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Review article

# Reducing Alzheimer's disease risk with SGLT2 inhibitors: From glycemic control to neuroprotection

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ABSTRACT

Recent research has established a strong link between metabolic abnormalities and an increased risk of dementia. In parallel, there is growing epidemiological evidence supporting the neuroprotective effects of antidiabetic medications against cognitive impairments. Among these, sodium-glucose co-transporter (SGLT2) inhibitors have emerged as pharmacological candidates with promising potential in alleviating the burden of age-related diseases, particularly neurodegenerative diseases (NDD). SGLT2 inhibitor therapies are FDA-approved medications routinely prescribed to manage diabetes. This novel class was initially developed to address cardiovascular disorders and to reduce the risk of hypoglycemia associated with insulin-secretagogue agents. It subsequently attracted growing interest for its beneficial effects on central nervous system (CNS) disorders. However, the molecular mechanisms through which these glucose-lowering therapies mitigate cognitive decline and limit the progression of certain brain degenerative diseases remain largely unexplored. Consequently, the neuroscientific community needs further studies that gather, analyze, and critically discuss the available mechanistic evidence regarding the neuroprotective effects of SGLT2 inhibitors. This review aims to critically examine the most relevant published findings, both *in vitro* and *in vivo*, as well as human studies evaluating the impact of SGLT2 inhibitors exposure on Alzheimer's disease (AD). It seeks to integrate the current understanding of their beneficial effects at the molecular level and their role in addressing the pathophysiology and neuropathology of AD. These insights will help extend our knowledge of how SGLT2 inhibitor therapies are associated with reduced risk of dementia and thus shed light on the link between diabetes and AD.

## 1. Introduction

Neurodegenerative diseases (NDD) are a group of chronic irreversible conditions that affect millions of people worldwide. Alzheimer's disease (AD) is the most prevalent NDD and the leading cause of dementia. This pathology is regarded as one of the most pressing epidemics of our time, characterized by progressive, extensive, and specific loss of distinct neuronal populations, leading to a gradual memory decline, language impairment, and reduced ability to perform daily activities (Verma and Howard, 2012; Smith et al., 2007). Recent publications, including the "2023 Alzheimer's Disease Facts and Figures" report (Anon, 2023), listed AD as the seventh-leading cause of death worldwide. In 2017, a new case of Alzheimer's dementia was recorded every 66 seconds, and this timing is expected to shorten to 33 seconds by 2050 (Frost et al., 2019). From an economic perspective, and according to recent estimates, the cost of dementia was projected to reach $345 billion in 2023 (Anon, 2023), and this number may increase as the prevalence of AD continues to grow. This silent epidemic, coupled with economic pressure, underscores the urgent need to develop new potential therapies that can prevent, slow, or even cure AD.

Type 2 diabetes (T2D) is a chronic, heterogeneous, and lifelong metabolic disease that is characterized by persistent hyperglycemia, insulin resistance, and insufficient insulin production. T2D is associated with obesity, atherosclerosis, and other metabolic dysfunctions (Poznyak et al., 2020; Esser et al., 2014). It is believed that insulin resistance, caused at least in part by an increased concentration of

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circulating free fatty acids (FFAs) (Roden et al., 1996), reduced secretion of adiponectin hormone (Gil-Campos et al., 2004), as well as persistent systemic inflammation (Xu et al., 2003), could directly drive the pathological development of T2D. This pathology is associated with low quality of life, co-morbidities, and mortality, particularly due to cardiovascular complications (Xu et al., 2003). In 2015, 415 million adults, which represents about 1 in 11 adults aged between 20–79 years, were diagnosed with T2D worldwide (Zheng et al., 2018). This health crisis is expected to grow in the future to affect about 642 million by 2040 (Zheng et al., 2018), posing thereby a growing global health threat. Genetic predisposition, suboptimal diet characterized by low intake of whole grains, fruits, non-starchy vegetables, and nuts, combined with high consumption of refined grains, red and processed meats, sugar-sweetened beverages, and fruit juice, as well as reduced physical activity, are recognized as risk factors contributing to the global rise in T2D.

Increasing evidence from pharmacological and epidemiological studies has clearly demonstrated that T2D and AD share several key pathological features, such as: (i) increased accumulation of amyloid-beta (Aβ) and Tau-deposits in the pancreas of patients with T2D (Miklossy et al., 2010; Stanciu et al., 2020); (ii) the brains of patients suffering from AD undergo impaired insulin and insulin-like growth factor expression (Steen et al., 2005); (iii) 30–40 % of elderly people affected with T2D experience learning difficulties and accelerated memory decline (Mastro et al., 2014; Munshi et al., 2006); (iv) the induction of hyperinsulinemia in patients suffering from AD dementia results in a significant improvement in memory ability (Craft et al., 1996). Conversely, a community-based controlled study following patients living with AD concluded that AD patients were associated with a higher risk of developing T2D (Janson et al., 2004).

This body of evidence, among others, suggests that AD may be a neuroendocrine disorder and has been referred to as type 3 diabetes in multiple studies (De Keyser et al., 2012; Michailidis et al., 2022). Therefore, further exploration of innovative pharmacological approaches, particularly those targeting hyperglycemia, could yield promising therapeutic outcomes. Additionally, these findings have opened the door to new interventions aimed at investigating novel pathways through the use of emerging classes of antidiabetic agents. In this perspective, sodium-glucose cotransporter-2 (SGLT2) inhibitors, a novel class of oral FDA-approved antidiabetic drugs, have emerged as potential candidates with neuroprotective properties (Pawlos et al., 2021). These therapies were first developed to address the hypoglycemia risk associated with insulin-secretagogue agents, as they can reduce hyperglycemia independently of insulin secretion. They are capable of inhibiting SGLT2 receptors at the proximal tubules of the kidney, promoting the urinary excretion of glucose, and thereby reducing blood glucose concentration. Numerous scientific studies have recently reported that these agents can reverse cognitive decline and provide a beneficial neuroprotective effect in T2D patients (Lardaro et al., 2024). Their neuroprotective impact can be primarily linked to the modulation of several pathological molecular risk factors, such as Tau-phosphorylation, Aβ-related neurotoxicity, brain oxidative stress, and neuroinflammation (Sim et al., 2023; Khan et al., 2021). Additionally, they may exert indirect effects by normalizing glycemic parameters. Moreover, given that SGLT2 inhibitors can easily cross the blood-brain barrier (BBB) and that SGLT receptors are expressed in various brain regions (Chiba et al., 2020), it is plausible that these drugs exert pleiotropic effects on the CNS.

The purpose of the present review is not to provide a comprehensive overview nor to endorse the neuroprotective properties of SGLT2 inhibitors. Rather, it aims to present a deep analysis of the mechanistic and molecular pathways targeted by these drugs, extending the neuroscientific community's understanding of how SGLT2 inhibitors reduce the risk of AD dementia.

## 2. History of SGLT2 inhibitors development

The historical development of SGLT2 inhibitors dates back to 1835, when two Belgian chemists Laurent-Guillaume De Koninck and Jean-Servais Stas extracted the phlorizin molecule from the apple tree. In 1886, glucosuric and antihyperglycemic properties were attributed to the phlorizin molecule (SGLT2inhibitors, 2016), and in 1962, it was demonstrated that phlorizin is a powerful competitive inhibitor of glucose active transport. Later (in 1987), a study demonstrated that the phlorizin molecule can reduce plasma glucose concentrations and improve insulin resistance. However, its development was halted due to poor absorption across the gastrointestinal barrier. This highlights the importance of exploring novel SGLT2 inhibitors molecules with better bioavailability. A few years later, efforts led to developing a new series of phlorizin derivatives. In 2000, Adachi and colleagues published their discovery of T-1095, a new renal $Na^+$-glucose transporter inhibitor (Pawlos et al., 2021). Eight years later, dapagliflozin (Dapa) was the first compound tested for specificity to SGLT2 receptors, followed by empagliflozin (Empa) in 2012. Both therapies successfully met the approval criteria set by the US Food and Drug Administration (FDA) and the European Medicines Agency between 2012 and 2015, paving the way for their commercialization as diabetes treatments Table 1.

## 3. β-pancreatic glucose sensing function and insulin secretion

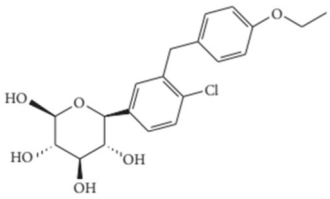
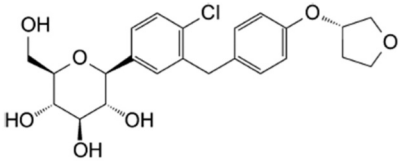
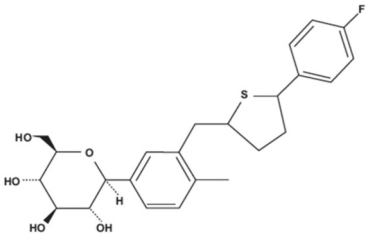
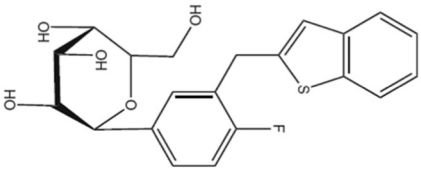
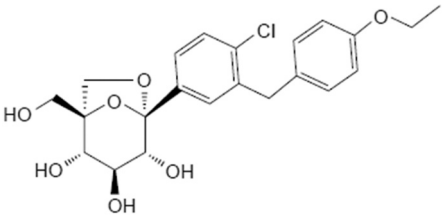
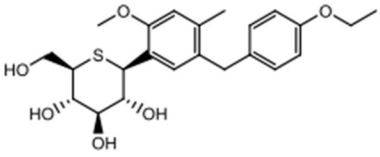
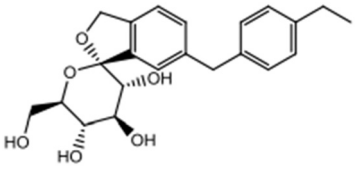
β-cells are sensitive to blood glucose changes and respond by releasing insulin. Under hyperglycemic conditions, pancreatic β-cells initiate glucose catabolism. This process involves a series of biochemical reactions, including glucose uptake, glycolysis, and mitochondrial respiration. The resulting ATP molecules increase the ATP/ADP ratio, leading to the closure of the ATP-sensitive potassium channel ($K_{ATP}$). This event induces the opening of the voltage-gated $Ca^{2+}$ channels (VG $Ca^{2+}$ channels), resulting in an elevated intracellular concentration of $Ca^{2+}$ (Fig. 1). This increase initiates a cascade of molecular events culminating in the exocytosis of insulin vesicles. Once secreted, insulin maintains plasma glucose concentration within a narrow range and mediates various anabolic effects, such as protein and glycogen synthesis. Insulin exerts its effects through two major signaling pathways. The first involves phosphatidylinositol 3-kinase (PI3K) activation, which promotes lipogenesis, proteogenesis, and glycogenesis. The second pathway, associated with mitogen-activated protein kinases (MAPK), regulates mitogenic processes such as cellular differentiation and gene expression (Fig. 2A). However, several pathological conditions, including excessive production of free fatty acids and chronic inflammation, can disturb this physiological regulation, leading to a chronic state of insulin resistance (Fig. 2B).

