Review Article

Beyond glycemic control: the neuroprotective potential of tirzepatide

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Abstract

Type 2 diabetes mellitus is linked to cognitive decline and an increased risk of neurodegenerative diseases. Tirzepatide, a medication that targets both the glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors, has shown therapeutic benefits beyond blood sugar regulation, particularly in protecting the nervous system. Recent preclinical studies suggest that tirzepatide may help prevent neurodegeneration, reduce inflammation in the brain, and improve cognitive function. Its effects are attributed to the modulation of insulin signaling, suppression of inflammatory molecules, and promotion of neurotrophic factors that support brain health. Evidence indicates that tirzepatide could offer a disease-modifying approach for conditions such as Alzheimer's and Parkinson's disease. This review examines the latest research on its neuroprotective properties, emphasizing its potential to preserve brain function and prevent cognitive decline. Further clinical studies are necessary to confirm its long-term benefits in humans.

Keywords

Tirzepatide, neuroprotection, type 2 diabetes, cognitive impairment, neurodegeneration

Introduction

Diabetes mellitus is one of the most prevalent metabolic disorders of modern times, with the number of diagnosed cases steadily rising each year. As of 2022, an estimated 828 million adults were living with diabetes, marking a significant increase from 198 million cases in 1990—an exponential growth of 630 million cases over the past three decades (NCD Risk Factor Collaboration 2024).

The overwhelming majority of diabetes cases are attributed to type 2 diabetes mellitus (T2DM), which accounts for over 90% of all diagnoses. The rising prevalence of T2DM is closely linked to various lifestyle factors, including unhealthy diets high in sugars, refined carbohydrates, and saturated fats but low in fiber; obesity; prolonged physical inactivity; aging populations; and genetic predisposition (Kyrou et al. 2020; Hossain et al. 2024).

T2DM significantly diminishes long-term patient quality of life due to its chronic complications. Persistent hyperglycemia has profound systemic effects, contributing to macrovascular complications such as ischemic heart disease, stroke, and peripheral artery disease, as well as microvascular complications, including neuropathy, nephropathy, and retinopathy (Paul et al. 2020). Among these, diabetic encephalopathy represents one of the most severe chronic microvascular complications, directly affecting the central nervous system. It manifests through neurochemical, structural, behavioral, and cognitive alterations. This condition is particularly concerning in the elderly, as aging increases the risk of neurodegenerative disorders and cognitive decline. Despite its severity, diagnosing diabetic encephalopathy remains challenging, and its pathogenesis is not yet fully understood. Hyperglycemia, insulin resistance, amyloid accumulation,

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neuroinflammation, and oxidative stress are key cellular pathways implicated in its development (Nagayach et al. 2024). Glucose serves as the primary energy source for the brain, fueling neuronal activity and neurotransmission. Any disruption in glucose metabolism can directly impair brain function, independent of environmental stressors (Fried et al. 2019; Bolo et al. 2020). Beyond its role in energy production, glucose also provides essential precursors for synthesizing key neurotransmitters. However, chronic hyperglycemia can induce neurodegeneration and synaptic deterioration, leading to disruptions in neurotransmission systems (Duarte 2015; d'Almeida et al. 2020). Evidence suggests that dysfunction in these systems contributes to the cognitive impairments observed in patients with T2DM (Hristov et al. 2023).

In this context, various therapeutic approaches have been explored for the treatment of diabetic encephalopathy. Antioxidant-based therapies have shown promise in alleviating neuronal damage caused by oxidative stress. Additionally, growing evidence suggests that probiotics, prebiotics, and synbiotics may help restore gut microbial balance, thereby reducing neuroinflammation. Furthermore, several antidiabetic drugs have demonstrated neuroprotective properties through distinct mechanisms, offering potential benefits beyond glycemic control (Nagayach et al. 2024). In recent years, glucagon-like peptide-1 (GLP-1) receptor agonists, a class of drugs primarily used for the treatment of T2DM, have gained significant attention for their neuroprotective potential (Hölscher 2022; Reich and Hölscher 2022). Of particular interest is tirzepatide, a novel dual agonist that targets both the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. Due to its dual action, there is growing interest in its potential neuroprotective effects in diabetes-related neurodegeneration. This review aims to summarize current evidence on tirzepatide's neuroprotective effects, focusing on its mechanisms and therapeutic potential in neurodegenerative and diabetes-related cognitive disorders.

