuroprotection. Notably, AKT phosphorylation is linked to Alzheimer's disease (AD) pathogenesis and cognitive dysfunction.Cerebrospinal fluid (CSF) insulin levels are significantly lower than plasma insulin levels but are closely related. Brain insulin is primarily derived from the blood, but can also originate from local synthesis within the brain. Peripheral insulin resistance and aging can reduce the CSF-to-plasma insulin ratio, possibly due to impaired insulin transport across the BBB. Local insulin synthesis in the brain is supported by the presence of mRNA for insulin coding genes in rodents, the identification of C-peptide in neuronal cells, and insulin production by choroid plexus epithelial cells. The latter is regulated by serotonin, which activates the 5HT2C receptor and induces insulin secretion through intracellular calcium mobilization.

Insulin's roles in the brain are varied and significant, largely due to the widespread expression of insulin receptors in cortical and subcortical structures. High concentrations of these receptors in the hippocampus and cerebral cortex suggest insulin signaling is crucial for memory processing. Insulin can influence cognitive function by modulating excitatory and inhibitory receptor activities, which trigger signal transduction cascades essential for long-term memory consolidation and learning.Further research is needed to fully understand the presence, localization, and function of insulin synthesis in the CNS. The evidence suggests that insulin produced within the brain may play important roles in local neural circuits and overall brain function.

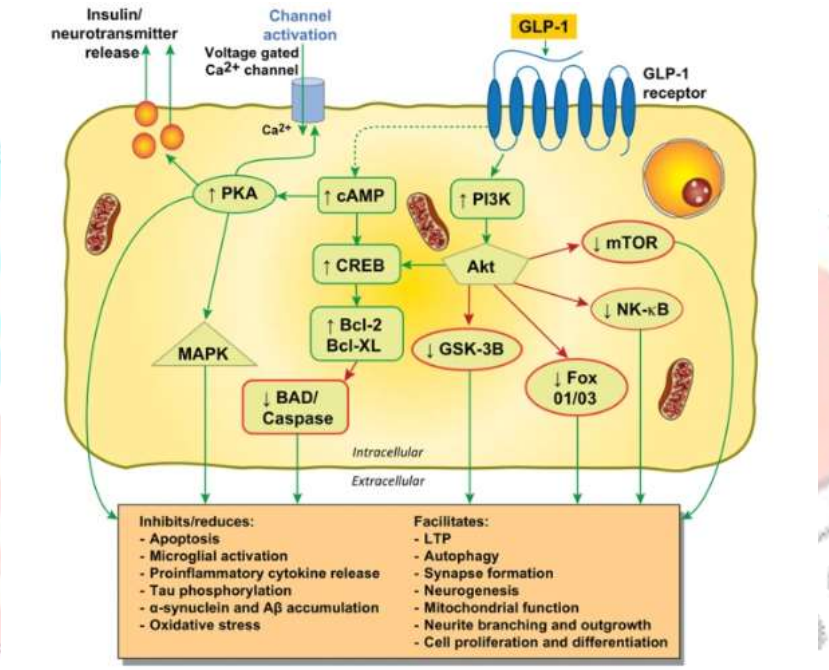
Insulin's Role in Alzheimer's Disease (AD) and Parkinson's Disease (PD) :

Insulin resistance refers to a diminished response to insulin. This dysfunction in brain insulin signaling is increasingly seen as a key factor in neurodegenerative diseases, particularly Alzheimer's Disease (AD). Although insulin resistance in the brain and the periphery are both linked to cognitive decline, they can occur independently, highlighting that central nervous system (CNS) insulin resistance is not just an extension of peripheral insulin resistance. In AD, brain insulin resistance is evidenced by elevated serine phosphorylation of insulin receptor substrate 1 (IRS-1) in the hippocampus and cerebral cortex. This abnormal phosphorylation is associated with hyperphosphorylated tau and amyloid-β, key markers of AD. Studies of neuronal-derived exosomes support the idea that brain insulin resistance correlates with neurodegeneration. Inflammatory responses, driven by pro-inflammatory cytokines, can exacerbate this resistance by promoting serine phosphorylation of IRS-1 and reducing its tyrosine phosphorylation. Insulin resistance may contribute to AD pathology, including the buildup of extracellular amyloid-β (Aβ) plaques and intracellular tau tangles. Insulin-

degrading enzyme (IDE), crucial for regulating Aβ levels, is less effective in the presence of central insulin resistance, leading to Aβ accumulation. Other proteases, like neprilysin, endothelin-converting enzymes, and cathepsin D, also play roles in Aβ degradation. Increased IDE expression in insulin-cultured astrocytes has been shown to facilitate Aβ plaque degradation via extracellular signal-regulated kinase (ERK) signaling. Genetic variations in IDE are linked to late-onset AD, indicating that insulin resistance may hinder Aβ clearance and promote neurodegeneration.