## 4. Glucose sensing mechanisms and SGLT receptors expression in the brain

Glucose is the primary energy substrate for the mammalian brain, and the CNS's function critically depends on its availability. Consequently, fluctuations in glucose levels, whether due to hyper- or hypoglycemia, can cause irreparable damage to neuronal cells, leading to permanent cellular loss. Therefore, maintaining blood glucose concentrations within physiological ranges is a vital biological process. To ensure this life-sustaining mechanism, the brain is endowed with glucose-sensing neurons capable of detecting, integrating, and regulating changes in glucose level via appropriate compensatory hormonal responses.

Different brain parts were reported to contain this type of "sensing neurons", particularly in the hypothalamus (Burdakov et al., 2005) and the brain stem (Maekawa et al., 2000). In the hypothalamic region, the arcuate nucleus (ARN) is considered one of the major glucose sensing sites. However, other brain regions are also recognized as important monitoring centers of glucose metabolism, and are also capable of

**Table 1**
Chemical structure of Giflozins.

| Molecule | Chemical structure | Ref |
|---|---|---|
| Dapagliflozin |  | (De Meira et al., 2017) |
| Empagliflozin |  | (McGill, 2014) |
| Canagliflozin |  | (Salvatore et al., 2011) |
| Ipragliflozin |  | (Poole and Dungo, 2014) |
| Ertugliflozin |  | (Kao and Parulekar, 2019) |
| Luseogliflozin |  | (Haider et al., 2019) |
| Tofogliflozin |  | (Haider et al., 2019) |

influencing feeding and energy consumption. In the ARN, there are two distinct populations of glucose-sensing neurons (Burdakov et al., 2005; Melnick et al., 2011): "Glucose-Excited" neurons (GEN) and "Glucose-inhibited" neurons (GIN) (ANAND et al., 1964; Oomura and Yoshimatsu, 1984). These specific neurons are highly sensitive to glucose changes and can initiate many regulatory biological processes to keep glucose levels at normal concentrations. Mechanistically, circulating glucose can cross BBB to reach the neuronal microenvironment via GLUT1 (Patching, 2017). Once it enters the brain, it can activate GEN in the ARN (Routh, 2010; Wang et al., 2004), promoting a series of catabolic and hormonal responses similar to those employed by pancreatic β-cells. These glycolytic and catabolic reactions give rise to pyruvate molecules, which then undergo further degradative reactions through mitochondrial respiration, leading to the synthesis of ATP, the only energy currency of the cell, which accumulates in the cytosol, increasing the ATP/ADP ratio.

The altered energetic state of GEN neurons acts upstream of critical neuropeptidergic pathways in the ARN, notably influencing the activity

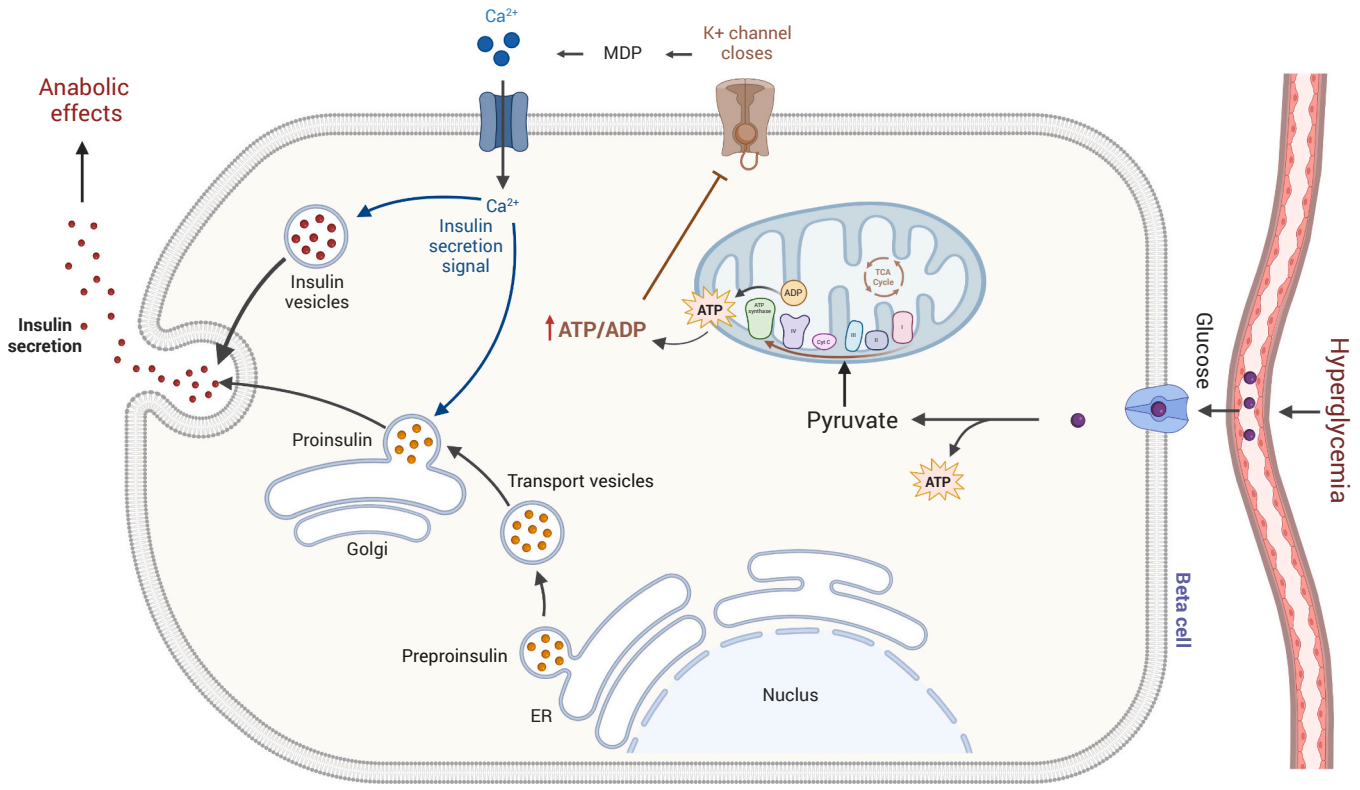



**Fig. 1.** Glucose-sensing and insulin secretion mechanism in pancreatic β-cells (islets of Langerhans). The Fig. 1 illustrates key intracellular events following glucose uptake, including ATP generation, modulation of ion channels, and insulin granule exocytosis. Mechanistically, mitochondrial ATP production increases ATP/ADP ratio, triggering the closure of ATP-sensitive $K^+$ channels, membrane depolarization, and opening of voltage-gated $Ca^{2+}$ channels. The resulting $Ca^{2+}$ influx activates insulin vesicle trafficking and release. The endoplasmic reticulum (ER) and Golgi apparatus are involved in proinsulin processing and insulin packaging. Released insulin exerts anabolic effects in peripheral tissues. **Abbreviations:** MDP: membrane depolarization; ATP: adenosine triphosphate; ADP: adenosine diphosphate; ER: endoplasmic reticulum; VG $Ca^{2+}$ channel: voltage-gated calcium channel; $K_{ATP}$ channel: ATP-sensitive potassium channel.