Incretin hormones and their neuroprotective role

GLP-1 is a 28-amino-acid peptide secreted primarily by L-cells in the ileum and colon in response to nutrient intake. The preproglucagon gene, located on chromosome 2, encodes GLP-1 along with other incretin-related peptides such as GLP-2 and oxyntomodulin. GLP-1 secretion occurs rapidly after food intake, with levels peaking 30–60 minutes postprandially, particularly in response to carbohydrates and lipids, though proteins also contribute to its release. GLP-1 binds to GLP-1 receptors (GLP-1R), which are expressed in pancreatic β-cells, the gastrointestinal tract, cardiovascular tissues, and the central nervous system (particularly in the hypothalamus and brainstem). Activation of GLP-1R leads to cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA)

pathway activation, which enhances insulin secretion in a glucose-dependent manner (Müller et al. 2019; Reich and Hölscher 2022; Liu 2024). GLP-1 also suppresses glucagon secretion, thereby reducing hepatic glucose production via decreased glycogenolysis and gluconeogenesis (Ramracheya et al. 2018). Additionally, GLP-1 delays gastric emptying, promoting postprandial satiety, which contributes to reduced caloric intake and weight loss in individuals with diabetes and obesity (Müller et al. 2019).

Numerous studies have demonstrated the neuroprotective effects of GLP-1R activation (Bomba et al. 2013; Cai et al. 2014, 2017, 2018; Solmaz et al. 2015; Barreto-Vianna et al. 2017; Chen et al. 2017; Batista et al. 2018; Zhou et al. 2019; Ferrari et al. 2022; Gateva et al. 2024). Intracerebroventricular administration of GLP-1 and [Ser(2)]exendin(1-9)—a peptide related to the glucagon/GLP-1 family—enhances associative and spatial learning through GLP-1R activation, with [Ser(2)]exendin(1-9) also being effective when administered peripherally (During et al. 2003). GLP-1R-deficient mice exhibit cognitive deficits that can be reversed by hippocampal Glp1r gene transfer, whereas rats overexpressing GLP-1R in the hippocampus show improved learning and memory. Additionally, GLP-1R-deficient mice demonstrate greater seizure susceptibility and increased neuronal damage after kainate administration, an effect that is partially observed in heterozygotes and fully reversed by hippocampal Glp1r gene transfer. Notably, systemic administration of [Ser(2)]exendin(1-9) in wild-type animals prevents kainate-induced hippocampal apoptosis, emphasizing its neuroprotective potential (During et al. 2003). GLP-1R activation also protects glial cells; for instance, liraglutide prevents oxidative stress, inflammation, caspase activation, and cell death in primary rat cortical astrocytes exposed to advanced glycation end-products, while also restoring intracellular cAMP levels, protein kinase A (PKA) activity, and phosphorylation of cAMP response element-binding protein (CREB). These protective effects are entirely dependent on GLP-1R signaling, as they are abolished by GLP-1R knockdown or inhibition of adenylyl cyclase (SQ22536) and PKA (Rp-cAMP) (Bao et al. 2015). Beyond these mechanisms, GLP-1R activation promotes synaptic integrity, cognitive function, and neurogenesis; reduces amyloid and tau pathology; mitigates calcium dysregulation and endoplasmic reticulum stress; and exerts anti-inflammatory, antioxidant, and anti-apoptotic effects. It also improves neuronal insulin sensitivity, mitochondrial function, and energy metabolism while enhancing autophagy, mitophagy, and neurotrophic factor synthesis (Hölscher 2022; Reich and Hölscher 2022). Studies in various diabetic animal models further highlight the neuroprotective potential of GLP-1R agonists such as exenatide, liraglutide, lixisenatide, and semaglutide, supporting their therapeutic relevance for neurodegenerative diseases and diabetes-associated cognitive impairment (Table 1). It should also be noted that some studies suggest GLP-1R agonists may provide neuroprotective effects in diabetic patients (Monney et al. 2023). Clinical trials have shown that GLP-1R agonists,

including semaglutide, liraglutide, and dulaglutide, can reduce cognitive impairment in individuals with T2DM (Zhang et al. 2019; Cukierman-Yaffe et al. 2020; Vadini et al. 2020; Li et al. 2021; Cheng et al. 2022; Nørgaard et al. 2022). Interestingly, some researchers propose that dulaglutide, which has the highest brain penetration among available GLP-1 agonists at 61.8%, may offer the most pronounced neuroprotective effects (Fessel 2024).