In addition to Aβ, insulin resistance impacts tau pathology. Impaired insulin signaling reduces Akt phosphorylation, which in turn increases glycogen synthase kinase 3 beta (GSK3β) activity, leading to tau hyperphosphorylation. This relationship between insulin resistance, glucose hypometabolism, and neurodegenerative disease was examined in the Wisconsin Registry for Alzheimer's Prevention (WRAP) study. Researchers found that higher insulin resistance was associated with decreased glucose metabolism in

Fig 1 : action of GLP-1



AD-vulnerable brain regions, such as the left medial temporal lobe (MTL), predicting worse memory performance.A study involving 150 cognitively normal, late middle-aged adults assessed the connection between peripheral insulin resistance and cerebral glucose uptake. Participants underwent neuropsychological testing, insulin resistance assessment (HOMA-IR), and [18F]-fluorodeoxyglucose positron emission tomography ([18 F]FDG). The findings revealed that increased insulin resistance correlated with reduced glucose metabolism in several AD-affected brain regions, potentially predicting memory decline.Another study focused on the impact of insulin resistance on hippocampal volume in women at risk for AD. Fifty postmenopausal women (ages 50-65) underwent MRI scans, cognitive testing, and HOMA-IR assessment. The results indicated that higher insulin resistance was associated with changes in brain structure and function, further linking insulin resistance to neurodegenerative processes.

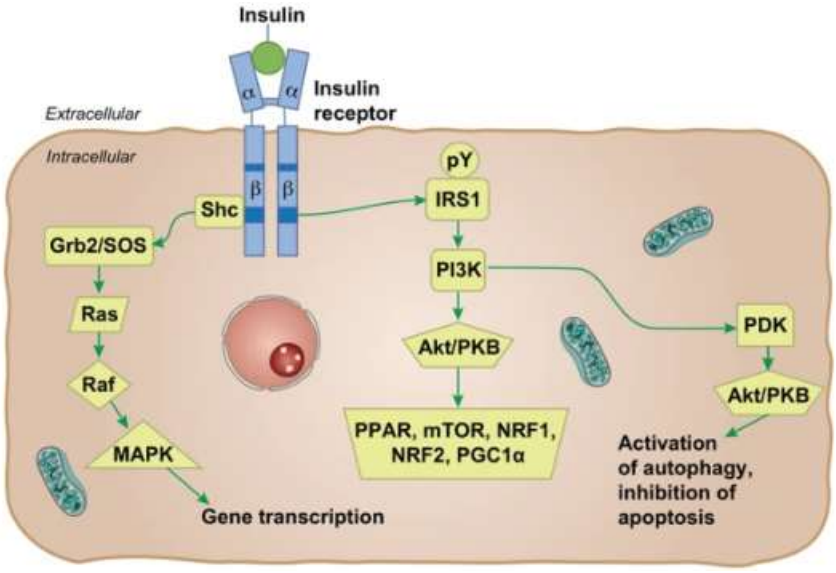


Fig 2 : role of insulin in neurons

Antidiabetic Drugs for Neurodegenerative Diseases:

Potential Therapeutic Strategies for AD and PD

Alzheimer's Disease (AD) and Parkinson's Disease (PD) are complex neurodegenerative disorders characterized by the accumulation of toxic proteins, chronic inflammation, synaptic dysfunction, neuronal loss, astrocyte activation, and potentially insulin resistance. These conditions share pathophysiological similarities with diabetes mellitus (DM), particularly involving insulin dysregulation and metabolic disturbances. This convergence has spurred interest in exploring the therapeutic potential of antidiabetic agents for managing AD and PD, aiming to slow disease progression and improve patient outcomes.

- **GLolP-1 analogues in AD**

Incretins, a group of peptide hormones including glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), have paved the way for GLP-1 receptor agonists, developed primarily for managing diabetes. GLP-1 specifically triggers insulin release in response to elevated blood sugar levels, ensuring it doesn't cause low blood sugar (hypoglycemia) (Meier, 2012). However, native GLP-1 has a brief lifespan due to degradation by dipeptidyl-peptidase IV (DPP IV), prompting modifications in synthetic versions to extend their effectiveness (Muller et al., 2019).GLP-1 receptors are found in various brain regions, including the brainstem, hypothalamus, and limbic areas, suggesting potential roles beyond glucose regulation (Daniels and Mietlicki-Baase, 2019). Synthetic GLP-1 receptor agonists like exenatide, liraglutide, lixisenatide, and albiglutide have been engineered to resist degradation, thus prolonging their action periods (Aroda, 2018; Nauck, 2016). For instance, liraglutide, a once-daily injection, boasts a half-life exceeding 13 hours and shares significant similarity to native GLP-1 (Aroda, 2018; Nauck, 2016). On the other hand, albiglutide offers weekly dosing due to its extended half-life of 5 days, achieved through genetic fusion technology (Aroda, 2018; Nauck, 2016).

The latest addition, semaglutide, is notable for being the first GLP-1 receptor agonist available in both injectable and oral forms, providing flexibility in treatment options (Nauck, 2016). These advancements underscore their potential not only in diabetes management but also in exploring therapeutic avenues for conditions like Alzheimer's Disease and other neurodegenerative disorders, where their neuroprotective effects could prove beneficial.

