Adipokine dysregulation and oxidative stress in type 2 diabetes: Implications for neurodegeneration and neuroprotective effects of antidiabetic therapies

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Background: Neurodegeneration is accelerated by Type 2 diabetes mellitus through adipokine dysregulation, insulin resistance, oxidative stress, and neuroinflammation. This could link metabolic imbalance to Alzheimer's disease, Parkinson's disease, and cognitive decline. The aim of this review is to clarify the roles of adipokines in type 2 diabetes-induced neurodegeneration, their molecular pathways, and the possible neuroprotective potential of antidiabetic agents. **Methods:** Literature was searched in PubMed, Google Scholar, and Scopus for English-language articles published up to November 2025, using keywords like adipokines, diabetes mellitus, neurodegeneration, neuroinflammation, and antidiabetics. **Results:** Results highlight those elevated levels of pro-inflammatory adipokines, such as TNF-α, IL-6, and resistin, together with reduced levels of neuroprotective adipokines, including adiponectin and leptin, may drive NF-kB activation, suppression of Nrf2 signaling, and amyloid and tau pathology. This is further exacerbated by oxidative stress and mitochondrial dysfunction. Antidiabetic agents like metformin, GLP-1 agonists, thiazolidinediones, and SGLT2 inhibitors restore adipokine balance, enhance AMPK/PPARγ signaling, and show cognitive benefits in mild cognitive impairment cohorts per clinical trials. **Discussion:** In conclusion, repurposing antidiabetics via biomarker-guided multiple therapies offers disease-modifying promise for type 2 diabetes-linked neurodegeneration, necessitating large randomized controlled trials in prediabetic populations.

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INTRODUCTION

The most common devastating neurological complications of diabetes are Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) (Moroz et al., 2008). These complications are associated with a progressive loss of structure and function of specific neurons, which causes functional and cognitive deficits (Umegaki, 2014). Recent data have revealed that type 2 diabetes mellitus (T2DM) can precipitate cognitive dysfunction or dementia, especially those related to AD, where a positive correlation has been revealed between T2DM and AD (Kan et al., 2025; Zeng et al., 2025). Additionally, a meta-analysis that has pooled data from 28 prospective observational studies reported 56% and 73% more risk of dementia and AD among individuals with T2DM compared to non-diabetic controls (Gudala et al., 2013). The metabolic function of peripheral cells and the nervous system is one typical pathophysiological alteration seen in neurodegenerative disorders (Ahmed et al., 2018). Risk factors for neurodegenerative disorders include dysregulated adipokines, hyperglycemia, oxidative and nitrosative stress, and inflammatory mediators (Rojas-Gutierrez et al., 2017; Khan et al., 2021). The brain insulin resistance, commonly referred to as type 3 diabetes, is a significant factor in this regard. It reduces the activity of the insulin-degrading enzyme (IDE), inhibits glucose metabolism, and promotes the formation of amyloid beta (Aβ) plaque (Abdalla, 2024; Cerasuolo et al., 2025). Similarly, elevated blood glucose levels can result in advanced glycation end products (AGEs), which worsen neuroinflammation while also reducing harmful Aβ oligomer (Vlassara and Uribarri, 2014). Notably, adipokines are thought to play a crucial role in the pathologies of the CNS, due to their influence blood-brain barrier (BBB) permeability and communication between the brain and body. Depending on their balance, adipokines can protect against or contribute to neurological diseases and may serve as biomarkers for CNS disorders (Huber et al., 2023). Despite this, the particular role of adipokines in connecting metabolic imbalance, neuroinflammation and neurodegeneration in diabetes is not fully understood (Szablewski, 2025). Additionally, their molecular pathways and clinical significance as biomarkers or therapeutic targets in neurodegeneration are still insufficiently defined. Accordingly, this review aims to clarify how adipokine dysregulation contributes to neurodegeneration in diabetic patients by exploring their molecular pathways, effects on neuroinflammation and metabolic imbalance, and their potential value as biomarkers or therapeutic targets.