GIP is a 42-amino-acid peptide secreted primarily by K-cells in the duodenum and proximal small intestine in response to nutrient ingestion. Its secretion increases postprandially and is stimulated by carbohydrates, lipids, and proteins. GIP binds to GIP receptors (GIPR), which are expressed in pancreatic β-cells, adipocytes, cardiomyocytes, and neurons in the central nervous system. Similar to GLP-1, GIP activates the cAMP-PKA signaling pathway, enhancing insulin secretion in a glucose-dependent manner (Ferrari et al. 2022; Liu 2024; Müller et al. 2025).

Evidence suggests that GIP exerts neuroprotective effects (Buhren et al. 2009; Nyberg et al. 2005; Ferrari et al. 2022). Gault and Hölscher (2008) investigated the effects of an enzyme-resistant GIP analogue, N-AcGIP, on synaptic plasticity. N-AcGIP is a stable, long-acting peptide hormone that regulates glucose homeostasis and insulin release. In their study, they examined the effects of native GIP and the GIP agonist N-AcGIP on synaptic plasticity—specifically long-term potentiation (LTP)—in the hippocampus. Their findings revealed, for the first time, that both peptides enhance LTP, while the GIP antagonist Pro(3)GIP reduced LTP. Furthermore, they investigated the effects of beta-amyloid (Aβ 25–35), a peptide that aggregates in the brains of Alzheimer's disease patients, and found that its injection impaired LTP. However, when N-AcGIP was administered 30 minutes prior to Aβ(25–35) injection, it fully reversed the LTP impairment induced by beta-amyloid. These findings suggest that GIP not only

Table 1. Summary of studies investigating the effects of GLP-1 analogs in animal models of diabetes, with a focus on neuroprotection, cognitive function, and mood-related behaviors. The table outlines various GLP-1 analogs, their treatment regimens, corresponding diabetes models, and key findings. These studies highlight the potential of GLP-1 receptor agonists in mitigating diabetes-associated cognitive decline, neuroinflammation, synaptic dysfunction, oxidative stress, and gut-brain axis alterations. Abbreviations: ACOX1 (acyl-CoA oxidase 1), Akt (protein kinase B), AMPK (AMP-activated protein kinase), Cyt-c (cytochrome c), GFAP (glial fibrillary acidic protein), GSK-3A (glycogen synthase kinase-3 alpha), HFD (high-fat diet), i.p. (intraperitoneal), JNK (c-Jun N-terminal kinase), LC3-II (microtubule-associated protein light chain 3), mTOR (mechanistic target of rapamycin), NRF2 (nuclear factor erythroid 2-related factor 2), NTRK2 (neurotrophic receptor tyrosine kinase 2), p-JNK (phosphorylated c-Jun N-terminal kinase), p-c-JUN (phosphorylated c-Jun), p62 (sequestosome 1), PI3K (phosphoinositide 3-kinase), s.c. (subcutaneous), STZ (streptozotocin), T2DM (type 2 diabetes mellitus).