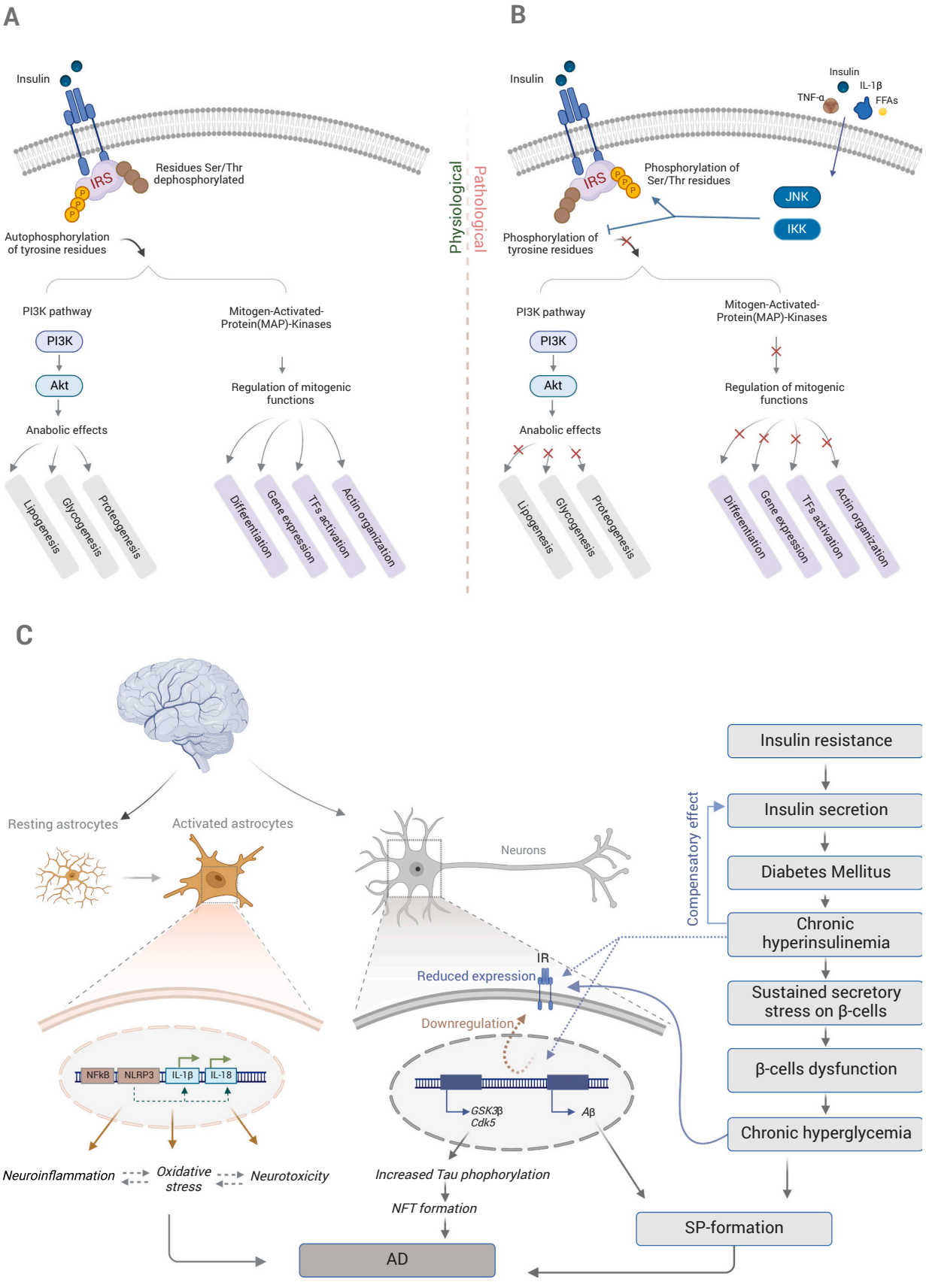
of pro-opiomelanocortin (POMC) neurons, which are central to appetite and metabolic control. Increased ATP levels within glucose-excited POMC neurons lead to the secretion of alpha-melanocyte-stimulating hormone (α-MSH) (Frihauf et al., 2010). This hormone binds directly to melanocortin receptors to exert its anorexigenic effects, leading to rapid caloric regulation. Conversely, under hypoglycemic conditions, glucose-inhibited (GIN) neurons, namely NPY/AgRP neurons, are activated and release neuropeptide Y (NPY) and agouti-related peptide (AgRP) (Nijenhuis et al., 2001). AgRP acts as an inverse agonist at the melanocortin receptors, resulting in the direct inhibition of α-MSH and stimulating feeding behavior (Nijenhuis et al., 2001).

SGLT receptors are expressed in multiple brain areas (Yu et al., 2010; Wright et al., 2011; Poppe et al., 1997; O'Malley et al., 2006), potentially influencing feeding behavior. For instance, the intra-cerebroventricular administration of phlorizin resulted in a significant increase in food intake (Tsujii and Bray, 1990), suggesting their role in glucose-responding systems. However, other SGLT2 inhibitors have the opposite effect on food intake. According to Neeland *et al.*, the SGLT2 inhibitor empagiflozin may reduce body weight (Neeland et al., 2016). Similarly, a 24-week randomized, placebo-controlled, phase II trial by Lundkvist and colleagues found that Dapa reduced body weight compared to placebo-treated participants (Lundkvist et al., 2017) and was proposed as an emerging treatment for obesity (Pereira and Eriksson, 2019). This outcome is thought to be related to caloric loss through glucose excretion in urine. SGLT2 receptors mediate the bidirectional transport of glucose and $Na^{2+}$ in the brain, modulating neuronal electrical activity. This is closely associated with the opening of voltage-gated calcium channels (VGCCs), which may have functional consequences for neuronal sensing and responsiveness.

## 5. Brain insulin resistance and antidiabetic agents

For many decades, the brain was considered an insulin-insensitive organ (Hasselbalch et al., 1999; Hom et al., 1984). However, progress in research has rendered this idea outdated, as cumulative outcomes have now confirmed the presence of insulin in some brain regions (Baskin et al., 1983; Havrankova et al., 1978), along with its various neuromodulatory actions in the CNS (Duarte et al., 2012). This particularly includes insulin bioeffects on neuronal metabolism by enhancing GLUT transporters expression (Havrankova et al., 1978; Ramnanan et al., 2013). In addition, insulin has neuropsychiatric effects, including improvements in memory function (Benedict et al., 2007), enhancement of learning processes (Zhao and Alkon, 2001), and increased attention (Craft, 2009). Furthermore, insulin has been shown to exert neuroprotective effects by reducing Aβ-induced neurotoxicity (Craft, 2009) and pTau-induced Tau pathology, improving synaptic plasticity (Ferrario and Reagan, 2018) and reducing neuroinflammation (Bortoluzzi Canteiro et al., 2019) and brain oxidative stress (Bortoluzzi Canteiro et al., 2019). Therefore, a reduced brain insulin sensitivity can result in multiple brain dysregulations, contributing to a progressive decline in cognitive functions (Fig. 2C).

Such circumstances are observed in the brains of patients with T2D who have ineffective insulin signaling. The development of insulin resistance increases susceptibility to neuronal loss and exacerbates AD via multiple patho-mechanisms: (i) it enhances amyloidopathies and Tau-pathology (Salkovic-Petrisic et al., 2009; Mullins et al., 2017); (ii) it reduces neuronal outgrowth and promotes cell death, contributing to impaired neural connectivity and the progression of neurodegeneration (Song et al., 2015); (iii) it compromises mitochondrial functioning and alters autophagy phenomenon (Galizzi et al., 2021), as well as (iv)




(caption on next page)

**Fig. 2.** Insulin signalling pathways in physiological and pathological conditions and its role in brain Homeostasis and Neurodegeneration. (A): Represent the insulin signalling pathway under physiological conditions. (B): Illustrates the alteration of insulin signalling pathway in pathological circumstances. In physiological state (A), insulin bind directly to insulin-receptors. These receptors possess tyrosine kinase activity, leading to the autophosphorylation of tyrosine residues on substrate proteins, known as Insulin Receptor Substrate (IRS). After phosphorylation, two pathways can be activated. The first is the phosphatidylinositol-3-kinase pathway, which stimulates the PI3K-Akt/PkB cascade to induce a multitude of anabolic effects, such as lipogenesis, gluconeogenesis, and proteogenesis. The second pathway is the mitogen-activated protein (MAP)-kinase pathway, which regulates mitogenic functions, including, differentiation, actin organization, transcriptional factors activation, and gene expression. These pathways can be altered in pathological situations (B). Dysregulation of insulin signaling is thought to be triggered by excess circulating free fatty acids, certain pro-inflammatory mediators (TNF-α and IL-1β), and even insulin itself. These molecules act by phosphorylating the Ser/Thr residues of the IRS, mediated by IKK-β or JNK-MAP-kinase, which block insulin signal transduction and limit the previously physiological mentioned effects of insulin. **(C):** Represents the involvement of insulin resistance/hyperglycemia/T2D in brain dyshomeostasis. Indeed, chronic hyperglycemia can reduce brain GLUT expression, activate Tau-kinases (GSK3-β and CdK5), and activate microglia, leading to increased neuroinflammation and oxidative stress. These events progressively alter brain homeostasis contributing to chronic NDD development, including AD.

increases oxidative stress (Maciejczyk et al., 2019) and the release of proinflammatory cytokines in the CNS (Vinuesa et al., 2021). Moreover, it (v) reduces hippocampal plasticity (Spinelli et al., 2019), and influences other factors contributing to brain degeneration. Consequently, enhancing insulin sensitivity can be considered as a promising pharmacological approach to mitigate the cognitive impairment associated with AD.

To this end, several antidiabetic agents, including SGLT2 inhibitors, have been tested for their neuroprotective potential (Pawlos et al., 2021; Khan et al., 2021). Studies have shown that SGLT2 inhibitors can improve brain insulin resistance and ameliorate cognitive impairment *in vivo (*Sa-nguanmoo et al., 2017*)*. These findings have been translated into a clinical setting. For instance, a randomized, double-blind, placebo-controlled, phase 2 trial conducted by Kullmann and colleagues found that patients treated with Empa (25 mg/day) experienced reduced hypothalamic insulin resistance after 8 weeks compared to the placebo group (Kullmann et al., 2022). SGLT2 inhibitors are undergoing extensive investigation for possible therapeutic effects on central regulation, extending beyond their previously studied roles in T2D, cardiovascular, and kidney diseases.

All this evidence supports the pathological involvement of brain insulin resistance in neurodegeneration and highlights the protective effects of antidiabetic medication. In particular, it underscores the potential of SGLT2 inhibitors in mitigating this age-associated cognitive abnormality.

## 6. SGLT2 inhibitors and glycemic control

SGLT2 inhibitors are hypoglycemic drugs that target SGLT2 receptors, the primary glucose transporters in the kidney. These receptors are responsible for approximately 90 percent of glucose reabsorption from primary urine (Scheen, 2015). The SGLT2 proteins, encoded by SLC5A2 gene (Abdul-Ghani et al., 2011), are primarily located in the kidney's proximal tubule. While SGLT2 is mainly expressed in the kidney, SGLT1 is primarily expressed in the intestine (Vallon and Thomson, 2017; Ferrannini and Solini, 2012). SGLT1 transports two $Na^+$ ions with one D-glucose molecule, whereas SGLT2 transports one $Na^+$ ion with one D-glucose molecule (Wright et al., 2011). Studies have shown that SGLT2 inhibition leads to negative caloric balance and weight loss (Bolinder et al., 2012). So far, several derivatives have been developed from phlorizin, the first natural SGLT2 inhibitor, which was never clinically used as an anti-hyperglycemic agent due to poor bioavailability. Some examples of SGLT2 inhibitors include empagliflozin, dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin, luseogliflozin and ertugliflozin.

Four of them (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) are approved by the FDA and the European Union (Fediuk et al., 2020; Ni et al., 2020). Additionally, ipragliflozin, tofogliflozin, and luseogliflozin have been approved in Japan (Poole and Dungo, 2014; Markham and Elkinson, 2014). Beyond their structural differences, these inhibitors exhibit varying selectivity for SGLT1 and SGLT2 (Liu et al., 2021). Specifically, dapagliflozin, empagliflozin, and ertugliflozin are the most selective inhibitors for SGLT2, whereas canagliflozin has the highest potential to inhibit SGLT1 receptors (Malhotra et al., 2015). Sotagliflozin, known for its high affinity for SGLT1 receptors, is often referred to as a "dual SGLT1/SGLT2 inhibitor". However, as the most recent addition to the class of flozins, it has not yet been widely adopted for use among diabetic patients (Bhatt et al., 2021).