ADIPOKINES AND NEURODEGENERATION IN DIABETIC PATIENTS

Adipokines are signaling molecules secreted by adipose tissue which are considered as passive energy reservoir, now recognized as a dynamic endocrine organ (Wang et al., 2008; Proença et al., 2014). They play an essential role in maintaining metabolic and neuronal homeostasis, particularly they can be regulated by the intake of fat, which regulate multiple cellular functions (Blüher, 2013). Adiponectin, the highly abundant adipocytokine in human circulation, performs a protagonist effect in the metabolic dysfunction associated with AD (Dezonne et al., 2023). Literature show that adiponectin level in T2DM to be usually reduced, even in the relative early stages of the disease, while high levels are linked with lower risk of T2DM even after adjustment for various factors that could affect this relationship (Li et al., 2009). The brain's high expression of the adiponectin receptors, AdipoR1 and AdipoR2, suggests that adiponectin signaling may be closely linked to neurologic function and, in turn, neurological disease (Yang et al., 2015). In a mouse model of neurodegenerative disease, adiponectin has been demonstrated to improve neuropathological characteristics (Waragai et al., 2017). Sasaki et al. demonstrated, using multiple regression analysis, that hypoadiponectinemia is concurrently implicated in the pathophysiology of atherosclerosis in individuals with cerebral infarction and that adiponectin is an independent contributor to cerebral infarction (Sasaki et al., 2010). Adiponectin has been shown by Nishimura et al. to have a cerebroprotective effect through a mechanism dependent on endothelial nitric oxide synthase (Nishimura et al., 2008). Chen et al. showed that NF-κB plays a crucial role in the anti-inflammatory impact of adiponectin, which has strong cerebroprotective activity (Chen et al., 2009). Shen and colleagues showed that adiponectin overexpression reduces ischemia-induced brain shrinkage and enhances neurological function due to increased localized angiogenesis using a mouse model of acute unilateral middle cerebral artery blockage (Shen et al., 2013). Concerning leptin, it is a peptide hormone mainly secreted by white adipose tissue and works on the hypothalamus, causing increased energy expenditure and decreased appetite, thereby controlling body

weight (Obradovic et al., 2021). Other functions of leptin include immunity, reproduction, and endocrine function modulation (Akeel Al-hussaniy, Hikmate Alburghaif and Akeel Naji, 2021). Leptin receptors are expressed in high level in the hippocampus, a brain region that has a role in memory and learning, which severely affected during AD (Marwarha and Ghribi, 2012). Epidemiological studies have demonstrated that higher circulating leptin levels are associated with lower risk of dementia including AD, and lower circulating levels of leptin have been reported in patients with AD (Ülker and Kenangil, 2018). In laboratory setting, it has been demonstrated that supplementation with leptin may decrease tau phosphorylation and Aβ production, two main biochemical events that provide key players for the pathogenesis of AD. Therefore, the reduction of Aβ production and tau hyperphosphorylation, as well as increased synaptogenesis, by leptin may lead to increased spatial learning, memory, and neurogenesis (CA et al., 2015). This makes leptin as a unique therapeutic option and a valuable tool in the interpretation of biochemical pathways involved in the etiology of the sporadic form of AD (McGuire and Ishii, 2016). Furthermore, elevated amounts of resistine and visfatin are associated with higher Aβ burden and inflammatory cytokines that they may be associated with neurodegeneration (McGuire and Ishii, 2016). Chemerin-9 has shown to be a neuroprotective ameliorator of cognitive deficits in mice model by boosting a neuroprotective microglial phenotype (Zhang et al., 2025). Omentin is an adipokine that has pleiotropic effects on several disorders, where therapeutic methods to raise its levels have resulted in positive outcomes in the treatment or prevention of several diseases related to metabolic dysfunction, neural and cardiovascular health, as well as some inflammatory disorders and certain cancers (Biegański, Dąbrowski and Różańska-Walędziak, 2025). It possible to use circulating omentin-1 as a biomarker of numerous disorders including neurological diseases. This may be obtained via AMP-activated protein kinase/Akt/nuclear factor-kB/mitogen-activated protein kinase (ERK, JNK, and p38) signaling (Kumar Kushawaha, Sharma and Singh Ashawat, 2025). Regarding interleukin-6 (IL-6), it is a proinflammatory cytokine that can significantly contribute to insulin resistance and development of T2DM. Although IL-6 is normally present in tissues, its chronic overproduction triggers inflammation that disrupt insulin signaling (Rehman et al., 2017). Additionally, it influences nerve cell activity and is a key factor in neuroinflammation. Additionally, as elevated IL-6 levels have been regularly linked to a number of neurodegenerative illnesses, they may serve as a biomarker for the course and outcome of these conditions (Shan, Zhang and Zhang, 2024). One important transporter of retinoic acid and its derivatives is retinol binding protein 4 (RBP4). It is an adipokine that controls insulin signaling, which growing evidence have shown that many mechanisms, like as retinoic acid signaling and systemic metabolism, may play a role in the development of AD. (Das, Dasgupta and Ray, 2019). Also, retinoid and retinoid-associated signaling plays an essential role in normal neurodevelopment and appears to remain active in the adult CNS. Although previous research revealed changes in RBP4 levels in the brain and CSF in later stages of AD, it is unknown whether circulating RBP4 is changed in preclinical AD or whether it can be a helpful biomarker for dementia and cognitive decline (Ishii, Kamel and Iadecola, 2019). Additionally, RBP4 is recognized as a component of the repair capacity that could be activated to induce protection and regeneration in the mature nervous tissue (Lake and Heuckeroth, 2013). In addition to being an adipokine, dipeptidyl peptidase 4 (DPP4) is primarily released by adipose tissue, primarily from mature adipocytes in the visceral compartment, where it performs both autocrine and paracrine functions. In the adipocyte and other target cells and tissues, DPP4 can interfere with insulin transmission, which promotes the growth of a proinflammatory region that increases the risk of neurodegeneration (Barchetta et al., 2022). Likewise, tumor necrosis factor-alfa (TNF-α) is an important pro-inflammatory mediator that plays a crucial role in the pathophysiology of T2DM and the development of insulin resistance. Adipocytes and/or peripheral tissues are the primary producers of TNF-α, which causes tissue-specific inflammation by generating reactive oxygen species (ROS) and activating several transcriptionally driven pathways (Akash, Rehman and Liaqat, 2018). TNF-α plays a crucial role in cell survival, gene expression, and synaptic function. While controlled neuroinflammation helps repair damage, uncontrolled or persistent inflammation leads to chronic neuroinflammation, causing neuronal dysfunction and death. Elevated TNF-α is a common feature of major neurodegeneration disease such as AD, PD and amyotrophic lateral sclerosis (Fischer and Maier, 2015). Lipocalin 2 (LCN2/NGAL) is an adipokine with potential importance in insulin resistance associated with obesity (Yan et al., 2007). LCN-2 shows conflicting roles in inflammation and