GLP-1 analog treatment	Animal model of diabetes	Key findings	Reference
Liraglutide (250 µg/kg/day, s.c., 6 weeks)	STZ-induced type 1 diabetes in male C57BL/6J mice	Improved learning and memory, preserved hippocampal neuron and synapse ultrastructure, reduced oxidative stress and neuronal apoptosis, and restored the PI3K/Akt signaling pathway.	Yan et al. 2019
Liraglutide (75 or 200 µg/kg/day, s.c., 28 days)	Goto-Kakizaki rats (spontaneous T2DM model, 32 weeks old)	Improved learning and memory, restored autophagy markers (Beclin-1, LC3-II), modulated PI3K/Akt, AMPK/mTOR signaling, and reduced apoptosis.	Yang et al. 2018
Liraglutide (200 µg/kg/day, i.p., 8 weeks)	STZ-induced type 1 diabetes in male C57BL/6 mice	Prevented cognitive decline, reduced neuronal and synaptic damage in hippocampal CA1, promoted autophagy (↑LC3-II, Beclin-1; ↓p62), and increased autophagic vacuole formation.	Kong et al. 2018
Lixisenatide (50 nmol/kg, s.c., twice daily, 40 days)	HFD-induced obese and insulin-resistant male Swiss NIH mice (T2DM model)	Improved glycemic control, enhanced insulin secretion and sensitivity, improved recognition memory, upregulated hippocampal NTRK2 and mTOR expression, increased progenitor cell proliferation, and immature neurons in the dentate gyrus.	Lennox et al. 2014
Exenatide (3 µg/kg, i.p., twice daily, 16 weeks)	STZ-induced diabetic male Sprague-Dawley rats on a high-sugar, high-fat diet (T2DM model)	Improved cognitive function, reduced neuronal apoptosis, inhibited JNK/c-JUN pathway activation, and downregulated Cyt-c, Caspase-3, p-JNK, and p-c-JUN expression.	Wang et al. 2022
Exendin-4 (3.2 µg/kg, i.p., twice daily, 28 days)	STZ-induced diabetic male Sprague-Dawley rats on an HFD (T2DM model)	Reduced tau hyperphosphorylation (Ser199/202, Thr217), improved insulin signaling in the hippocampus, increased PI3K/AKT activity, and decreased GSK-3A activity.	Xu et al. 2015
Semaglutide (10 µg/kg, s.c., 16 weeks)	STZ-induced diabetic male C57BL/6J mice on an HFD (T2DM model)	Improved learning and memory, reduced hippocampal damage, downregulated ACOX1 in oxidative stress, and restored neuronal function.	Yang et al. 2025
Semaglutide (0.05 mg/kg, i.p., weekly)	HFD-induced T2DM in mice	Reduced depressive- and anxiety-like behaviors, improved cognitive function, preserved synaptic plasticity, reduced neuroinflammation, increased serotonergic and glutamatergic signaling, and improved gut microbiota profile and gut-brain axis integrity.	de Paiva et al. 2024
Semaglutide (50 nmol/kg, gastric gavage, once daily, 4 weeks) ± Metformin (250 mg/kg, gastric gavage, once daily, 4 weeks)	Rotenone-induced Parkinson's disease in STZ-induced diabetic male Wistar rats on an HFD (T2DM model)	Lowered glucose, HbA1c, cholesterol, and oxidative-inflammatory stress; improved antioxidant status, neurobehavioral function, and striatal histology; downregulated caspase-3 and GFAP; upregulated NRF2 expression; combined treatment more effective than individual therapies.	Salem et al. 2025

modulates neurotransmitter release and promotes LTP formation but also protects synapses from the neurotoxic effects of beta-amyloid peptides (Gault and Hölscher 2008). This highlights the potential of enzyme-resistant GIP analogues as promising therapeutic agents for preventing neurodegeneration in Alzheimer's disease and related disorders. In another study, researchers investigated the effects of GIP on learning and memory deficits in mice injected with Aβ(1–40) (Figueiredo et al. 2010). Both learning and memory impairments induced by Aβ(1–40) were abolished by co-administration of GIP, further supporting its neuroprotective role. Additionally, GIP may contribute to neurogenesis, as exogenously administered GIP was shown to stimulate the proliferation of adult-derived hippocampal progenitor cells both in vitro and in vivo. Notably, adult GIP receptor knockout mice exhibited a significantly lower number of newborn neurons in the hippocampal dentate gyrus compared to wild-type mice, reinforcing the role of GIP signaling in adult neurogenesis. Moreover, prolonged GIP activation has been shown to be equally effective, if not superior, to dietary interventions in improving glucose intolerance, cognitive function, and hippocampal synaptic plasticity in high-fat diet-fed mice (Figueiredo et al. 2010). These findings collectively suggest that GIP-based therapies hold significant potential in the treatment of neurodegenerative disorders and cognitive decline associated with metabolic dysfunction.