- Possible neuroprotective mechanism

Within the brain, activation of GLP-1 receptors may potentially counteract disrupted insulin signaling pathways, suggesting a neuroprotective role (Gault and Holscher, 2018). GLP-1 functions through its receptor, a member of the G protein-coupled receptor family well-known for enhancing insulin secretion in pancreatic β cells (Smith et al., 2019). Beyond its effects on insulin, GLP-1 is believed to enhance synaptic neurotransmitter release and promote long-term potentiation (LTP) in neurons (Calsolaro and Edison, 2015). Binding of GLP-1 to its receptor triggers an increase in cyclic adenosine monophosphate (cAMP), leading to activation of pathways like PKA/CREB and EPAC, and the opening of L-type voltage-gated Ca2+ channels (Grieco et al., 2019; Smith et al., 2019).Moreover, GLP-1 signaling is associated with anti-inflammatory responses, reduction of oxidative stress, modulation of gene expression, and regulation of autophagy, all of which contribute to its neuroprotective potential (Calsolaro and Edison, 2015; Grieco et al., 2019; Smith et al., 2019). Variations in these intracellular signaling pathways may depend on factors such as the specific brain region, underscoring the complexity and potential nuances of GLP-1's effects within the central nervous system (Calsolaro and Edison, 2015; Grieco et al., 2019; Smith et al., 2019). For a visual representation, see Figure 3 depicting GLP-1 signaling pathways in the brain.

- The Influence of GLP-1 in Various Tissues

GLP-1 receptors are widely expressed in islet alpha and beta cells as well as in peripheral tissues such as the pancreas, heart, gastrointestinal tract, adipose tissue, kidney, and muscles (Ceccarelli et al., 2013; Lund et al., 2014) (Fig. 4). This broad distribution implicates GLP-1 in multiple physiological systems and processes. In pancreatic alpha cells, GLP-1 regulates glucagon secretion, while in beta cells, it enhances insulin biosynthesis and promotes pancreatic beta cell proliferation in a glucose-dependent manner, as observed in rodent studies (Zhang et al., 2019). GLP-1 also affects lipid metabolism by influencing lipogenic and lipolytic activities and improves glucose uptake in adipose tissue (Ejarque et al., 2019). In the kidney, GLP-1 reduces albumin excretion and natriuresis, and in muscles, it upregulates glycogen synthesis and glucose oxidation. Cardioprotective effects of GLP-1 include lowering systolic blood pressure and potentially increasing heart rate. GLP-1 receptor agonists are also being investigated for their anti-inflammatory effects on liver tissues, suggesting potential benefits in treating non-alcoholic fatty liver disease (Seghieri et al., 2018). In blood vessels, GLP-1 signaling suppresses pro-atherosclerotic factors and promotes vasodilation, which may help improve vascular health and reduce cardiovascular complications by mitigating vascular inflammation (Kimura et al., 2018; Helmstadter et al., 2020).

- Preclinical Evidence

Preclinical studies strongly support the potential of GLP-1 receptor agonists to protect against progressive neurodegeneration. In 7-month-old APP/PS1 mice, daily treatment with liraglutide for 8 weeks prevented memory loss and reduced synaptic loss, preserving synaptic plasticity in the hippocampus (McClean et al., 2011). Liraglutide also mitigated β-amyloid accumulation and suppressed inflammation by reducing activated microglia (McClean et al., 2011). Subsequent research in aged 14-month-old APP/PS1 mice confirmed liraglutide's sustained neuroprotective effects, suggesting benefits not only in early AD stages but also in reversing key disease features (McClean and Holscher, 2014). In SAMP8 mice, liraglutide prevented memory decline and hippocampal neuronal loss compared to controls (Hansen et al., 2015). Additionally, liraglutide normalized cortical β-amyloid levels, reduced inflammation, and restored oxidative stress and mitochondrial function in 3xTg-AD mice (Xie et al., 2021). Cognitive improvements observed with liraglutide treatment in

rodent models were linked to enhanced astrocytic glycolysis and PI3K/Akt signaling (Zheng et al., 2021). Liraglutide also restored brain insulin signaling pathways and attenuated synaptic loss via cAMP/PKA signaling (Batista et al., 2018; Talbot et al., 2011; Paladugu et al., 2021). Other GLP-1 receptor agonists, such as exenatide and semaglutide, have shown similar promise in preclinical AD models by improving memory deficits, reducing β-amyloid accumulation, and enhancing neuronal function and survival (Garabadu and Verma, 2019; An et al., 2019; Chang et al., 2020). Notably, exenatide has demonstrated enhanced blood-brain barrier penetration compared to other GLP-1 agonists, suggesting potential advantages for neurodegenerative disease treatment (Salameh et al., 2020).

- Clinical Evidence

In a pilot trial of liraglutide, 38 patients diagnosed with AD were randomly assigned to receive either active treatment (n = 18) or placebo (n = 20) (Gejl et al., 2016). Over 6 months, liraglutide treatment preserved cerebral glucose metabolism, although it did not affect cognitive scores or amyloid load. Another study involving 43 patients with subjective memory complaints found that liraglutide improved intrinsic connectivity within default-mode network structures compared to placebo, as measured by resting-state functional MRI (Watson et al., 2019). A large-scale phase II b trial, Evaluating Liraglutide in Alzheimer's Disease (ELAD), conducted over 12 months, is pending publication (Femminella et al., 2019).In an 18-month pilot trial evaluating exenatide in AD, 11 patients received exenatide twice daily, while 10 received placebo (Mullins et al., 2019). Although exenatide was safe and well-tolerated, it did not show significant differences in neuropsychological or MRI outcomes compared to placebo. However, exenatide did reduce Aβ42 levels in extracellular vesicles over 18 months, suggesting a potential for reducing brain amyloidosis that warrants further investigation in AD (Mullins et al., 2019).Additionally, in a large multicenter trial evaluating weekly dulaglutide treatment in patients with T2DM, dulaglutide was associated with reduced cardiovascular outcomes and a 14% lower risk of substantive cognitive impairment compared to controls (Cukierman-Yaffe et al., 2020). Moreover, a pooled analysis from cardiovascular outcome trials demonstrated that liraglutide and semaglutide halved the risk of dementia diagnosis compared to placebo in T2DM patients, although the implications for broader AD populations remain uncertain (Ballard et al., 2020).