Table 1. Adipokines and their roles in neurodegeneration

Adipokine	Main actions in diabetes	Role in neurodegeneration
Adiponectin	Anti-inflammatory, improves insulin sensitivity	Neuroprotective; reduces neuroinflammation and oxidative stress; low levels linked to AD and cognitive decline
Leptin	Regulates appetite and metabolism; impaired signaling in obesity/T2DM	Enhances synaptic plasticity; low or resistant states linked to memory impairment and AD pathology
Resistin	Pro-inflammatory; promotes insulin resistance	Increases neuroinflammation and microglial activation; associated with cognitive dysfunction
TNF-α	Strong pro-inflammatory cytokine; elevated in diabetes	Drives neuroinflammation, neuronal apoptosis, and contributes to AD, PD, and MS progression
IL-6	Mediator of chronic inflammation in diabetes	Promotes neuroinflammation and synaptic dysfunction; elevated in many neurodegenerative diseases
Visfatin (NAMPT)	Modulates glucose metabolism; increases during inflammation	Contributes to oxidative stress and neuronal injury; may worsen neuroinflammation
DPP4	Degrades incretins; linked to inflammation and endothelial dysfunction	Impairs neurovascular integrity, increases inflammation, and may contribute to cognitive decline
LCN2	Stress-induced adipokine elevated in obesity and T2DM	Strong inducer of neuroinflammation, BBB damage, and neuronal death; linked to AD and MS
Omentin	Anti-inflammatory; improves insulin signaling	Potentially neuroprotective; low levels associated with increased inflammation and metabolic stress
Chemerin	Regulates glucose and lipid metabolism; promotes inflammation	Contributes to microglial activation and neuroinflammatory responses
RBP4	Promotes insulin resistance and inflammation	Impairs neuronal insulin signaling and can contribute to cognitive dysfunction
Progranulin	Involved in insulin signaling; affected in diabetes	Linked to frontotemporal lobar degeneration; regulates inflammation and neuronal survival

insulin resistance, and its function in skeletal muscle remain unclear. Early findings suggest that exercise increases LCN-2 expression in muscle, LCN-2 is a novel exercise-induced myokine that appears to induce lipolysis and decrease lipid accumulation in adipocytes. Additionally, LCN-2 is an iron-regulating antibacterial protein involved in inflammation and immune responses. It contributes to pathology in several organs, including the brain. In the nervous system, LCN2 promotes glial activation, iron accumulation, and neuroinflammation, and it can cross the BBB through MC4R-mediated transport, linking it to neurodegenerative prosses (Lim, Jeong and Song, 2021). Table 1 summarizes the main roles of adipokines in neurodegeneration.

METABOLIC DYSREGULATION AND NEURONAL VULNERABILITY IN DIABETES

Metabolic pathways are regulated by various key enzymes, where dysregulation of these processes suggests the presence of organic impairment of mitochondria and damage to related metabolic enzymes. In addition, oxygen and glucose metabolic rates are drastically changed in many neurodegenerative diseases, including AD due to marked alterations in the glycolytic pathway and TCA cycle. (Yan et al., 2020) .