Brief pharmacological overview of tirzepatide

Tirzepatide is a synthetic peptide consisting of 39 amino acids, structurally modeled on human GIP with additional motifs from GLP-1 and the GLP-1 analogue semaglutide. The peptide is conjugated to a C20 fatty dicarboxylic acid (eicosanedioic acid) via lysine, which serves as a hydrophilic linker. These structural modifications enhance tirzepatide's affinity for albumin, resulting in a high protein binding rate of 99% and an extended elimination half-life of approximately 116.7 hours (around five days) (Nauck and D'Alessio 2022). This pharmacokinetic profile allows for once-weekly subcutaneous administration, with steady-state serum concentrations achieved after four weeks of treatment (Chavda et al. 2022). Tirzepatide undergoes metabolism primarily through β-oxidation of the C20 fatty diacid moiety, proteolytic cleavage of the peptide backbone, and amide hydrolysis. The drug's metabolites are predominantly excreted via urine and feces, with no intact tirzepatide detected in either route (Sweta et al. 2024).

As a dual incretin receptor agonist, tirzepatide simultaneously activates both GLP-1R and GIPR. Notably, it has a higher affinity for GIPR, binding to it with the same strength as native GIP, while its affinity for GLP-1R is approximately five times weaker than that of native GLP-1. The term "twincretin," introduced by Finan et al., encapsulates the synergistic effect of dual GLP-1 and GIP receptor activation in enhancing insulin secretion and sensitivity (Finan et al. 2013).

Tirzepatide is a novel antidiabetic and anti-obesity agent that received approval from the U.S. Food and Drug Administration in May 2022, followed by marketing authorization from the European Commission in September 2022 (Frías 2023). The SURPASS-1 trial, a double-blind, randomized, placebo-controlled Phase 3 study, demonstrated that tirzepatide significantly improves glycemic control and promotes weight loss without increasing the risk of hypoglycemia (Rosenstock et al. 2021). Additionally, the SURPASS-2 trial established tirzepatide's non-inferiority and superiority to semaglutide in reducing glycated hemoglobin levels over a 40-week period in patients with T2DM (Frías et al. 2021).

Evidence of the neuroprotective effects of tirzepatide

Previous studies have shown that GIP analogues can enhance the effects of GLP-1 (Hölscher 2018). Novel GLP-1/GIP dual receptor agonists have been developed with improved brain penetration, potentially leading to greater neuroprotective benefits. The enhanced efficacy of these compounds suggests they may outperform single GLP-1 receptor agonists and offer disease-modifying treatment for patients with neurodegenerative disorders (Hölscher 2018; Pathak et al. 2018). In this context, interest in tirzepatide as a neuroprotective agent has significantly increased over the past two years (Table 2).

One of the first studies demonstrating the neuroprotective role of tirzepatide, as shown by Guo et al. (2023), indicates that this GLP-1/GIP dual agonist significantly alleviates diabetes-induced cognitive impairment. In a rat model of diabetes induced by a high-fat diet (HFD) and streptozotocin injection, tirzepatide improved spatial learning and memory deficits, as demonstrated by the Morris water maze test. Mechanistically, it reduced Aβ accumulation, prevented structural damage in hippocampal regions (CA1, CA3, DG, and hilus), and restored synaptic integrity by increasing the expression of synaptic proteins such as PSD95 and SYT1. Additionally, tirzepatide promoted the formation of dendritic spines, which are essential for synaptic plasticity and memory function. Importantly, the drug exhibited potent anti-inflammatory effects by downregulating IL-1β, IL-6, and TNF-α levels and suppressing the phosphorylation of NF-κB and IKKα in the hippocampus. Furthermore, it counteracted diabetes-induced insulin signaling deficits by preventing the hyperphosphorylation of IRS-1 at Ser307 and reactivating the PI3K/Akt/GSK3β pathway, which plays a crucial role in neuronal survival and synaptic function. These findings suggest that tirzepatide mitigates diabetes-associated cognitive decline through a multifaceted mechanism involving reduced neuroinflammation, restored insulin signaling, and enhanced synaptic plasticity (Guo et al. 2023).