In patients with T2D, SGLT2 inhibitors increase glucose excretion and osmotic diuresis without significantly activating the Renin–Angiotensin–Aldosterone System (RAAS). This may be due to sympathetic inhibition through an unknown pathway. Studies in diabetic rats have shown that SGLT2 inhibitors reduce oxygen and ATP consumption by proximal tubular cells, alleviating renal cortical hypoxia and reversing interstitial changes in the renal cortex, ultimately improving kidney structure and function (Hesp et al., 2020). As a result, SGLT2 inhibitors can be combined with other oral glucose-lowering medications and insulin to enhance their blood sugar-lowering effects. This combination therapy provides an additional mechanism of action, contributing to better control of blood glucose levels in patients with T2D (Ferrannini and Solini, 2012).

## 7. SGLT2 inhibitors in neurodegeneration

In the last decade, compelling preclinical and clinical evidence has emerged supporting that SGLT2 inhibitors can exert neuroprotective effects, extending their normoglycemic impact. Indeed, these inhibitors have shown their ability to modulate several pathways involved in brain degeneration directly (Abdel-latif et al., 2020) and subsequently attracted significant interest, especially among research groups working on Alzheimer's pathology. For example, Empa (1 and 10 mg/kg/day), a powerful SGLT2 inhibitor, has demonstrated significant efficacy in reducing neuronal apoptosis in male Wistar rats subjected to global cerebral I/R injury. Treatment with Empa resulted in a dose-dependent reduction in infarct size and improvement of neurobehavioral alterations (Abdel-latif et al., 2020). Empa was also reported to prevent streptozotocin-induced neuronal injury, ameliorate brain histopathological changes, and reduce cerebral infarct volume, oxidative stress, inflammation, and apoptotic markers in hyperglycemic I/R-injured rats (Amin et al., 2020).

Similarly, Dapa, another SGLT2 inhibitor, has been recognized as a promising neuromodulatory therapy. According to Sa-nguanmoo et al. (2017) short-term administration of Dapa (1 mg/kg/day) significantly improved several pathological risk factors involved in neuronal degeneration, such as ROS production, B-cell lymphoma-2 protein (Bcl-2), and nuclear factor-kappa B (NFκB) expression. Additionally, Dapa improved the insulin signaling cascade, brain mitochondrial functioning, and hippocampal synaptic plasticity.

Moreover, Dapa increased p-GSK-3β-(Ser9)/total GSK-3β ratio, enhanced beclin-1 levels, improved the p-AMPK/total AMPK ratio, and improved hippocampal Bcl-2 levels. It also reduced pro-apoptotic markers in the hippocampus and stimulated the antioxidant response by increasing nuclear factor erythroid-2-related factor-2 (Nrf2), heme oxygenase-1 (HO-1) and glutathione peroxidase (GPx) (Arab et al., 2023). Furthermore, recent *in vivo* evidence from Samman and colleagues indicates that Dapa therapy (1–5 mg/Kg/day) resulted in a

noticeable improvement in cognitive performance, acquisition, and the endogenous antioxidant system, including enhanced activities of catalase, superoxide dismutase (SOD), and glutathione (GSH). The treatment also reduced markers of hippocampal degenerative changes, depressive behavior, AChE activity, Aβ production, and MDA level.

Canagliflozin has also been shown to mitigate cognitive impairments in streptozotocin-induced sporadic AD (Khamies et al., 2024). This benefit appears to be related to the anti-neuroinflammatory and antioxidant activities of canagliflozin, possibly through the p-AMPK/SIRT-1 pathway (Khamies et al., 2024). Similarly, data from the Khedr study indicate that canagliflozin might exert anti-inflammatory and neuroprotective actions via TRY/KYN and AMPK/mTOR signaling pathways (Khedr et al., 2023). In another study, canagliflozin (10 mg/kg/day) demonstrated the ability to ameliorate cisplatin-induced cerebral cortex injury (Hassanein et al., 2023). The results indicated reduced oxidative stress, increased levels of enzymatic antioxidant defences, and suppression of cisplatin-induced cortical JNK/AP-1 signal in treated rats compared to the control group (Hassanein et al., 2023).

In line with this, recent findings indicate that treatment with Eurthygliflozin (5 mg/kg and 10 mg/kg/day) can mitigate cognitive deficit in male Wistar rats subjected to intra-cerebroventricular injection of streptozotocin (Pang et al., 2023). The authors also observed suppression of hippocampal AChE activity, expression of pro-apoptotic markers, and mitochondrial dysfunction. One of the most significant findings in this study was that Eurthygliflozin reduced Tau-pathology, as evidenced by a decrease in Tau-hyperphosphorylation in the hippocampal region (Pang et al., 2023).

Similarly, recent evidence from Abd Elmaaboud et al. (2023) highlighted the corrective capacity of short-term Dapa treatment (1 mg/kg/day) of several cellular alterations in a rat model of AD. The *in vivo* outcomes suggest that Dapa can reduce MDA and NFκB, while downregulating NLRP3-inflammasome, IL-18, TGF-β1, IL-1β, TLR4, and LC3-II expression. Additionally, Dapa decreased the expression of caspase 3 and 9 (Abd Elmaaboud et al., 2023). Moreover, Dapa increased total antioxidant capacity and SOD activity. Previously, Arab and colleagues showed that Dapa can mitigate cognitive dysfunction in cadmium-intoxicated rats (Arab et al., 2023). Their results indicate that Dapa (1 mg/kg/day) alleviated the cadmium-evoked cognitive deficits, improved spatial memory retention, and mitigated hippocampal histomorphological abnormalities. It also downregulated p-Tau and limited $A\beta_{1-42}$ peptide formation while upregulating p-GSK-3β, the inactive form of GSK-3β, an upstream effector of p-Tau. Furthermore, Dapa reduced microglial infiltration and pyknosis Fig. 3.

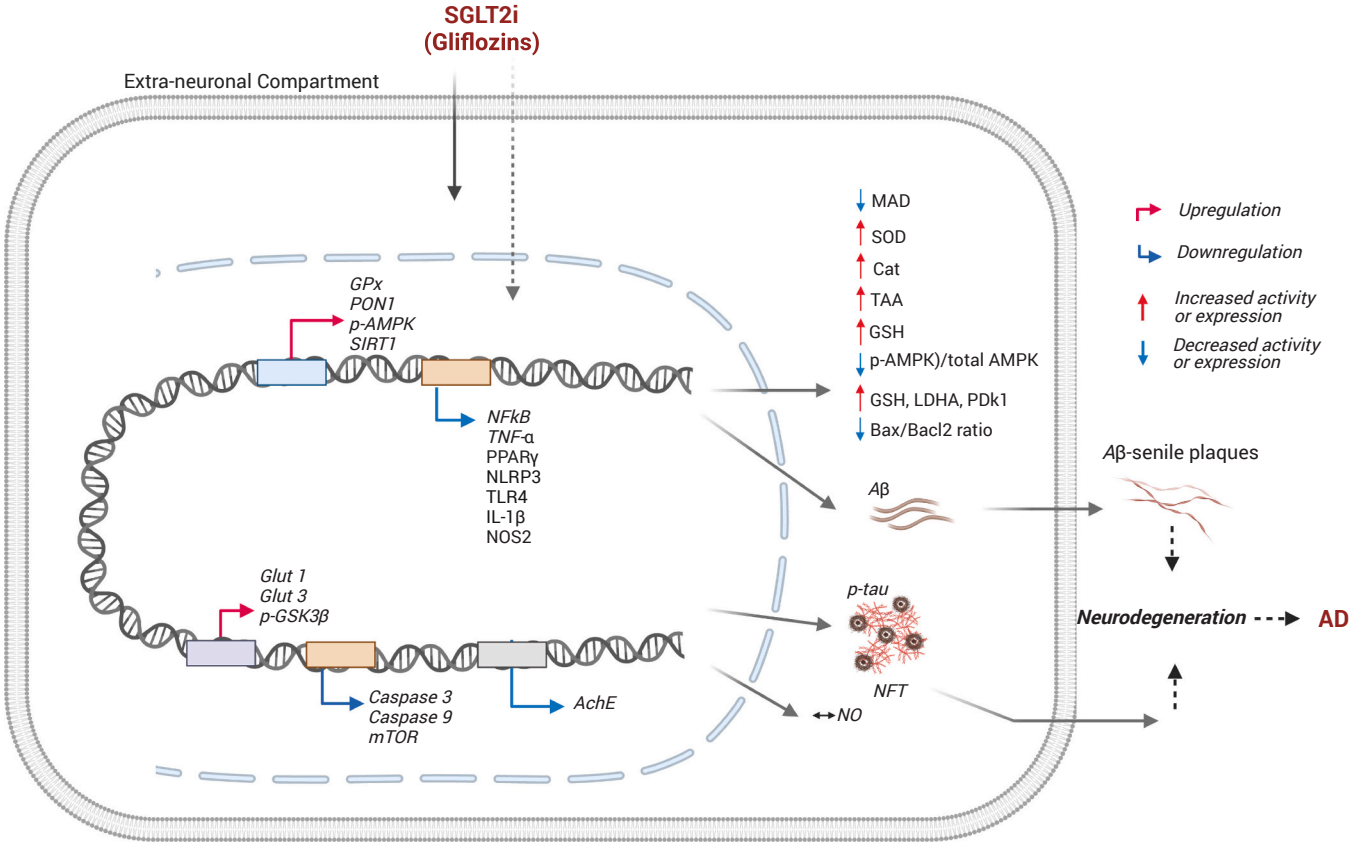



**Fig. 3.** SGLT2 inhibitors molecular modulation of the main pathological events involved in AD. SGLT2 inhibitors modulate key molecular pathways involved in Alzheimer's disease. *In-vivo* and *in-vitro* evidence shows that gliflozins modulate the expression of genes involved in several pathological events associated with AD. They activate AMPK signaling, enhance antioxidant defenses (e.g., SOD, CAT, GSH), and reduce oxidative stress and inflammation (e.g., NF-κB, TNF-α, IL-1β, NLRP3). They also regulate apoptosis by decreasing caspase-3 and Bax/Bcl-2 ratio, and improving mitochondrial functioning. Subsequently, SGLT2 inhibitors reduce Tau-hyperphosphorylation and Aβ production, contributing to reduced neuronal damage, limiting plaque formation, and attenuating neurodegeneration. Abbreviation: SIRT1: silent-information-regulated transcription factor 1; SOD: superoxide dismutase; p-AMPK: phospho-AMP-activated protein kinase; BCAE1: beta-site amyloid precursor protein cleaving enzyme 1; PPAR-γ: peroxisome proliferator-activated receptor gamma; ACh-E: acetylcholinesterase; NFκB: nuclear factor-kappa B; mTOR: mechanistic target of rapamycin; Glut: glucose transporters; GPx: glutathione peroxidase; p-Tau: phospho-Tau protein; NFT: neurofibrillary tangles; Aβ: amyloid beta; GSK-3β: glycogen synthase kinase 3 beta; NO: nitric oxide; Nos2: Nitric oxide synthase 2; TNF-α: tumor necrosis factor; Cat: catalase; NLRP3: NOD-like receptor family pyrin domain containing 3; IL-1β: interleukin-1 beta; IL10: interleukin-10; PON1: paraoxonase 1; PDK1: pyruvate dehydrogenase kinase 1; LDH-A: lactate dehydrogenase A; MDA: malondialdehyde; TAA: total antioxidant capacity; Bcl2: B-cell lymphoma-2; Bax: Bcl-2 associated X-protein; TLR4: Toll-like receptor 4.