MECHANISM OF DIABETES-INDUCED METABOLIC DYSREGULATION AND NEURODEGENERATION

Although the exact mechanism causing T2DM-related cognitive deterioration, particularly AD, is still mysterious, a number of theories have been put up. One of the main pathogenic features of diabetes is high glucose content, which can harm brain neurons by oxidative stress and osmotic shocks (Naguib et al., 2020). Maintaining persistently high blood sugar also increases the production of AGEs, which may be harmful to neurons. AGEs are the end-products of the Maillard reaction, during which reducing sugar can reacts with amino groups of protein to produce cross-link complexes and unstable compounds. AGEs have been found in CNS of diabetics, and couple with free

radicals to create oxidative stress, which in turn leads to neuronal damage (Umegaki, 2012). Furthermore, chronic elevation of glucose concentration leads to excessive production of ROS, which are considered as the main cause in neuronal injury and damaging of neuronal membrane. ROS activate microglial cells and inflammatory pathways, resulting neuroinflammation and neuronal degeneration. Accordingly, the pro-inflammatory molecules will access easily to CNS as the integrity of blood-brain barrier (BBB) is affected by ROS (Pun, Lu and Moochhala, 2009). Additionally, the development of insulin resistance leads to impaired glucose uptake and increased glucose production. It triggers compensatory hyperinsulinemia, which together with ongoing metabolic stress, form a cycle that worsens insulin resistance, obesity, and eventually leads to β-cell failure and T2DM (Silva Rosa et al., 2020). Insulin signaling is vital for brain function, supporting neuronal growth, synapse formation, and energy balance. When insulin activates its receptor, it triggers pathways that enhance neurotransmission, promote long-term potentiation for learning and memory, regulate glutamate and GABA receptors, and activate the P13K-AKt pathway to boost energy use and protect neurons from apoptosis (Hölscher, 2020). Besides, defects in brain cholesterol metabolism result in neuroinflammation and BBB degradation. Moreover, oxidized low-density lipoprotein (ox-LDL) accumulation causes ER stress, which disrupts calcium flow to mitochondria, leading to oxidative stress and apoptosis, a process linked to cardiovascular disease and Alzheimer's. apolipoprotein E (ApoE) helps clear cholesterol, affecting Aβ levels and reducing ER stress, while defects in LDL receptors (LDLR) exacerbate these issues, causing cellular damage and potentially hypoxia through failed clearance and chronic stress, tying lipid metabolism to neurodegeneration (Hong et al., 2022). Neuroglia-are cells that provide homeostatic support and form defense of the nervous system contribute to all neurological disorders (Bronzuoli et al., 2018). They play a key role in brain health, and lipid accumulation in neurons and glial cells contributes to neurodegeneration. Lipid droplet formation, driven by metabolic imbalance, oxidative stress, and glia-neuron interactions, is increasingly recognized as a factor in the onset and progression of neurodegenerative disorders (Yang et al., 2022). Furthermore, a major contributing factor to neurodegeneration, is mitochondrial dysfunction that can severely impair neuronal survival. Due to neuron-high energy demands and limited regenerative capacity, evidence suggests that impaired mitochondrial function is a cause, rather than a consequence of neurodegeneration (Johri and Beal, 2012; Tapias, 2019). Chronic inflammation is strongly linked to neurodegeneration. While temporary inflammatory responses protect the CNS, prolonged or excessive inflammation triggers apoptosis and necrosis in neurons, contributing to diseases like Alzheimer's and MS. This could be due to increased cytokine production during sustained inflammation that accelerates neuronal damage (Amor et al., 2010).

EFFECTS OF REACTIVE OXYGEN SPECIES ON NERVOUS SYSTEM IN DIABETIC PATIENTS

Reactive oxygen species have long been linked to oxidative damage to proteins, fatty acids, DNA, and other cellular constituents, which results in a variety of illnesses. By overwhelming natural systems and harming DNA, proteins, and lipids, oxidative stress, which results from an imbalance between excessive ROS production and insufficient antioxidant defenses, is linked to a number of pathologies, including age-related disorders, cancer, cardiovascular disease, inflammation, and neurodegenerative conditions like AD and PD (Dash et al., 2025). Numerous sources can produce ROS either intracellularly or exogenously. Many physiological and metabolic mechanisms result in their production. The production of ROS has been linked to a number of distinct enzymes. Another significant source of intracellular ROS generation is mitochondria (Krumova and Cosa, 2016). Apoptosis, necrosis, cell growth, and carcinogenesis are just a few of the biological processes that free radicals and ROS are engaged in. Numerous sites for the generation of ROS and a few mechanisms for their destruction are found in cells. The subsequent downstream consequences of the ROS generated on cellular function may depend on whether of these locations is activated by a particular stimulation (Chandimali et al., 2025). Protein phosphatases, protein kinases, and transcription factors are some of the intracellular signaling pathways that ROS can alter. This suggests that most of the effects of ROS on cells are caused by their actions on signaling pathways rather than by nonspecific damage to intracellular macromolecules (Maher* and Schubert, 2000). Diabetes is characterized by high glucose concentrations that lead, via several mechanisms, to an increased production of ROS. The resulting oxidative stress can play a key role in diabetes pathogenesis. In diabetes, either acute or chronic elevated glucose causes the β-cells to undergo apoptosis and produce more ROS.