A recent study investigated the neuroprotective effects of tirzepatide in a mouse model of HFD-induced cognitive impairment (Ma et al. 2024). The findings showed that

Table 2. Effects and mechanisms of tirzepatide in experimental models of neurodegenerative and metabolic disorders. This table summarizes the therapeutic effects of tirzepatide across various preclinical models, including diabetic cognitive impairment, Alzheimer's disease, Parkinson's disease, and colistin-induced neurotoxicity. The table outlines the treatment regimen (dose, route, and duration), experimental model, key outcomes, and underlying molecular mechanisms. Tirzepatide demonstrates neuroprotective effects through anti-inflammatory, antioxidant, and anti-apoptotic pathways, as well as modulation of glucose metabolism and synaptic integrity. Abbreviations: i.p. (intraperitoneal), s.c. (subcutaneous), HFD (high-fat diet), Aβ (amyloid-beta), SIRT3 (sirtuin 3), NLRP3 (nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3), STZ (streptozotocin), IL (interleukin), TNF-α (tumor necrosis factor-alpha), ROS (reactive oxygen species), MDA (malondialdehyde), SOD (superoxide dismutase), GSH (glutathione), CAT (catalase), NF-κB (nuclear factor kappa B), IKKα (inhibitor of nuclear factor kappa-B kinase alpha), IRS-1 (insulin receptor substrate 1), PI3K (phosphatidylinositol 3-kinase), Akt (protein kinase B), GSK3β (glycogen synthase kinase 3 beta), BACE1 (beta-secretase 1), GFAP (glial fibrillary acidic protein), GLUT (glucose transporter), HK (hexokinase), G6PD (glucose-6-phosphate dehydrogenase), PFK (phosphofructokinase), MAP2 (microtubule-associated protein 2), GAP43 (growth-associated protein 43), AGBL4 (ATP/GTP binding protein-like 4), CREB (cAMP response element-binding protein), BDNF (brain-derived neurotrophic factor), AMPK (AMP-activated protein kinase), Nrf2 (nuclear factor erythroid 2-related factor 2), ER (endoplasmic reticulum), ATF4 (activating transcription factor 4), CHOP (C/EBP homologous protein), p-CREB (phosphorylated CREB), TrkB (tyrosine kinase B).