## 8. SGLT2 inhibitors: a novel approach to reduce Alzheimer's disease risk in T2D

While the effectiveness of FDA-approved drugs for AD is still limited, AChE inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists remain the primary treatment options for patients (Wiciński et al., 2020). Shaikh et al. (2016) explored the molecular interactions between AChE and SGLT2 with Dapa. They concluded that Dapa might be a potent dual inhibitor of SGLT2 and AChE (Shaikh et al., 2016). Similar results were observed with ertugliflozin and sotagliflozin (Rizvi et al., 2014; Shakil, 2017). Besides previous mechanisms, other studies have revealed that SGLT inhibition may be involved in the process of Aβ plaque formation and neurofibrillary tangles (NFTs), which arise from the aberrant aggregation of hyperphosphorylated Tau proteins following their detachment from microtubules, ultimately leading to cytoskeletal disruption and neuronal dysfunction (Holtzman et al., 2011; Medina and Avila, 2014).

Moreover, Empa treatment effectively maintained insulin levels in diabetic mice while reducing cortical thinning, neuronal loss, haemorrhage, microglial burden, and accumulation of senile plaques. These effects were associated with enhanced cognitive function in treated APP/PS1xdb/db mice (Carranza-Naval et al., 2021). For instance, Ni *et al.,* showed that SGLT2 inhibitor treatment in T2D patients not only increased glucose elimination but also improved insulin secretion by β-cells and enhanced peripheral insulin sensitivity (Ni et al., 2020). This is particularly notable given that previous studies have shown that a decline in brain glucose metabolism can occur more than 10 years before the onset of AD symptoms (Butterfield and Halliwell, 2019). Additionally, cognitive functions gradually deteriorate in diabetic patients, a decline that may be ameliorated by intranasal insulin administration (Craft et al., 2000; Benedict et al., 2004).

In the brain, the insulin/p-IRS/PI3K/Akt signaling pathway promotes the growth of nerve fibers and the formation of synapses by increasing the levels of BDNF and postsynaptic density protein 95 (PSD-95). Abnormal insulin signaling through the PI3K/Akt/GSK3-β pathway contributes to AD and T2D. This dysfunction activates the GSK3-β pathway, leading to hyperphosphorylation of Tau proteins and the formation of NFTs, a hallmark of AD. Additionally, impaired function of the insulin-degrading enzyme (IDE) disrupts the clearance of insulin and Aβ, further linking insulin resistance to both AD and T2D. Furthermore, insulin receptor substrate 1 (IRS1) disruption adversely affects insulin and IGF-1 signalling, exacerbating both conditions (Sim et al., 2021).

Research has shown that BDNF increases synaptic plasticity through CaMKII, synaptophysin and PSD-95 (Lee et al., 2005; GROWTH, 1991). In conditions of insulin resistance, microglia and astrocytes remain activated and release proinflammatory cytokines, which reduce BDNF levels (Schur et al., 2015; Prakash and Kumar, 2014; Lull and Block, 2010). Therefore, these findings suggest that SGLT2 inhibitors can decrease hyperglycemia while reducing insulin resistance through elucidated mechanisms. Further research is needed to elucidate the various effects and pathways influenced by SGLT2 inhibitors.

Low concentrations of arginine and citrulline have been reported in AD (Martínez-González et al., 2021; Ibáñez et al., 2012). One study showed that citrulline supplementation in mice with AD increased arginine levels in the cerebrospinal fluid and significantly improved spatial memory (Martínez-González et al., 2021). Another study demonstrated that receiving citrulline supplements for 3 months can attenuate age-related alterations in hippocampus rafts, restoring a structural profile resembling that of young animals.

It has also been reported that all citrulline-treated rats demonstrated low levels of amyloid precursor protein (APP) and low levels of C99-APP-Cter, the first-step fragment of amyloidogenic APP (Marquet-De Rougé et al., 2013). Current investigations on Empa showed that after 12 weeks of Empagliflozin administration, it increased plasma levels of citrulline, histidine, and α-aminobutyric acid in patients with T2D (Jojima et al., 2024). Therefore, another possible mechanism for Empa might be modifying plasma amino acid concentrations. However, some studies have failed to demonstrate any changes in arginine levels in patients with AD (Mulder et al., 2002). Moreover, citrulline is a precursor to L-arginine, which is converted into nitric oxide (NO) by the action of endothelial nitric oxide synthase (eNOS) (Lorin et al., 2014). While a deficiency of endothelial-derived NO has been associated with neurodegenerative processes, such as endothelial dysfunction, impaired synaptic plasticity, and increased amyloid accumulation, its role in inflammation remains complex and context-dependent. Some studies report that reduced NO bioavailability may indirectly contribute to neuroinflammation by impairing vascular and immune regulation (Katusic and Austin, 2014). However, other evidence suggests that excessive or dysregulated NO production, particularly from inducible NOS (iNOS), can directly promote neuroinflammation and oxidative stress in the later stages of AD (Dubey et al., 2018; Liy et al., 2021). These findings suggest a potential dual role for NO in AD pathophysiology, possibly varying with disease stage.

In summary, while exploring SGLT2 inhibitors as a potential therapeutic option for T2D is relatively new, the evidence suggests promising outcomes. At the central level, pre-clinical studies indicate that SGLT2 inhibitors can reduce neuroinflammation, enhance synaptic plasticity, and promote neuronal survival through various direct and indirect mechanisms. Clinical studies have also linked SGLT2 inhibitors use to a reduced risk of dementia in older individuals with T2D. However, more research is needed to fully understand the underlying mechanisms of SGLT2i in AD and assess their long-term safety and efficacy in humans.

## 9. Link between the use of SGLT2 inhibitors and neuroprotection in T2D

T2D is associated with an increased risk of cognitive dysfunction, often impacting multiple cognitive domains (Casagrande et al., 2021). Although the underlying mechanisms in patients with T2D are not yet fully understood, a combination of vascular and neurodegenerative damage has been proposed (Cholerton et al., 2016). Factors such as defects in insulin receptor sensitivity, brain inflammation, mitochondrial metabolism and oxidative stress contribute to the process (Maciejczyk et al., 2019; Milstein and Ferris, 2021; Sergi et al., 2019). Particularly, brain regions where SGLT receptors are present are known to be involved in learning, food intake, energy and glucose homeostasis, as well as central cardiovascular and autonomic regulation (Nguyen et al., 2020; Gaur et al., 2014). This suggests that SGLT receptors could serve as potential therapeutic targets not only in T2D but also in neurodegenerative diseases. On the one hand, fluctuations in blood sugar levels have been reported to impact cognitive function (Srikanth et al., 2020).

On the other hand, the presence of SGLT receptors in mammalian CNS has been reported (Yu et al., 2013). For instance, the SGLT1 receptor is discovered in areas like CA1, CA3 (regions 1 and 3 of hippocampal cornu ammonia), and the dentate gyrus hippocampal subfields. At the same time, high expression of SGLT2 has been identified in the hippocampus, cerebellum, and BBB endothelial cells (Poppe et al., 1997; Jurcovicova, 2014; Enerson and Drewes, 2006; Shah et al., 2012). SGLT2 inhibitors are lipid-soluble, enabling them to cross the BBB and reach the brain. The concentration of these drugs in the brain relative to the blood varies, with Dapagliflozin showing a ratio of 0.3, while Empagliflozin has a ratio of 0.5 (Gyimesi et al., 2020). A preclinical study published by Khan et al. (2021) demonstrated that Empagliflozin Canagliflozin mitigates cognitive decline, inflammatory process and oxidative stress in high fructose diet-induced hyperglycemic mice. This effect may be attributed to reduced cerebral NADPH oxidase and superoxide levels, attributing to Empa the potential to attenuate oxidative stress in the brain (Lin et al., 2014).

Recent studies have shown that the expression of SGLT1 in the brain is higher than SGLT2, yet both SGLT1 and SGLT2 are co-expressed in several regions of CNS (Bhatt et al., 2021). It is now established that

glucose uptake into neurons can occur not only via glucose transporter (GLUT), particularly GLUT3 (Dakic et al., 2019), but also through SGLT receptors (Navale and Paranjape, 2016). Unlike GLUT transporters, which facilitate glucose transport into cells (Holman, 2020), SGLT receptors modulate their activity in response to fluctuation in extracellular glucose level, effectively acting as glucose sensors that utilize transmembrane sodium gradient (Gyimesi et al., 2020). Consequently, SGLTs can also be considered "electrogenic" proteins (Ferrannini, 2017).