Both necroptosis and apoptosis play significant roles in the development of diabetes complications and can result in tissue damage to the kidneys, heart, retina, and nervous system (Maher* and Schubert, 2000).

Several ion transporting systems are quite susceptible to disruption under conditions of oxidative stress and observations that the activity of calcium ion transporters is decreased in aged brain, hypothesized that the Ca2+-ATPase activity in synaptic plasma membranes is quite sensitive to in vitro exposure to oxidative stress (Zaidi and Michaelis, 1999).

MOLECULAR SIGNALING PATHWAYS INVOLVED IN NEURODEGENERATION

Several molecular signaling are involved in neurodegeneration in patients with T2DM. Peroxisome Proliferator-Activated Receptor (PPAR) activation has shown to stimulate metabolic and mitochondrial functions, resulting in promotion of axonal growth, induction of progenitor cells to differentiate into myelinating oligodendrocytes, improvement of brain clearance of toxic molecules such as Aβ, modulation of adipokines expression and reduction of neuroinflammation. (Zolezzi et al., 2017) . Another factor that is involved in the process is the nuclear factor erythroid 2-related factor 2 (Nrf2). It is a basic area leucine-zipper transcription factor that is essential for the coordinated expression of antioxidant and detoxifying enzyme genes, supporting cell survival in metabolic disorders. Following production, the Kelch-like ECH-associated protein 1 suppressor (Keap1) stops Nrf2 in the cytoplasm, causing its ubiquitin-dependent destruction (Zgorzynska, Dziedzic and Walczewska, 2021). One Nrf2 activation mechanism relies on disconnection from the Keap1 homodimer through the oxidation of cysteine at specific sites of Keap1. Free Nrf2 enters the nucleus, dimerizes with small musculoaponeurotic fibrosarcoma proteins (sMafs), and binds to the antioxidant response element (ARE) sequence of the target genes (Silva-Islas and Maldonado, 2018).

Neurodegenerative illnesses have also been linked to the transcriptional regulatory nuclear factor kappa B (NF-kB) protein, which modulates cellular biological activity by attaching to a promoter area in the nucleus and transcribing different protein genes. IKB kinase/NF-kB signaling pathway activation may be the cause of this, leading to neurodegeneration (Guo et al., 2024). Generally, IKB kinase/NF-kB transcriptional activity is often closely monitored at many cascade pathways. The expression of pro-inflammatory genes, such as cytokines, chemokines, and adhesion molecules, is significantly influenced by the NF-kB pathway. After connecting with an inhibitor molecule protein (IKB) in response to a variety of stimuli, the cytosolic sequestered NF-kB in an inactivated form is phosphorylated and translocated into the nucleus, where it continues to transcribe different genes required for altering different cellular activities (Liu et al., 2017). Numerous studies verified the function of distinct NF-kB family member proteins involved in the expression of diverse gene products and the mediation of different cellular cascades (Singh and Singh, 2020). Pro-inflammatory cytokines like TNF-α and IL-6 generate further molecular signaling by activating Ikβ kinase (IKKβ), which phosphorylates IkBα and causes proteasomal IκB to degrade. This releases active NF-kB, which then translocate into the nucleus and stimulates the activation of inflammatory target genes in a positive feedback loop that increases inflammation even further. Interestingly, some studies have indicated that AMPK activation provide therapeutic effect on neuroinflammation of the CNS. One study demonstrated that AMPK activation blocks IFN-γ-induced gene expression, including CCL2, TNF-α, CXCL10 and inducible nitric oxide synthase (iNOS), in primary astrocytes and microglia through the modulation of signal transducer and activator of transcription 1 (STAT1). Likewise, the deletion of AMPKα1 and AMPKα2 in primary astrocytes enhanced signal transducer and activator of transcription (STAT1), a transcription factor involved in inflammation and immune responses (Peixoto et al., 2017).