- **GLP-1 Analogues in Parkinson's Disease (PD)**

Even with available symptomatic treatments for Parkinson's disease (PD), the search for effective disease-modifying therapies remains crucial (Stoker and Barker, 2020). Repurposing anti-diabetic treatments, particularly GLP-1 receptor agonists, has emerged as a promising avenue (Victorino et al., 2021). Patients with PD often exhibit diminished postprandial plasma levels of GLP-1 compared to healthy controls (Manfready et al., 2021).Evidence from a large cohort study involving diabetes patients suggests that those treated with a DPP-4 inhibitor or a GLP-1 receptor agonist had significantly lower incidence ratios of PD—36% and 62% lower, respectively—indicating that targeting GLP-1 signalling could be a potent neuroprotective and potentially disease-modifying strategy for PD (Brauer et al., 2020). This underscores the potential of GLP-1 analogues in altering the course of PD progression, warranting further exploration in clinical trials.

- Possible Mechanism

The neuroprotective effects of GLP-1 in Parkinson's disease (PD) may be mediated through the modulation of the PI3K-AKT signalling pathway (Victorino et al., 2021). Activation of the GLP-1 receptor triggers Akt activation, which in turn inhibits glycogen synthase kinase 3β (GSK3β), reducing the aggregation of toxic proteins such as α-synuclein (Victorino et al., 2021). Additionally, activation of mechanistic target of rapamycin (mTOR) by GLP-1 may promote regeneration of nigrostriatal axons and prevent neurodegeneration

(Victorino et al., 2021). The involvement of nuclear factor kappa beta (NF-κB) signalling may contribute by downregulating pro-inflammatory cytokines, thus reducing inflammation in the brain (Victorino et al., 2021).Furthermore, GLP-1 receptor activation leads to an increase in cyclic adenosine monophosphate (cAMP), which stimulates various downstream pathways known to mitigate inflammation, oxidative stress, and apoptosis in PD pathology (Glotfelty et al., 2020). Similar to Alzheimer's disease (AD), GLP-1 may also protect against PD by restoring insulin signalling (Glotfelty et al., 2020). Moreover, GLP-1's protective influence on the blood-brain barrier (BBB) integrity has been suggested, potentially maintaining the barrier's function and reducing neuroinflammation (Glotfelty et al., 2020; Liu et al., 2017; Victorino et al., 2021).These mechanisms highlight the multifaceted neuroprotective potential of GLP-1 analogues in Parkinson's disease, suggesting their role as promising candidates for disease-modifying therapies in PD. Further research and clinical trials are needed to fully elucidate their therapeutic benefits in PD patients.

- Preclinical evidence

Preclinical studies have demonstrated the neuroprotective effects of GLP-1 receptor agonists in Parkinson's disease (PD) models. Exenatide treatment in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD has been shown to protect dopaminergic neurons and improve motor function (Li et al., 2009). Additionally, exenatide attenuates substantia nigra pars compacta neuron loss and preserves striatal dopaminergic fibers in these mice (Kim et al., 2009). In both in vivo and in vitro models, exenatide promotes neurogenesis and restores dopaminergic neurotransmission, further highlighting its therapeutic potential (Bertilsson et al., 2008).Moreover, extended-release formulations like PT302, based on exendin-4, effectively reduce motor impairments and neurodegeneration in a 6-hydroxydopamine rat model of PD (Chen et al., 2018). Semaglutide has also demonstrated efficacy in alleviating motor deficits and inflammation, and it shows superior neuroprotective properties compared to liraglutide by restoring levels of tyrosine hydroxylase and enhancing autophagy (Zhang et al., 2018a).These findings underscore the potential of GLP-1 receptor agonists as promising therapeutic agents for Parkinson's disease, warranting further investigation in clinical settings.

- Clinical Evidence

a proof-of-concept single-blind trial, 45 patients with moderate Parkinson's disease (PD) were randomly assigned to receive exenatide (n = 20 completed trial) or act as controls (n = 24 completed trial) over 12 months (Aviles-Olmos et al., 2013). Exenatide was well tolerated, and participants showed improved motor performance with a mean increase of 2.7 points on the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), compared to a decrease of 2.2 points in controls. These motor improvements persisted off-medication even 2 months after treatment cessation. Cognitive performance measured by the Mattis dementia rating scale–2 (MDRS) also improved in exenatide-treated patients versus controls, and benefits were observed up to 12 months post-treatment (Aviles-Olmos et al., 2014).In a larger phase II trial by Athauda et al., involving 62 patients with idiopathic PD, those treated with exenatide once weekly for 48 weeks demonstrated significant improvements in MDS-UPDRS part 3 scores compared to placebo during the off-medication phase at 48 and 60 weeks (Athauda et al., 2017). While the effects on motor function suggest symptomatic relief, the sustained benefits post-treatment suggest a potential influence on PD pathophysiology. Younger patients and those with lower disease severity tended to respond better, emphasizing the potential for early intervention (Athauda et al., 2019b). Additionally, patients with higher insulin resistance or obesity at baseline showed improved cognitive outcomes following exenatide treatment, suggesting a role for GLP-1 in modulating brain insulin signalling pathways (Athauda et al., 2019b).