SGLTs may play a crucial role in neuronal survival, especially under conditions of low glucose availability or during anoxia, such as in stroke or ischemia, when there is a notable increase in SGLT1 and SGLT2 expression (Koekkoek et al., 2017). A study conducted in a murine model suggests that inhibiting SGLT1 following brain injury could yield beneficial effects on the area of the brain lesions, the volume of damaged tissue, oedema, and motoric disability (Sebastiani et al., 2018). However, these protective effects of SGLT2 inhibitors after acute ischemic stroke remain unclear (Al Hamed and Elewa, 2020). In murine models for epilepsy, Erdogan et al. (2018) demonstrated that SGLT2 inhibitors may reduce glucose uptake by neurons, thereby lowering their membrane excitability and reducing depolarization. Notably, Dapgliflozina significantly decreased both clinical and electro-encephalographic manifestations of brain seizure activity, which might be similar to the effects of a ketogenic diet that can improve brain seizure activity (Szekeres et al., 2021). Even in rat models of Parkinson's disease (PD), the potential neuroprotective effects of SGLT2 inhibitors were observed (Arab et al., 2021). Particularly, Dapagliflozin reduced neuronal oxidative stress by lowering lipid peroxide, which helped restore the disturbed DJ-1/Nrf2 pathway. In addition, it decreased neuron damage caused by oxidative stress and increased the production of glial cell-derived neurotrophic factor (GDNF) along with activating its related PI3K/AKT/GSK-3β pathway. It also lowered neuroinflammation by blocking the activation of the NF-κB pathway and reducing TNF-α level. In obese rats fed a high-fat diet, Dapagliflozin demonstrated anti-inflammatory and antioxidant effects and improved brain mitochondrial functioning (Arab et al., 2021). The beneficial effects of Empagliflozin, canagliflozin, ertugliflozin and Dapagliflozin on the inflammatory profile in diabetic patients have also been reported (Mancinetti et al., 2023).

SGLT2 inhibitors have also shown other effects, such as reducing cholinergic neurons' activity (Shaikh et al., 2016), the accumulation of Aβ, and intraneuronal formation of NFTs, and mTOR hyperactivation (Rizzo et al., 2022). Hyperactivation of the mTOR pathway in mice is associated with increased amyloid plaque formation, hyperphosphorylation of Tau proteins, and reduced BBB selectivity (Stanciu et al., 2021).

Emerging evidence suggests that SGLT2 inhibitors may also affect the composition of cerebrospinal fluid (CSF), which plays a role in the pathology of neurodegenerative disorders (Pearson et al., 2020). Notably, the expression of SGLT2 protein has been observed in the choroid plexus epithelial cells and ependymal cells of the human brain (Chiba et al., 2020). In a randomized controlled trial, elderly patients with T2D were assigned to either SGLT2 inhibitors or an incretin therapy group for 12 months. There was no statistically significant change in cognitive performance in either group compared to baseline or between the groups (Perna et al., 2018). In addition, an association between the use of SGLT2 inhibitors and lower risks of dementia, PD and cerebrovascular mortality has been seen compared with dipeptidyl peptidase-4 inhibitors (DPP4I) in patients with T2D (Mui et al., 2021). Despite these findings, further studies are necessary to elucidate the specific effects of SGLT2 inhibitors on neuronal functions in this population Tables 2 and 3.

## 10. Conclusions and future directions

SGLT2 inhibitors, particularly Empa and Dapa, demonstrate potential in slowing the progression of neurodegenerative processes, and could serve as candidates for repurposing studies, especially for diseases like AD which currently lacks effective treatments. Some of these drugs

**Table 2**
Summary of major human studies reporting the beneficial bioeffects of SGLT2 inhibitors.

| CTI or trial registration | population | Total participants | SGLT2 inhibitors | Dose and period of treatment | Findings | Ref |
|---|---|---|---|---|---|---|
| NCT01958671 | T2D patients | 461 participants | Ertugliflozin | 5 or 15 mg/day; 52 weeks | ↓ Fasting plasma glucose; ↓ body weight; ↓ systolic blood pressure; ↑ genital mycotic infections. | (Aronson et al., 2018) |
| NCT01177813 | T2D patients | 228 patients | Empagliflozin | 10–25 mg/day; 24 weeks | ↓ HbA1c; ↓ systolic blood pressure; ↓ diastolic blood pressure. | (Roden et al., 2013) |
| NCT01131676 | T2D patients with kidney disease | 4124 patients | Empagliflozin | 10–25 mg/day | ↓ Progression of kidney disease; ↓ rates of clinically relevant renal events. | (Wanner et al., 2016) |
| NCT01131676 | T2D patients | 4687 patients | Empagliflozin | 10–25 mg/day | ↔ Myocardial infarction; ↔ stroke; ↓ cardiovascular death; ↓ hospitalization for heart failure; ↑ genital infection. | (Steiner, 2016) |
| | Patients with metabolic syndrome | 12 patients | Dapagliflozin | 10 mg/day; for 90 days | ↓ Body weight; ↓ BMI; ↓ waist circumference; ↓ total cholesterol; ↓ triglycerides; ↓ total insulin secretion. | (González-Ortiz et al., 2018) |
| UMIN000021552 | T2D patients | 51 patients | Empagliflozin | 10 mg/day; 1 year | ↓ BMI; ↓ HbA1c, ↓ AST; ↓ ALT; ↓ gamma-glutamyl transpeptidase; ↔ LDL-cholesterol, ↔ HDL-cholesterol, and ↔ triglycerides; ↓ insulin resistance; ↓ systolic and diastolic blood pressure. | (Hattori, 2018) |
| UMIN000023574 | NASH associated with T2D | 11 patients with NASH | Dapagliflozin | 5 mg/day for 24 weeks | ↓ BMI; waist circumference; ↓ waist-to-hip ratio; ↓ body fat mass; percent body fat; ↓ lean mass; ↓ total body water; Improved AST, ALT, and ferritin. | (Tobita et al., 2017) |
| NCT03227484 | Humans with prediabetes | 40 patients | Empagliflozin | 25 mg/day; 8 weeks | ↓ Brain insulin sensitivity; ↓ fasting glucose; ↓ liver fat. | (Kullmann et al., 2022) |
| 205119002/ NCT04018365 | Patients with insulin resistance syndrome and lipoatrophic diabetes | 8 patients | Empagliflozin | 10–25 mg/day; 24 weeks | ↓ HbA1c; ↓ mean fasting plasma glucose concentration; ↓ glucose levels; mean body mass; ↓ serum ketone body concentration. | Hirota et al., (2024) |
| NCT03057951 | Patients with metabolic disorders | 5988 patients | Empagliflozin | 10 mg/day; for 26 months | ↓ Hospitalization; ↓ heart failure; ↓ cardiovascular death; ↔ hypoglycemic events | (Anker et al., 2021) |

**Abbreviations.** CTI: clinical trial identifier; T2D: type 2 diabetes; HbA1c: hemoglobin A1c or glycated hemoglobin; BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDL: low-density lipoprotein; HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; NASH: nonalcoholic steatohepatitis. ↑: increase; ↓: decrease: ↔: no effect; SGLT2 inhibitors: sodium-glucose cotransporter-2 inhibitors.

**Table 3**
Summary of the major *in vivo* and *in vitro* findings related to the central bioeffects of SGLT2 inhibitors.