NEURODEGENERATION AND THE MODIFYING ROLE OF ANTIDIABETICS

With extensive and selective expression of the insulin receptor in the olfactory bulb, hypothalamus, hippocampus, cerebellum, amygdala, and cerebral cortex, the brain is thought to be an insulin-sensitive organ. Neuronal growth, glucose regulation, eating behavior, body weight, and cognitive functions all depend on insulin receptor signaling in the brain (Milstein and Ferris, 2021). Recent study has shown that insulin receptor signaling is compromised in a number of neurological conditions. Additionally, dendritic expansion, neuronal survival, circuit development, synaptic plasticity, and postsynaptic neurotransmitter receptor trafficking are all known to depend on insulin receptor signaling (Derakhshan and Toth, 2013).

Metformin can readily cross the BBB to directly affect brain function in addition to acting on peripheral systems to control glucose and lipid metabolism. Metformin is a perfect medication choice to treat neurological degenerative illnesses since it can activate several processes in the central nervous system, such as neuroprotection, neural regeneration, angiogenesis, and anti-inflammation, as well as increase brain-derived neurotrophic factor (Loan et al., 2024a). Metformin modulates brain function through a variety of signaling pathways, such as energy sensing (AMPK signaling), phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) signaling, lipid signaling (phospholipids and eicosanoids), inflammatory signaling, and mitochondrial-related signaling. Numerous metformin-mediated mechanisms have been studied to mitigate behavioral impairments and pathology markers of AD. The AMPK-mTOR-S6K-BACE1 and AMPK-P65 NF-kB signaling pathways both lessen oxidative damage and neuroinflammation and contribute to metformin-improved neurological impairments (Loan et al., 2024b). Conversely, there is limited information on the impact of metformin on adiponectin levels; however, this antidiabetic agent may lead to a notable reduction in leptin and resistin levels. Furthermore, this compound exhibits additional advantageous effects on the levels of leptin and adiponectin in individuals with an elevated BMI, suggesting beneficial role in neurodegeneration-derived adipokine dysregulation (Zhao et al., 2024).

Glibenclamide has shown neuroprotective and neurorestorative effects in various experimental models of CNS injuries and neurodegenerative diseases. It primarily achieves this by blocking specific ion channels, which in turn reduces inflammation, oxidative stress, and brain edema (Qiu et al., 2021). Glibenclamide treatment has shown promise in improving memory impairment and reducing hippocampal neuroinflammation in rat models of T2DM and sporadic AD (Jiang et al., 2021). Additionally, it has been shown that glibenclamide suppresses nitric oxide production and pro-inflammatory cytokine expression in LPS-stimulated microglial cells and exerts anti-inflammatory effects in APP/PS1 transgenic mice. These findings suggest glibenclamide may have potential as a therapeutic option for AD (Ju et al., 2020).

Growth factor glucagon-like peptide-1 (GLP-1) has been associated to increased expression of genes related to cell growth, repair, and replacement, as well as improved cell metabolism, suppression of apoptosis, and reduction of inflammatory responses. It's also noticeable that GLP-1 mimetics have anti-inflammatory and neuroprotective qualities (Athauda and Foltynie, 2016). GLP-1 receptor expression has been shown to be induced by both activated microglia and activated astrocytes, which participate in the immune/inflammatory response. GLP-1 mimetics exhibit a remarkable array of protective benefits on neurogenesis, synaptogenesis, cell repair, the decrease of the chronic inflammatory response, and the reduction of brain amyloid plaque levels (Hölscher, 2014a). Novel GLP-1 analogues, such as liraglutide or exendin-4, which are DPP4 inhibitors, have significant impacts on memory formation and synaptic plasticity in the brain, according to prior studies on synaptic plasticity in the hippocampus. Furthermore, GLP-1 mimetics can shield synapses from Aβ's harmful effects on hippocampal synaptic plasticity. The majority of these new mimetics have the ability to pass the BBB, which is crucial if they are to be employed to treat CNS neurodegenerative diseases (Hölscher, 2014b). On the other hand of the axis, GLP-1 may elevate the secretion of protective via several mechanisms such as activation of AMPK, that increase adiponectin, supporting PPAR activity and reducing oxidative stress by improving mitochondrial biogenesis, while reducing the pro-inflammatory adipokines (Li et al., 2015; Yaribeygi et al., 2021).