- **GIP-GLP receptor Co-agonists**

GIP, another important incretin hormone akin to GLP-1, activates the GIP receptor to enhance cAMP secretion and has diverse physiological effects, including insulinotropic actions and influencing various tissues such as pancreatic β-cells, cardiovascular system, bone, and brain regions like the hippocampus and substantia nigra. Unlike GLP-1, GIP stimulates postprandial glucagon response and bone formation. In neurodegenerative conditions like Alzheimer's disease (AD) and Parkinson's disease (PD), GIP receptor agonists have shown neuroprotective and anti-inflammatory properties in preclinical studies. They reduce amyloid plaque load, oxidative stress, inflammation, and promote synaptic plasticity and neurogenesis.
Dual GIP/GLP-1 receptor agonists, such as tirzepatide, are being explored for their potential benefits in AD and PD. These compounds have shown enhanced neuroprotective effects compared to single receptor agonists in animal models. They improve memory, reduce toxic protein aggregation, enhance synaptic function, and restore neuronal signaling pathways like PI3K/Akt/GSK3β. Promising candidates like DA4-JC and DA5-CH demonstrate superior efficacy over liraglutide in improving motor deficits, protecting dopaminergic neurons, and reducing inflammation in PD models. However, challenges remain in understanding their blood-brain barrier penetration and ensuring optimal dosing strategies.

- **DPP-IV**

Dipeptidyl peptidase-IV (DPP-IV) is an enzyme that degrades various peptides, including GLP-1 and GIP, leading to their rapid inactivation. Inhibiting DPP-IV extends the half-life of these incretins, enhancing their biological activity. This approach has shown potential therapeutic benefits in neurodegenerative disorders like Alzheimer's disease (AD) and Parkinson's disease (PD).Studies indicate that DPP-IV inhibitors, such as linagliptin, can mitigate AD pathology by reducing Aβ-mediated cytotoxicity and mitochondrial dysfunction in neuronal cells. In animal models, linagliptin improves cognitive function, reduces amyloid-beta levels, tau phosphorylation, and neuroinflammation. Although linagliptin does not penetrate the blood-brain barrier (BBB) significantly, its effects are believed to be mediated through increased incretin levels in the brain (Angelopoulou and Piperi, 2018; Kosaraju et al., 2017).In PD models, DPP-IV inhibition has demonstrated normalization of motor function, suppression of cerebral inflammation, and protection against neuronal apoptosis. Combined inhibition of DPP-IV and P2X7 purinoceptors further enhances neuroprotection in PD models (Abdelsalam and Safar, 2015; Jamali-Raeufy et al., 2020).Clinical studies suggest that DPP-IV inhibitors may benefit cognitive function in elderly patients with mild cognitive impairment and AD. Patients treated with DPP-IV inhibitors showed improvements in attentional and executive functions compared to controls (Rizzo et al., 2014; Isik et al., 2017). These findings underscore the potential of DPP-IV inhibition as a therapeutic strategy for neurodegenerative disorders, either alone or in combination with existing treatments. Further research is needed to explore their efficacy in non-diabetic AD patients and to optimize treatment protocols.

- **Intranasal insulin**

Commonly used for managing type 2 diabetes mellitus (T2DM), offers a promising non-invasive approach for treating neurodegenerative disorders like Alzheimer's disease (AD) and Parkinson's disease (PD). This delivery method bypasses the blood-brain barrier, utilizing paracellular transport to achieve therapeutic drug levels in the brain without causing systemic hypoglycemia (Nedelcovych et al., 2018; Roque et al., 2021).Preclinical studies demonstrate that intranasal delivery of short-acting (regular) insulin effectively reaches deep brain

structures such as the hippocampus and nigrostriatal pathways (Fan et al., 2019). Initial small-scale trials suggested cognitive benefits in mild cognitive impairment (MCI) and AD, particularly in non-ApoE ε4 carriers, enhancing verbal memory and functional abilities (Reger et al., 2006; 2008b).Larger randomized controlled trials (RCTs) confirmed these findings, showing that intranasal short-acting insulin preserves cognitive function and stabilizes brain glucose metabolism in AD patients. It was associated with reduced amyloid-beta and tau levels in cerebrospinal fluid (CSF), supporting its potential disease-modifying effects (Craft et al., 2012; 2017). However, cognitive improvements were not universal, with benefits primarily observed in non-ApoE ε4 carriers (Avgerinos et al., 2018).The use of long-acting insulin analogs like detemir did not replicate these cognitive benefits, suggesting a specific role for short-acting insulin in preserving brain function in AD (Craft et al., 2017; Claxton et al., 2015). Recent studies, including a large-scale 12-month trial, yielded mixed results, underscoring the need for improved delivery devices and further investigation into patient-specific responses, particularly concerning ApoE ε4 status (Craft et al., 2020).In PD and multiple system atrophy (MSA), intranasal insulin also shows promise, improving motor performance and potentially stabilizing disease progression over short-term trials (Novak et al., 2019). Safety profiles have been favorable, with minimal adverse effects reported.