| Animal model/Cell line | Disease induction | SGLT2 inhibitors | Dose and period of treatment | Findings | Ref |
|---|---|---|---|---|---|
| Animal studies | | | | | |
| Male wistar rats | Cerebral ischemia/ reperfusion injury | Empagliflozin | 1 and 10 mg/kg; 1 and 24 h after reperfusion | ↓ Neuronal apoptosis; ↓ infarct size; ↓ neurobehavioral alterations; ↓ neuronal caspase−3. | (Abdel-latif et al., 2020) |
| Hyperglycemic male wistar rats | Cerebral I/R injury | Empagliflozin | 10 mg/kg/day; 1 and 24 h after reperfusion | ↓ Neuronal injury; ↓ TNF-α; ↓ neuronal caspase−3; ↓ % of degenerated neurons; ↓ cerebral MDA; ↑ GSH; ↑ Cat. | (Amin et al., 2020) |
| Obese male wistar rats | High-fat diet | Dapagliflozin | 1 mg/kg/day; 4 weeks | ↓ Weight gain; ↑ peripheral insulin sensitivity; ↑ brain mitochondrial function; ↑ IR tyrosine phosphorylation; ↓ Cognitive decline; ↑ hippocampal synaptic plasticity; ↓ Brain oxidative stress; ↓ Bax; ↑ Bacl2; ↓ Bax/Bacl2 ratio; ↓ NFκB; ↓ p-NFκB p−65/ NFκB p−65. | Sa-nguanmoo et al., (2017) |
| Male wistar rats | Intraperitoneal injection of LPS (250 μg/kg, 3 day; for 1 week) | Dapagliflozin | 1 mg/kg; 7 days before and continued concomitantly with LPS. | ↓ MDA; ↑ TAA; ↑ SOD; ↑ PON1; ↑ Nrf2; ↓ IL1β; ↓ IL−8; ↓ IL−18; TGF-β1; ↓ MCP1; NLRP3-inflammasome; ↓ NFκB; ↓ TLR4; ↓ p-AKT/total AKT ratio; ↓ mTOR; ↓ Beclin 1; LC3-II; ↓ caspase 3 and 9. | (Abd Elmaaboud et al., 2023) |
| Wistar albino rats | Cadmium chloride; (5 mg/ kg/day) | Dapagliflozin | 1 mg/kg/day; for 2 months | ↑ Spatial memory; ↓ hippocampal microglial cell infiltration; ↓ brain edema; ↓ hippocampal degeneration; ↓ Pyramidal neuron pyknosis; ↓ p-Tau; ↓ $A\beta_{1-42}$; ↑ p-GSK−3β; ↓ Ach-E; ↑ Ach levels; ↓ SQSTM−1/p62; ↑ Beclin 1; ↑ (p-AMPK)/total AMPK; ↑ Bcl−2; ↓ caspase 3; ↑ Nrf2; ↑ HO−1; ↑ GPx; ↑ SIRT1; ↓ lipid peroxide. | (Arab et al., 2023) |
| Male albino swiss rats | Aluminum chloride (AlCl3)-induced AD | Dapagliflozin | 1 and 5 mg/kg/day; for 4 weeks | ↓ Depressive behavior; ↓ memory impairments; ↓ Brain Aβ deposition; ↓ MDA; ↑ SOD; ↑ Cat; ↑ GSH; ↓ Ach-E; ↓ pyknotic cells; ↓ capillary congestion; ↓ angles; ↓ structural and cellular damage; ↑ histological pattern of the hippocampus; ↓ cytoplasmic vacuolation; ↓ brain glucose levels compared to the $AlCl_3$ group; ↑ Glut 1 and Glut 3; ↑ PDK−1; ↑ LDH-A; ↑ p-AMPK; ↑ p-mTOR; ↑ HO−1. | (Samman et al., 2023) |
| Rat primary activated microglial cells | LPS-induced neuroinflammation | Empagliflozin | 0.5–50 μM; 30 min to 24 h | ↓ Nos2; ↔ NO; ↓ IL−6; ↓ IL−1β; ↓ IL−10; ↓ TNF; pERK/ERK ratio; ↓ pERK1/2; ↓ NFkB; ↔ Nhe−1 mRNA expression. | (Heimke et al., 2022) |
| C57BL mice | Scopolamine hydrobromide | Canagliflozin | 10 mg/kg/day; for 3 weeks | ↑ NPI; ↓ AChE activity; ↓ mTOR; ↓ glial fibrillary acidic protein; ↓ microgliosis; ↓ astrogliosis. | (Stanciu et al., 2023) |
| Mice | STZ | Canagliflozin | 10 mg/kg/day; for 21 days | ↑ Cognitive performances; ↓ neurotoxicity; ↑ p-AMPK/ SIRT−1/BDNF; ↓ GSK−3β; ↓ AChE; ↓ NFκB-p65; ↓ IL−6; ↓ BACE−1; ↓ Aβ plaque; ↑ IDE; ↑ Nrf−2. | (Khamies et al., 2024) |
| Rat | Cisplatin | Canagliflozin | 10 mg/kg/day; for 10 days | ↓ Cortical changes; ↓ MDA; ↑ GSH content; ↑ SOD activity; ↑ GST; ↑ Cat; ↑ GPx; ↑ HO−1; ↑ PPARγ; ↑ SIRT1/ FOXO−3 signals; ↓ cortical MPO; ↓ $NO_2^-$; ↓ IL−6; ↓ TNF-α; ↑ IL−10; JNK/AP−1; ↓ TLR4/iNOS/NO; ↓ Ang II/Ang 1–7. | (Hassanein et al., 2023) |
| Male wistar rats | Intra-cerebroventricular injection of streptozotocin (3 mg/kg) | Ertugliflozin | 5 mg/kg and 10 mg/ kg; for 20 days | ↓ Cognitive deficit; ↓ hippocampal AChE activity; ↓ p-Tau; ↓ phospho- IRS−1Ser307/total IRS−1 ratio; ↑ p-AktSer473/total.Akt ratio; ↑ p-GSK3βSer9/total GSK3β ratio; ↓ pro-apoptotic marker expression. | (Pang et al., 2023) |
| Primary microglial cells | LPS | Empagliflozin | 0.5–50 μM; 30 min to 24 h | ↓ Nos2; ↔ NO; ↓ IL−6; ↓IL−1β; ↓IL−10; ↓ TNF; pERK/ERK ratio; ↓ pERK1/2; ↓ NFkB; ↔ Nhe−1 mRNA expression. | (Heimke et al., 2022) |
| BV−2 microglia | High glucose | Canagliflozin | 10 or 20 μM; pretreatment for 30 min | ↓ HG-induced cytotoxicity; ↓ apoptosis; ↓ autophagic degradation; ↓ iNOS; ↓ NLRP3; ↓ IL−1β; ↓ TNF-α; ↓ NFκB; ↓ JNK; ↓ p38; ↓ PI3K/Akt; ↓ COX−2. | (Lee et al., 2024) |

**Abbreviations.** TNF-α: Tumor necrosis factor; MDA: Malondialdehyde; GSH: Glutathione; IR: Insulin receptor; Bax: Bcl-2 associated X-protein; Bacl2: B-cell lymphoma-2; NFκB: Nuclear factor-kappa B; TAA: Total antioxidant activity; SOD: Superoxide dismutase; PON1: Paraoxonase 1; Nrf2: Nuclear factor (erythroid-derived 2)-like 2; IL-1β: Interleukin 1β; IL-8: Interleukin 8; IL-18: Interleukin 18; IL-6; Interleukin 6; IL-10: Interleukin 10; TGF-β1: Transforming growth factor-beta; MCP1: Monocyte chemoattractant protein-1; NLRP3-inflammasome: NOD-like receptor family pyrin domain containing 3; TLR4: Toll-like receptor 4; p-AKT: Phosphorylated protein kinase B; mTOR: Mechanistic target of rapamycin; LC3: Microtubule-associated protein 1 light chain protein 3; p-Tau: Phospho-Tau; $A\beta_{1-42}$; Amyloid beta 42; p-GSK-3β: Phospho glycogen synthase kinase-3 beta; Ach-E: Acetylcholinesterase; SQSTM-1/p62: Sequestosome-1; p-AMPK: Phospho AMP-activated protein kinase; Nrf2: Nuclear factor (erythroid-derived 2)-like 2; HO-1: Heme oxygenase; GPx: Glutathione peroxidase; SIRT1; Sirtuin1; Cat: Catalase; AlCl3: Aluminium chloride; Glut: Glucose transporter; PDK-1: pyruvate dehydrogenase kinase 1; Nos2: Nitric oxide synthase 2; NO: Nitric oxide; LDH-A: lactate dehydrogenase A; ERK: Extracellular signal-regulated kinases; pERK1/2; Phospho extracellular signal-regulated kinases ½; Nhe-1: Sodium/hydrogen exchanger 1; NPI: Novelty preference index; BDNF: Brain-derived neurotrophic factor: BACE1: Beta-site APP cleaving enzyme 1; IDE: Insulin-degrading enzyme; GST: Glutathione-S-transferase; PPARγ: Peroxisome proliferator-activated receptor gamma; FOXO-3: Forkhead box O3; MPO: Myeloperoxidase; NO2; Nitrogen dioxide; JNK: c-Jun N-terminal kinase; AP-1: Activator protein-1; Ang: Angiotensin; IRS: Insulin receptor substrate; HG: High glucose; iNOS: Inducible nitric oxide synthase; COX-2: Cyclooxygenase-2.

have already received FDA-approval for the treatment of T2D and more recently of heart failure. However, given their relatively recent clinical approval, their long-term safety cannot be guaranteed. Therefore, well-designed observational studies are needed to closely monitor patients currently receiving these drugs.

In-depth molecular studies are necessary to elucidate the mechanistic pathways targeted by these therapies to reduce dementia risks, particularly focusing on their interaction with Aβ fragments and Tau proteins. In this regard, it's noteworthy that while there are relatively sufficient *in vivo* studies, particularly involving Empa and Dapagliflozin

SGLT2 inhibitors, there is a substantial need for additional *in vitro* research and human clinical trials.

Nonetheless, several considerations could challenge the use of these treatments. Unlike other drug classes, where most issues are generally related to receptor specificity, the limitations associated with SGLT2 inhibitors seem to be primarily linked to their mechanism of action. While they effectively address hyperglycemia, they can lead to various complications. In particular, they affect kidney physiology in a multitude of ways, including, but not limited to: (i) increased glucosuria which may result in structural alterations, hypertrophy or inflammation in the kidney. (ii) these treatments not only enhance glucose excretion but also reduce sodium reabsorption, increasing the risk of electrolyte imbalance. Additionally, (iii) the energy loss due to glucose excretion could impact body weight. Finally, (iv) these therapies have been associated with increased risk of urinary tract infections, which is now considered one of the main side effects of these treatments.

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## CRediT authorship contribution statement

**Mehdi Alami, Hicham Berrougui, Abdelouahed Khalil, Tamas Fulop**: Conceptualization. **Mehdi Alami, Mojgan Morvaridzadeh**: Writing – original draft. **Hicham Berrougui, Abdelouahed Khalil, Tamas Fulop, Rachid El Fatimy, Abdellatif El Khayari**: Writing – review & editing. **Abdellatif El Khayari, Hicham Berrougui, Abdelouahed Khalil, Tamas Fulop, Kaoutar Boumezough, Rachid El Fatimy, Mojgan Morvaridzadeh**: Visualization. **Hicham Berrougui, Abdelouahed Khalil, Tamas Fulop**: Supervision, Funding acquisition. **Mehdi Alami, Abdellatif El Khayari**: Software.

## Declaration of Competing Interest

Authors have nothing to declare.

## Data availability

No data was used for the research described in the article.

## References

Abd Elmaaboud, M.A., Estfanous, R.S., Atef, A., Kabel, A.M., Alnemari, K.A., Naguib, T. M., Alsufyani, S.E., Darwish, H.W., Arab, H.H., 2023. Dapagliflozin/hesperidin combination mitigates lipopolysaccharide-induced Alzheimer's disease in rats. Pharmaceuticals 16, 1–25. https://doi.org/10.3390/ph16101370.

Abdel-latif, R.G., Rifaai, R.A., Amin, E.F., 2020. Empagliflozin alleviates neuronal apoptosis induced by cerebral ischemia/reperfusion injury through HIF-1α/VEGF signaling pathway. Arch. Pharm. Res. 43, 514–525. https://doi.org/10.1007/s12272-020-01237-y.

Abdul-Ghani, M.A., Norton, L., DeFronzo, R.A., 2011. Role of Sodium-Glucose Cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr. Rev. 32, 515–531. https://doi.org/10.1210/er.2010-0029.

Al Hamed, F.A., Elewa, H., 2020. Potential therapeutic effects of sodium glucose-linked cotransporter 2 inhibitors in stroke. Clin. Ther. 42, e242–e249. https://doi.org/10.1016/j.clinthera.2020.09.008.

Amin, E.F., Rifaai, R.A., Abdel-latif, R.G., 2020. Empagliflozin attenuates transient cerebral ischemia/reperfusion injury in hyperglycemic rats via repressing oxidative–inflammatory–apoptotic pathway. Fundam. Clin. Pharm. 34, 548–558. https://doi.org/10.1111/fcp.12548.

Anand, B.K., Chhina, G.S., Sharma, K.N., Dua, S., Singh, B., 1964. Activity of single neurons in the hypothalamic feeding centers: effect of glucose. Am. J. Physiol. 207, 1146–1154. https://doi.org/10.1152/ajplegacy.1964.207.5.1146.