Thiazolidinediones (TZDs), also known as insulin sensitizers, have shown to have beneficial impact against neurodegeneration. However, cognitive loss was observed in diabetic patients on TZDs. On the other hand, research using a rosiglitazone-treated rat model of T2DM revealed a notable improvement in spatial learning and memory tasks (Ma et al., 2015). This effect appears to be associated with the control of the insulin signaling system, which included a reduction in the expression of IR, IRS-1, Bcl-2 AKB, and p-CREB in the rat hippocampus neurons (Colca et al., 2023). Similarly, the memory impairment caused by the presence of Aβ oligomers was significantly improved when rosiglitazone was directly injected into the brain of Wistar rats (Yu et al., 2015). Additionally, pioglitazone treatment enhanced reversal learning in the A/T bitransgenic mouse, a crucial animal model utilized in AD research to generate senile plaques and overproduce Aβ and TGF-β1 (Papadopoulos et al., 2013). The improvement of ACh decrease, which causes cholinergic dysfunction in AD, may

be another mechanism of action for TZDs as PPARγ activators (Barage and Sonawane, 2015). A mouse model of the cholinergic deficiency in the brain provided evidence that pioglitazone enhanced learning and memory retention as well as performance on the passive avoidance test (Xiang et al., 2012). Additionally, TZDs have a role in adipokines secretion that shift from pro-inflammatory to anti-inflammatory effects. TZDs have been shown to interfere with expression and release of mediators of insulin resistance originating in adipose tissue (e.g., increased free fatty acids and decreased adiponectin) in a way that results in net improvement of insulin sensitivity (Sulston et al., 2016).

Newer hypoglycemic medications with numerous pleiotropic effects are flozins or sodium-glucose cotransporter 2 (SGLT2) inhibitors. Flozins have an affinity for the SGLT1 receptor, which is linked to protection against ischemia/reperfusion brain injury, and are not entirely SGLT2-selective. In addition to reducing proinflammatory cytokines, M2 macrophage polarization, JAK2/STAT1 and NLRP3 inflammasome suppression, and cIMT regression, SGLT2 inhibitors also reduce oxidative stress (Pawlos et al., 2021). SGLT2 inhibitors protect the neurovascular unit, BBB, pericytes, astrocytes, microglia, and oligodendrocytes while also enhancing endothelial function and preventing remodeling (Pawlos et al., 2021). Additionally, flozins can decrease ACh, which enhances cognitive function. Cerebral brain-derived neurotrophic factor (BDNF), which regulates neurotransmission and guarantees neuronal development, survival, and plasticity, is markedly elevated by empagliflozin. Additionally, they might be able to reestablish the circadian regularity of mTOR activation, which is a highly innovative discovery in the study of metabolic disorders and cognitive decline. In patients with T2DM, SGLT2 inhibitors have a significant potential to prevent atherosclerosis and cognitive decline (Stanciu et al., 2021). According to recent research, SGLT2 inhibitors can also influence body metabolism by controlling the levels of adipokines. The effects of SGLT2 inhibitor medication on circulating leptin and adiponectin levels in T2DM patients have been assessed by a meta-analysis. The beneficial effects of SGLT2 inhibitors on metabolic homeostasis and neural tissues may be attributed to improved insulin sensitivity, decreased circulating leptin levels, increased circulating adiponectin levels, and decreased inflammation when compared to placebo (Wu et al., 2019).

CLINICAL IMPLICATIONS AND FUTURE PROSPECTIVES

Based on the neuroprotective mechanisms of antidiabetic agents, combination of drugs such as pioglitazone with sitagliptin or metformin hold particular promise for mitigating neurodegeneration in T2DM patients. These drugs may synergize through several axes including PPARγ, GLP-1 and AMPK-Nrf2 to support synaptic plasticity, cognitive function, and neural survival while limiting neuroinflammation, oxidative stress and amyloid pathology in the brain. Recent clinical trials, including those evaluating sitagliptin added to metformin, have shown sustained improvements in glycemic control and metabolic markers over long periods, suggesting a broader CNS benefits in high-risk population with early cognitive decline. These strategies could prove, especially in diabetics prone to AD and PD, where insulin resistance overlaps with neural vulnerability (Moses et al., 2016; Khaloo et al., 2019). Ongoing Phase II-IV trials from 2020-2025 validate disease-modifying potential of antidiabetics in AD, PD, and related dementias, with GLP-1 receptor agonists and TZDs showing cognitive improvements (Koshatwar et al., 2023; Abou Elezz et al., 2025).

Future strategies include large-scale randomized control trials testing GLP-1 receptor agonists-SGLT2 inhibitors or TZD-metformin polytherapy in prediabetic or mild cognitive impairment patients, alongside biomarker-driven trials monitoring adipokines, Nrf2 activation, and brain glucose metabolism. Precision approaches targeting PPARγ-GLP-1-AMPK synergies, combined with artificial intelligence-optimized dosing or proteolysis targeting chimeras for tau/amyloid clearance, hold potential for halting progression in T2DM-linked neurodegeneration. Long-term safety data and head-to-head comparisons may guide repurposing for at-risk populations. Anti-TNF-α therapeutic strategies have been advanced to mitigate insulin resistance and reduce the progression toward T2DM, highlighting the role of inflammation modulation in metabolic disease management (Francés et al., 2013; Akash, Rehman and Liaqat, 2018). Oxidative stress, alongside neuroinflammation and mitochondrial dysfunction, constitutes a central hallmark of neurodegenerative disorders. Targeting the Nrf2/ARE signaling pathway, melatonin-mediated Nrf2 activation and Nrf2/Bach1 signaling axis represents a promising molecular intervention to enhance the transcriptional activation of cytoprotective genes,