Treatment	Model	Outcomes	Mechanisms	Reference
Tirzepatide (1.2 mg/kg, s.c., once a day for 4 weeks)	HFD-induced cognitive impairment in C57BL/6J mice	Attenuated cognitive decline, improved Morris water maze performance, reduced oxidative stress, and neuroinflammation.	Upregulation of SIRT3 in the hippocampus, suppression of NLRP3 inflammasome activation, reduced microglial activation, decreased IL-1β, IL-6, and TNF-α levels, decreased ROS and MDA levels, and restored antioxidant defenses (SOD, GSH, CAT).	Ma et al. 2024
Tirzepatide (1.35 mg/kg, i.p., once a week for 10 weeks)	HFD- and STZ-induced diabetic rats	Improved spatial learning and memory, reduced Aβ accumulation, restored synaptic integrity, and enhanced synaptic plasticity.	Downregulation of IL-1β, IL-6, and TNF-α; suppression of NF-κB and IKKα phosphorylation; prevention of IRS-1 hyperphosphorylation; and reactivation of the PI3K/Akt/GSK3β pathway.	Guo et al. 2023
Tirzepatide (10 nmol/kg, i.p., once weekly for 8 weeks)	APP/PS1 mice (Alzheimer's disease model) and cell-based models	Reduced Aβ plaque deposition, decreased neuroinflammation, lowered neuronal apoptosis, and enhanced synaptic protein expression.	Inhibition of BACE1, suppression of GFAP expression, regulation of brain glucose metabolism (upregulation of GLUT1, HK, G6PD, and PFK), and mitochondrial protection.	Yang et al. 2024
Tirzepatide (50 and 100 nmol/kg, s.c.)	Rotenone-induced Parkinson's disease model in rats	Prevented motor deficits, increased striatal dopamine levels, reduced oxidative stress, decreased alpha-synuclein aggregation, and inhibited neuroinflammation.	Downregulation of TNF-α and IL-6, reduction in oxidative stress, prevention of alpha-synuclein accumulation, and restoration of dopamine levels in the striatum.	Delvadia et al. 2025
Tirzepatide (0.2 μM)	SH-SY5Y human neuroblastoma cells exposed to normal (25 mM) and high glucose (150 mM) for 7 days	Promoted neuronal growth and differentiation, reduced apoptosis, and protected against high glucose-induced neurotoxicity.	Activation of CREB/BDNF signaling, upregulation of pAkt, MAP2, GAP43, and AGBL4, prevention of hypermethylation of CREB/BDNF genes, and restoration of GLUT1, GLUT3, and GLUT4 levels.	Fontanella et al. 2024
Tirzepatide (10 nM/kg, i.p.)	HFD-induced type 2 diabetes mellitus-like zebrafish model	Ameliorated cognitive impairment, improved behavioral parameters, restored antioxidant levels, reduced abnormal glucose and lipid profiles, and anti-inflammatory effects.	Antioxidant properties (restoration of GSH and CAT), improved anti-inflammatory markers (IL-10), anti-apoptotic effects, and enhancement of AMPK levels.	Misra et al. 2025
Tirzepatide (1.35 mg/kg on days 1, 4, and 7, s.c.)	Colistin-induced neurotoxicity and nephrotoxicity model in rats (300000 IU/kg/day, i.p. for 7 days)	Enhanced locomotor activity, reduced neurotoxicity, mitigated histopathological damage, and improved renal function.	Modulation of the PI3K/p-Akt/GSK3-β pathway, inhibition of NF-κB/TNF-α, upregulation of Nrf2/GSH, suppression of ER stress markers (ATF4, CHOP), reduction of GFAP immunoreactivity, and activation of p-CREB/BDNF/TrkB neuroprotective signaling.	Hassan et al. 2024

tirzepatide administration significantly attenuated cognitive decline associated with HFD by reducing oxidative stress and neuroinflammation. Mechanistically, tirzepatide upregulated sirtuin 3 expression in the hippocampus, which in turn suppressed nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation. This led to reduced microglial activation and decreased levels of inflammatory cytokines, including IL-1β, IL-6, and TNF-α. Additionally, tirzepatide mitigated oxidative stress by lowering reactive oxygen species and malondialdehyde levels

while restoring antioxidant defenses such as superoxide dismutase, glutathione, and catalase activity. However, the study primarily focused on hippocampal changes and did not assess white matter involvement, which is also crucial for cognitive function (Ma et al. 2024).

Recently, Fontanella et al. (2024) elucidated the molecular processes underlying the neuroprotective effect of tirzepatide. In a neuroblastoma (SH-SY5Y) cell model, the authors found that tirzepatide activates key molecular pathways involved in neuronal growth, such as the cAMP response element-binding protein (CREB) and brain-de-

rived neurotrophic factor (BDNF) signaling cascade, which are essential for synaptic plasticity, memory formation, and neuronal survival. Additionally, tirzepatide promotes anti-apoptotic mechanisms by modulating the balance between B-cell lymphoma 2 (Bcl-2), which prevents cell death, and Bcl-2-associated X protein (BAX), which promotes apoptosis. Furthermore, it enhances neuro-differentiation by upregulating phosphorylated protein kinase B (pAkt), microtubule-associated protein 2 (MAP2), growth-associated protein 43 (GAP43), and ATP/GTP binding protein-like 4 (AGBL4), all of which are crucial for neuronal growth and repair (Fontanella et al. 2024).