- **Metformin hydrochloride**

an established treatment for type 2 diabetes mellitus (T2DM), is known for its ability to regulate blood glucose levels and improve insulin sensitivity (Rena et al., 2017). While initially heralded for its potential neuroprotective effects, particularly in reducing the risk of Alzheimer's disease (AD) and Parkinson's disease (PD), recent research presents a more complex picture.Contrary to earlier findings, recent meta-analyses have not conclusively demonstrated a reduced risk of AD development with metformin use and have even suggested an increased risk of PD (Ping et al., 2020). Conflicting results also exist regarding cognitive outcomes, with some studies indicating a potential association between metformin use and cognitive impairment, possibly exacerbated by vitamin B12 deficiency (Imfeld et al., 2012; Moore et al., 2013; Campbell et al., 2017).However, large-scale studies, such as a nationwide case-control study, have shown that long-term metformin use in older individuals with diabetes significantly reduces the incidence of AD and other neurodegenerative disorders (Sluggett et al., 2020; Shi et al., 2019). This suggests that while short-term effects may be inconsistent, long-term treatment with metformin could be beneficial in preserving cognitive function in T2DM patients.Preclinical studies provide mechanistic insights into metformin's potential neuroprotective effects. In AD models, metformin has been shown to reduce phosphorylated tau, enhance neurogenesis, and reduce inflammation, thereby improving learning and memory (Farr et al., 2019; Ou et al., 2018; Saffari et al., 2020). Its impact on amyloid-beta burden reduction through enhanced insulin-degrading enzyme (IDE) activity further supports its therapeutic potential in AD (Lu et al., 2020).In PD, metformin has demonstrated protective effects on dopaminergic neurons, attenuating L-dopa-induced dyskinesia, reducing endoplasmic reticulum stress, and modulating inflammation in preclinical models (Ryu et al., 2018; Wang et al., 2020a; Saewanee et al., 2021). These findings suggest a broader neuroprotective role beyond its anti-diabetic properties.Clinical trials assessing metformin in AD and mild cognitive impairment (MCI) have shown mixed results. While some studies suggest modest improvements in verbal memory and executive function (Luchsinger et al., 2016; Koenig et al., 2017), others have not found significant changes in AD biomarkers or cognitive outcomes. Challenges such as patient tolerance to metformin and varying study designs underscore the need for further investigation into its efficacy and optimal use in neurodegenerative diseases.

- **PPAR-gamma agonists (PPAR-γ)**

PPAR-gamma agonists, such as thiazolidinediones (TZDs), activate a crucial transcription factor called PPARγ, which plays a significant role in regulating lipid metabolism and inflammation (Landreth, 2007).

Originally approved for managing type 2 diabetes since 1997, TZDs help control blood sugar levels, reduce triglycerides, and enhance insulin sensitivity. In Alzheimer's disease (AD), increased PPARγ expression in brain tissue suggests potential benefits in reducing inflammatory responses (Kitamura et al., 1999).In animal models of AD, pioglitazone, a PPARγ agonist, has shown promising effects by reducing amyloid-beta plaque burden, levels of Aβ42 in the brain, and markers of microglial activation and inflammation (Heneka et al., 2005; Yan et al., 2003). A small-scale 6-month trial involving 42 mild AD patients with diabetes found that pioglitazone treatment (15-30 mg daily) improved insulin sensitivity, lowered fasting plasma insulin levels, and enhanced cognitive function as assessed by multiple neuropsychological tests including MMSE. Additionally, regional cerebral blood flow in the parietal lobe increased among treated participants (Sato et al., 2011).Long-term studies investigating pioglitazone's association with dementia incidence in individuals free of dementia and type 2 diabetes suggest potential benefits, although large clinical trials are needed to confirm its effectiveness in non-diabetic AD patients or those at risk (Chou et al., 2017). The TOMMORROW phase 3 trial, involving 3500 participants worldwide, aimed to assess pioglitazone's ability to delay mild cognitive impairment due to AD biomarkers but was deemed unsuccessful following an interim analysis (Burns et al., 2019).Rosiglitazone, another PPARγ agonist, has shown cognitive benefits in pilot trials for AD and mild cognitive impairment (MCI), particularly improving delayed recall and attention in ApoE ε4 non-carrier patients (Watson et al., 2005; Risner et al., 2006). However, safety concerns and limited efficacy in larger clinical trials have restricted its use in AD populations (Harrington et al., 2011).

Recent studies highlight potential advantages of dual PPAR agonists targeting both PPAR δ and γ receptors, which are predominant in the brain and target distinct downstream insulin-responsive pathways (Reich et al., 2018). T3D-959, a dual agonist, has shown promising results in early AD stages by improving cognitive function and increasing [18 F]FDG signal, suggesting enhanced brain glucose metabolism (Chamberlain et al., 2020). The ongoing PIONEER trial, a phase 2 study involving 252 patients with mild to moderate AD, aims to further explore these compounds' efficacy and safety profiles (ClinicalTrials.gov Identifier: NCT04575517).