thereby potentially delaying the onset or progression of neurodegenerative diseases (Íñigo-Catalina et al., 2025; Soni et al., 2025). Furthermore, the role of microRNAs as critical regulators of NF-kB pathway, may help influencing the cellular inflammatory response. Consequently, selective inhibition of NF-kB and its family members provide a novel therapeutic opportunity to counteract neuroinflammation and prevent neurodegeneration (Yang et al., 2024). Molecular signaling pathways involving pro-inflammatory cytokines, such as IL-6 and TNF-α, activate IKKβ, precipitating phosphorylation and proteasomal degradation of the inhibitory protein IkBα. This process liberates NF-kB, enabling its nuclear translocation and subsequent upregulation of inflammatory gene expression, thereby creating a positive feedback loop that augments inflammation (Gurney et al., 2018). Attractively, activation of AMPK has been demonstrated to exert therapeutic effects by attenuating central CNS neuroinflammation, highlighting its potential as a target for intervention (Xu et al., 2024).

CONCLUSION

Adipokine dysregulation in T2DM drives neuroinflammation, oxidative stress, and metabolic dysfunction, accelerating neurodegeneration through pathways like NF-kB activation, Nrf2 suppression, and insulin resistance, as evidenced by elevated pro-inflammatory cytokines and reduced neuroprotective adipokines. Antidiabetic agents such as metformin, GLP-1 agonists, TZDs, and SGLT2 inhibitors offer multifaceted neuroprotection by restoring adipokine balance, enhancing AMPK/Nrf2 signaling, modulating PPARγ activity, and promoting amyloid/tau clearance, with clinical trials demonstrating cognitive benefits in patients with early AD and mild cognitive impairment.

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Adipokinek diszregulációja és oxidatív stressz 2-es típusú cukorbetegségben: a neurodegenerációra gyakorolt hatások és az antidiabetikus terápiák neuroprotektív potenciálja

Háttér: A 2-es típusú cukorbetegség az adipokinek egyensúlyának zavara, az inzulinrezisztencia, az oxidatív stressz, és a neuroinflammáció révén elgyorsítja a neurodegenerációt. Ez kapcsolódási pont lehet az anyagcsere-egyensúly felborulása, valamint az Alzheimer-kór, a Parkinson-kór és a kognitív hanyatlás között. Jelen áttekintés célja az adipokinek szerepének tisztázása a 2-es típusú cukorbetegség okozta neurodegenerációban, molekuláris útvonalainak feltérképezése, valamint az antidiabetikumok lehetséges neuroprotektív hatásának bemutatása. **Módszer:** A PubMed, a Google Scholar és a Scopus adatbázisokban keresést folytattunk 2025. novemberéig megjelent angol nyelvű cikkekre a következő kulcsszavakkal: adipokinek, cukorbetegség, neurodegeneráció, neuroinflammáció és antidiabetikumok. **Eredmények:** Az eredmények azt mutatják, hogy a proinflammátoros adipokinek, mint a TNF-α, IL-6 és resistin emelkedett szintje, valamint a neuroprotektív adipokinek, például az adiponektin és leptin csökkent szintje hozzájárulhat az NF-kB aktivációjához, az Nrf2 jelátviteli útvonal elnyomásához, valamint az amyloid- és tau-patológia kialakulásához. Ezt tovább súlyosbítja az oxidatív stressz és a mitokondriális diszfunkció. Az antidiabetikumok, mint a metformin, GLP-1 agonisták, tiazolidindionok, és SGLT2-gátlók, helyreállítják az adipokinek egyensúlyát, fokozzák az AMPK/PPARγ jelátvitelt, és klinikai vizsgálatok szerint kognitív előnyöket mutatnak enyhe kognitív károsodásban szenvedő populációkban. **Diszkusszió:** Összefoglalva, az antidiabetikumok biomarker-alapú, kombinált terápiás újrahasznosítása ígéretes lehet a 2-es típusú cukorbetegséghez kapcsolódó neurodegeneráció kezelésében. Az eredmények felhívják a figyelmet nagy, randomizált kontrollált vizsgálatok szükségességére prediabéteszes populációkban.

Kulcsszavak: Adipokinek, 2-es típusú cukorbetegség, neurodegeneráció, neuroinflammáció, antidiabetikumok