Tirzepatide was found to counteract the detrimental effects of high glucose (HG) exposure, which is known to contribute to neurodegeneration. It prevented the HG-induced downregulation of the pAkt/CREB/BDNF signaling pathway, suggesting a protective role against glucose-related neuronal damage. Additionally, tirzepatide reversed the hypermethylation of CREB and BDNF gene promoters and reduced miR-34a expression, which is typically upregulated in aging and neurodegenerative conditions, leading to impaired synaptic plasticity and cognitive decline (Fontanella et al. 2024). Importantly, tirzepatide prevented HG-induced downregulation of key glucose transporters, including glucose transporter 1 (GLUT1), glucose transporter 3 (GLUT3), and glucose transporter 4 (GLUT4), which are critical for maintaining neuronal glucose uptake and metabolism. Disruptions in these transporters contribute to insulin resistance in neurons, a hallmark of Alzheimer's disease. The restoration of these transporters suggests that tirzepatide may counteract hyperglycemia-induced neurodegeneration. These findings highlight tirzepatide's ability to modulate both molecular and epigenetic mechanisms implicated in neurodegenerative diseases (Fontanella et al. 2024).

A few studies in animal models of neurodegenerative diseases have also demonstrated the neuroprotective effects of tirzepatide. For example, in a rotenone-induced rat model of Parkinson's disease (PD), tirzepatide significantly prevented motor deficits, reduced oxidative stress, and alleviated neuroinflammation by inhibiting proinflammatory cytokines TNF-α and IL-6. Additionally, it upregulated striatal dopamine levels and reduced alpha-synuclein aggregation, a hallmark of PD pathology. These effects were found to be dose-dependent (Delvadia et al. 2025). Another study demonstrated the neuroprotective effects of tirzepatide in both APP/PS1 mice, a model of Alzheimer's disease, and in cell-based experiments (Yang et al. 2024). In APP/PS1 mice, tirzepatide modulated brain glucose metabolism, reduced amyloid-β (Aβ) accumulation, and attenuated neuroinflammation. It significantly decreased Aβ plaque deposition in the cortex, downregulated glial fibrillary acidic protein (GFAP) expression, and inhibited beta-secretase 1 (BACE1), suggesting a role in suppressing astrocyte reactivity and Aβ synthesis. Additionally, it reduced neuronal apoptosis and enhanced synaptic protein expression, particularly the glutamatergic synaptic subunits GluN2A and GluN2B in the hypothalamus, indicating potential benefits for synaptic function. Tirzepatide also lowered blood glucose levels and upregulated key metabolic genes, including GLUT1, hexokinase, glucose-6-phosphate dehydrogenase, and phosphofructokinase, thereby improving glucose transport and utilization (Yang et al. 2024). In cell culture models, tirzepatide protected neurons from Aβ-induced toxicity by mitigating oxidative stress, restoring mitochondrial membrane potential, and influencing ATP production in neurons and astrocytes. However, despite these biochemical changes that suggest enhanced neuronal resilience, tirzepatide did not improve cognitive function or alleviate anxiety-related behaviors in APP/PS1 mice (Yang et al. 2024). Given its ability to regulate systemic metabolism, inflammation, and mitochondrial function, tirzepatide holds promise as a potential therapeutic strategy for Alzheimer's disease, though further research is needed to fully understand its long-term efficacy and clinical applicability.

Conclusion

Tirzepatide, a dual GLP-1/GIP receptor agonist, has emerged as a promising therapeutic candidate not only for glycemic control in type 2 diabetes mellitus but also for neuroprotection. Preclinical studies suggest that tirzepatide exerts significant neuroprotective effects by reducing neuroinflammation, oxidative stress, and synaptic dysfunction while enhancing neurotrophic signaling. These mechanisms support its potential to mitigate cognitive decline and neurodegeneration associated with diabetes and other neurological disorders. Given the increasing prevalence of diabetes-related cognitive impairment and its association with neurodegenerative diseases, tirzepatide represents a potential disease-modifying intervention. However, while preclinical evidence is compelling, further clinical studies are necessary to confirm its efficacy in human populations and to explore its long-term benefits and safety. Future research should focus on elucidating the precise mechanisms underlying tirzepatide's neuroprotective properties and evaluating its therapeutic potential in patients at risk of neurodegenerative diseases.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Author contributions

Milen Hristov and Pavlina Andreeva-Gateva conceived the idea for the article. Milen Hristov, Gurjeet Cheema, and Heba Ali conducted the literature review, performed data analysis, and drafted the initial version of the manuscript. All authors critically revised the content and approved the final version of the manuscript.

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Data availability

All of the data that support the findings of this study are available in the main text.

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