- **Amylin analogs**

Amylin, also known as islet amyloid polypeptide, is a hormone co-secreted with insulin to regulate glucose levels by inhibiting glucagon secretion and slowing gastric emptying (Gedulin et al., 2006). Synthetic analogs of amylin, such as pramlintide (PRAM), are available in the US and have been studied in randomized controlled trials for treating 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). These analogs aim to replace native amylin signaling without causing amylin accumulation, effectively mimicking human amylin due to a slight difference in amino acid composition (Grizzanti et al., 2018).Research shows conflicting evidence regarding amylin's role in Alzheimer's disease (AD). Amylin oligomers and plaques have been observed alongside amyloid-beta plaques in AD brains (Jackson et al., 2013). Amylin receptors are upregulated in regions with high amyloid burden, and blocking these receptors reduces amyloid-beta toxicity (Jhamandas et al., 2011). Some studies suggest that diminished amylin signaling, rather than amylin misfolding, contributes to cognitive dysfunction in both type 2 diabetes and AD (Ly and Despa, 2015). Lower plasma amylin levels have been noted in AD and mild cognitive impairment (MCI) compared to cognitively intact individuals, independent of amyloid or diabetes status (Adler et al., 2014).In animal models, pramlintide has shown promise in mitigating AD-related pathology and cognitive symptoms. Studies in SAMP8 and 5XFAD mice demonstrate that pramlintide

administration improves memory and learning abilities while reducing synapse loss and oxidative stress (Adler et al., 2014; Zhu et al., 2015).

However, in TgSwDI mice, pramlintide increased Aβ levels, potentially exacerbating AD-associated pathology (Mousa et al., 2020). The dual role of pramlintide in AD pathology remains controversial.In clinical settings, pramlintide has been found safe for use in non-diabetic AD populations (Zhu et al., 2017). Although initial studies suggest pramlintide's potential role in regulating lipid metabolism, further research is needed to determine its therapeutic efficacy in neurodegenerative diseases like AD (Tao et al., 2018). Currently, pramlintide has only been explored for diagnostic purposes in AD and not yet evaluated as a treatment option.

- **PTP1B inhibitors**

Protein tyrosine phosphatases (PTPs) are enzymes crucial for regulating cellular processes by controlling protein tyrosine phosphorylation in a reversible manner (He et al., 2014). Among them, PTP1B plays a significant role in insulin and leptin signaling pathways by dephosphorylating key proteins like insulin receptors and JAK2, affecting downstream pathways like PI3K and Akt (Vieira et al., 2018). Inhibitors targeting PTP1B have shown promise in clinical trials for type 2 diabetes (T2DM), effectively reducing its overactivity (Eleftheriou et al., 2019; Hussain et al., 2019; Nguyen et al., 2013).Dysfunction in neuronal insulin and leptin signaling, associated with increased PTP1B activity, has implications for conditions like Alzheimer's disease (AD) (Vieira et al., 2017). Inhibiting PTP1B may help restore these signaling pathways, potentially benefiting AD treatment by mitigating synaptic disruption and neuronal death induced by AD pathology (Bomfim et al., 2012; Bonda et al., 2014). Additionally, PTP1B influences pathways involved in learning, memory, endoplasmic reticulum stress, neuroinflammation, and synaptic regulation (Vieira et al., 2017).

Recent studies in AD mouse models have explored trodusquemine, a PTP1B inhibitor, demonstrating its ability to prevent neuronal loss, reduce inflammation in the hippocampus, and improve cognitive function (Ricke et al., 2020). This inhibitor also restored insulin response and normalized phosphorylation levels of key proteins in the brain, suggesting potential therapeutic benefits. However, the precise role of PTP1B inhibition in delaying or alleviating AD symptoms in human populations requires further investigation due to potential off-target effects on other PTPs (Tamrakar et al., 2014).

- **Sodium-glucose cotransporter 2 inhibitors**

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are medications approved for treating type 2 diabetes (T2DM) by reducing blood sugar levels through inhibiting glucose reabsorption in the kidneys (Lin et al., 2021). Beyond diabetes management, these inhibitors show promise in neurodegenerative diseases like Alzheimer's (AD) and Parkinson's disease (PD). They reduce reactive oxygen species, preserve mitochondrial function, and lower inflammation, potentially modifying disease progression in AD and PD (Esterline et al., 2020; Lin et al., 2021).In AD animal models, dapagliflozin improved spatial memory, reduced AD-related pathology, and regulated autophagy (Ibrahim et al., 2022). Similarly, empagliflozin treatment in a combined AD and T2DM mouse model showed reduced brain atrophy, decreased amyloid plaques, and enhanced memory and learning abilities (Hierro-Bujalance et al., 2020). In PD models, empagliflozin improved motor function, reduced neuroinflammation, protected dopaminergic neurons, and promoted neuroplasticity (Motawi et al., 2022; Mousa et al., 2023).

Population-based studies indicate that SGLT2 inhibitor use is associated with a lower risk of dementia. Patients prescribed these inhibitors showed an 11% reduced risk of dementia compared to non-users (Siao et al., 2022). Furthermore, in large-scale cohorts of diabetic patients, SGLT2 inhibitor users had a 20% lower risk of dementia compared to users of DPP-IV inhibitors, with dapagliflozin demonstrating the lowest risk (adjusted hazard ratio = 0.67), followed by empagliflozin (adjusted hazard ratio = 0.78) (Wu et al., 2022).Clinical investigations are ongoing to explore the combined effects of intranasal insulin and empagliflozin in patients with amnestic mild cognitive impairment (MCI) or early AD (NCT05081219). These trials aim to further elucidate the potential of SGLT2 inhibitors in alleviating brain insulin signaling deficits and glutamate excitotoxicity observed in AD.

Sr. No.	Drug Class	Description	Effect in Alzheimer's Disease (AD)	Effect in Parkinson's Disease (PD)
1	GLP-1 (Glucagon-like peptide-1)	Incretin mimetic that increases insulin secretion and decreases glucagon secretion.	Improves cognitive function, reduces amyloid plaques and tau phosphorylation, neuroprotective effects	Potential neuroprotective effects, may improve motor symptoms and protect dopaminergic neurons.
2	GIP-GLP receptor Co-agonists	Dual agonists that activate both GIP and GLP-1 receptors, enhancing insulin secretion.	Synergistic effects on cognition, reduction in amyloid plaques, improved neuronal survival	Enhances motor function, may offer neuroprotection, improves glucose metabolism in the brain.
3	Sodium-glucose cotransporter 2 inhibitors	Reduces glucose reabsorption in kidneys, leading to increased glucose excretion in urine	Potentially reduces neuroinflammation and oxidative stress, improving cognitive function.	May provide neuroprotective effects, improves insulin sensitivity and glucose utilization in the brain
4	PTP1B inhibitors	Inhibit protein tyrosine phosphatase 1B, enhancing insulin signaling.	May improve insulin signaling in the brain, potentially reducing amyloid pathology and improving cognition.	Potential benefits in improving motor symptoms and providing neuroprotection through enhanced insulin signaling.
5	Amylin analogs	Mimic amylin, a hormone co-secreted with insulin, to regulate blood sugar levels.	Potential neuroprotective effects and reduction in amyloid plaques.	May offer neuroprotective effects and improve glucose metabolism in the

				brain.
6	DPP-IV (Dipeptidyl peptidase-4) inhibitors	Inhibit the enzyme DPP-IV, prolonging the action of incretin hormones like GLP-1.	Improves cognitive function, reduces amyloid plaques, potential neuroprotective effects	Potential benefits in motor function, neuroprotection, and improved brain glucose metabolism.
7	Metformin hydrochloride	Biguanide that decreases hepatic glucose production and increases insulin sensitivity.	Potential cognitive benefits, reduction in amyloid plaques, improves mitochondrial function.	May offer neuroprotective effects, improves glucose metabolism, reduces oxidative stress.
8	PPAR-gamma agonists (PPAR-γ)	Activate peroxisome proliferator-activated receptor gamma, improving insulin sensitivity.	Reduces inflammation, oxidative stress, and amyloid pathology, improves cognitive function	Improves motor function, reduces neuroinflammation and oxidative stress, potential neuroprotection.
	Table No. 1 : antidiabetic drugs and their effect on neurodegenerative disease			

Future Therapeutic Opportunities in Neurodegenerative Diseases

1. Antidiabetic Agents as Potential Treatments:
    - Antidiabetic agents, including GLP-1 receptor agonists, GIP agonists, and insulin sensitizers, are being evaluated for their neuroprotective effects in Alzheimer's disease (AD) and Parkinson's disease (PD).
    - These agents aim to enhance autophagy, support neuronal survival, reduce apoptosis, oxidative stress, and neuroinflammation, all of which are common features in AD and PD progression.
2. Targeting Pathological Hallmarks:
    - They target AD hallmarks such as amyloid plaques and tau tangles, and PD characteristics like dopaminergic neuron loss and α-synuclein accumulation.
    - Shared signaling pathways such as PI3K/Akt and GSK3β are crucial in mediating their effects on disease pathology.
3. Specific Benefits and Mechanisms:
    - They may enhance protease activity, such as IDE-mediated degradation of amyloid plaques in AD.
    - Effectiveness may depend on their ability to access and influence affected brain regions like the hippocampus in AD and the striatum/substantia nigra in PD.
4. GLP-1 Signaling in Neurodegeneration:
    - GLP-1 receptor agonists show promise in preclinical trials by reducing inflammation, oxidative stress, and toxic protein accumulation.

- They also improve impaired insulin signaling pathways, critical for maintaining neuronal health and function.

5. Future Directions and Clinical Trials:
   - Confirmatory Phase 3 trials are essential to establish the clinical efficacy of these agents in AD and PD.
   - Dual GLP-1/GIP agonists represent a novel approach and merit further investigation in human trials.
6. Other Promising Agents:
   - Metformin, PPARγ agonists, amylin analogs, and PTP1B inhibitors have shown initial promise in early evaluations for AD and PD.
   - Continued research is necessary to determine their potential as disease-modifying treatments.
7. Overall Potential and Implications:
   - Antidiabetic agents offer significant potential in modifying disease progression and alleviating cognitive and behavioral symptoms in AD and PD.
   - Their ability to address both the pathophysiology and clinical manifestations makes them promising candidates for future therapeutic strategies.

Conclusion:

The exploration of antidiabetic agents as potential therapeutic interventions for neurodegenerative diseases represents a promising frontier in medical research. By targeting shared pathological mechanisms such as insulin resistance, inflammation, and oxidative stress, these agents offer multifaceted approaches to mitigating disease progression in Alzheimer's disease (AD) and Parkinson's disease (PD). GLP-1 receptor agonists, GIP agonists, and insulin sensitizers have shown encouraging results in preclinical and early clinical studies, demonstrating their ability to enhance neuronal survival, reduce neuroinflammation, and modulate key signaling pathways implicated in disease pathology.Despite these advancements, challenges remain in translating preclinical findings into clinically effective treatments. Confirmatory Phase 3 trials are essential to validate the efficacy and safety profiles of these agents in large patient cohorts. Moreover, understanding the nuances of their mechanisms of action within the central nervous system (CNS) and optimizing drug delivery to target specific brain regions are critical for maximizing therapeutic outcomes.

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3)M. Huttunen, Kristiina. "Metformin – a Future Therapy for Neurodegenerative Diseases." p. 14.

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