Anker, S.D., Butler, J., Filippatos, G., Ferreira, J.P., Bocchi, E., Böhm, M., Brunner–La Rocca, H.-P., Choi, D.-J., Chopra, V., Chuquiure-Valenzuela, E., et al., 2021. Empagliflozin in heart failure with a preserved ejection fraction. N. Engl. J. Med. 385, 1451–1461. https://doi.org/10.1056/nejmoa2107038.

Anon, 2023. 2023 Alzheimer's disease facts and figures. Alzheimer'S. Dement 19, 1598–1695. https://doi.org/10.1002/alz.13016.

Arab, H.H., Safar, M.M., Shahin, N.N., 2021. Targeting ROS-dependent AKT/GSK-3β/NF-KB and DJ-1/Nrf2 pathways by dapagliflozin attenuates neuronal injury and motor dysfunction in rotenone-induced Parkinson's disease rat model. ACS Chem. Neurosci. 12, 689–703. https://doi.org/10.1021/acschemneuro.0c00722.

Arab, H.H., Eid, A.H., Alsufyani, S.E., Ashour, A.M., El-Sheikh, A.A.K., Darwish, H.W., Sabry, F.M., 2023. Targeting autophagy, apoptosis, and oxidative perturbations with dapagliflozin mitigates cadmium-induced cognitive dysfunction in rats. Biomedicines 11. https://doi.org/10.3390/biomedicines11113000.

Aronson, R., Frias, J., Goldman, A., Darekar, A., Lauring, B., Terra, S.G., 2018. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. Diabetes, Obes. Metab. 20, 1453–1460. https://doi.org/10.1111/dom.13251.

Baskin, D.G., Woods, S.C., West, D.B., Houten, M., Van; Posner, B.I., Dorsa, D.M., Porte, D., 1983. Immunocytochemical detection of insulin in rat hypothalamus and its possible uptake from cerebrospinal fluid. Endocrinology 113, 1818–1825. https://doi.org/10.1210/endo-113-5-1818.

Benedict, C., Hallschmid, M., Hatke, A., Schultes, B., Fehm, H.L., Born, J., Kern, W., 2004. Intranasal insulin improves memory in humans. Psychoneuroendocrinology 29, 1326–1334. https://doi.org/10.1016/j.psyneuen.2004.04.003.

Benedict, C., Hallschmid, M., Schultes, B., Born, J., Kern, W., 2007. Intranasal insulin to improve memory function in humans. Neuroendocrinology 86, 136–142. https://doi.org/10.1159/000106378.

Bhatt, D.L., Szarek, M., Pitt, B., Cannon, C.P., Leiter, L.A., McGuire, D.K., Lewis, J.B., Riddle, M.C., Inzucchi, S.E., Kosiborod, M.N., et al., 2021. Sotagliflozin in patients with diabetes and chronic kidney disease. N. Engl. J. Med. 384, 129–139. https://doi.org/10.1056/nejmoa2030186.

Bolinder, J., Ljunggren, Ö., Kullberg, J., Johansson, L., Wilding, J., Langkilde, A.M., Sugg, J., Parikh, S., 2012. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J. Clin. Endocrinol. Metab. 97, 1020–1031. https://doi.org/10.1210/jc.2011-2260.

Bortoluzzi Canteiro, P., Casagrande Antero, D., dos Santos Tramontin, N., Ugioni Simon, K., Mendes, C., Anastácio Borges Correa, M.E., Lock Silveira, P.C., Pastoris Muller, A., 2019. Insulin treatment protects the brain against neuroinflammation by reducing cerebral cytokines and modulating mitochondrial function. Brain Res. Bull. 149, 120–128. https://doi.org/10.1016/j.brainresbull.2019.04.011.

Burdakov, D., Luckman, S.M., Verkhratsky, A., 2005. Glucose-sensing neurons of the hypothalamus. Philos. Trans. R. Soc. B Biol. Sci. 360, 2227–2235. https://doi.org/10.1098/rstb.2005.1763.

Butterfield, D.A., Halliwell, B., 2019. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat. Rev. Neurosci. 20, 148–160. https://doi.org/10.1038/s41583-019-0132-6.

Carranza-Naval, M.J., del Marco, A., Hierro-Bujalance, C., Alves-Martinez, P., Infante-Garcia, C., Vargas-Soria, M., Herrera, M., Barba-Cordoba, B., Atienza-Navarro, I., Lubian-Lopez, S., et al., 2021. Liraglutide reduces vascular damage, neuronal loss, and cognitive impairment in a mixed murine model of Alzheimer's disease and type 2 diabetes. Front. Aging Neurosci. 13, 1–13. https://doi.org/10.3389/fnagi.2021.741923.

Casagrande, S.S., Lee, C., Stoeckel, L.E., Menke, A., Cowie, C.C., 2021. Cognitive function among older adults with diabetes and prediabetes, NHANES 2011–2014. Diabetes Res. Clin. Pr. 178, 108939. https://doi.org/10.1016/j.diabres.2021.108939.

Chiba, Y., Sugiyama, Y., Nishi, N., Nonaka, W., Murakami, R., Ueno, M., 2020. Sodium/Glucose Cotransporter 2 is expressed in choroid plexus epithelial cells and ependymal cells in human and mouse brains. Neuropathology 40, 482–491. https://doi.org/10.1111/neup.12665.

Cholerton, B., Baker, L.D., Montine, T.J., Craft, S., 2016. Type 2 diabetes, cognition, and dementia in older adults: toward a precision health approach. Diabetes Spectr. 29, 210–219. https://doi.org/10.2337/ds16-0041.

Craft, S., 2009. Reply from the authors. Neurology 72, 293–294. https://doi.org/10.1212/01.wnl.0000344246.91081.2c.

Craft, S., Newcomer, J., Kanne, S., Dagogo-Jack, S., Cryer, P., Sheline, Y., Luby, J., Dagogo-Jack, A., Alderson, A., 1996. Memory improvement following induced hyperinsulinemia in Alzheimer's disease. Neurobiol. Aging 17, 123–130. https://doi.org/10.1016/0197-4580(95)02002-0.

Craft, S., Asthana, S., Schellenberg, G., Baker, L., Cherrier, M., Boyt, A.A., Martins, R.N., Raskind, M., Peskind, E., Plymate, S., 2000. Insulin effects on glucose metabolism, memory, and plasma amyloid precursor protein in Alzheimer's disease differ according to apolipoprotein-e genotype. Ann. N. Y. Acad. Sci. 903, 222–228. https://doi.org/10.1111/j.1749-6632.2000.tb06371.x.

Dakic, T., Jevdjovic, T., Lakic, I., Djurasevic, S.F., Djordjevic, J., Vujovic, P., 2019. Food for thought: short-term fasting upregulates glucose transporters in neurons and endothelial cells, but not in astrocytes. Neurochem. Res. 44, 388–399. https://doi.org/10.1007/s11064-018-2685-6.

De Keyser, C.E., Eijgelsheim, M., Uitterlinden, A.G., Stricker, B.H., 2012. Pharmacogenetics of response to cardiovascular drug therapy: what is the current state of knowledge? Dialogues Cardiovasc. Med. 17, 281–292.

De Meira, R.Z.C., MaCiel, A.B., Murakami, F.S., De Oliveira, P.R., Bernardi, L.S., 2017. In vitro dissolution profile of dapagliflozin: development, method validation, and analysis of commercial tablets. Int. J. Anal. Chem. 2017. https://doi.org/10.1155/2017/2951529.

Duarte, A.I., Moreira, P.I., Oliveira, C.R., 2012. Insulin in central nervous system: more than just a peripheral hormone. J. Aging Res. 2012. https://doi.org/10.1155/2012/384017.

Dubey, H., Gulati, K., Ray, A., 2018. Amelioration by Nitric Oxide (NO) mimetics on neurobehavioral and biochemical changes in experimental model of Alzheimer's disease in rats. Neurotoxicology 66, 58–65. https://doi.org/10.1016/j.neuro.2018.03.001.

Enerson, B.E., Drewes, L.R., 2006. The rat blood-brain barrier transcriptome. J. Cereb. Blood Flow. Metab. 26, 959–973. https://doi.org/10.1038/sj.jcbfm.9600249.

Erdogan, M.A., Yusuf, D., Christy, J., Solmaz, V., Erdogan, A., Taskiran, E., Erbas, O., 2018. Highly selective SGLT2 inhibitor dapagliflozin reduces seizure activity in pentylenetetrazol-induced murine model of epilepsy. BMC Neurol. 18, 1–8. https://doi.org/10.1186/s12883-018-1086-4.

Esser, N., Legrand-Poels, S., Piette, J., Scheen, A.J., Paquot, N., 2014. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res. Clin. Pr. 105, 141–150. https://doi.org/10.1016/j.diabres.2014.04.006.

Fediuk, D.J., Nucci, G., Dawra, V.K., Cutler, D.L., Amin, N.B., Terra, S.G., Boyd, R.A., Krishna, R., Sahasrabudhe, V., 2020. Overview of the Clinical Pharmacology of Ertugliflozin, a Novel Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor. Clin. Pharm. 59, 949–965. https://doi.org/10.1007/s40262-020-00875-1.

Ferrannini, E., 2017. Sodium-glucose co-transporters and their inhibition: clinical physiology. Cell Metab. 26, 27–38. https://doi.org/10.1016/j.cmet.2017.04.011.

Ferrannini, E., Solini, A., 2012. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nat. Rev. Endocrinol. 8, 495–502. https://doi.org/10.1038/nrendo.2011.243.

Ferrario, C.R., Reagan, L.P., 2018. Insulin-mediated synaptic plasticity in the CNS: anatomical, functional and temporal contexts. Neuropharmacology 136, 182–191. https://doi.org/10.1016/j.neuropharm.2017.12.001.

Frihauf, J.B.; Zorrilla, E.P.; Fekete, E.M. Control of Food Intake. Encycl. Behav. Neurosci. Three-Volume Set, 1-3 2010, 1, V1-335-V1-344, doi:10.1016/B978-0-08-045396-5.00164-0..

Frost, G.R., Jonas, L.A., Li, Y.M., 2019. Friend, Foe or Both? Immune Activity in Alzheimer's Disease. Front. Aging Neurosci. 11, 1–20. https://doi.org/10.3389/fnagi.2019.00337.

Galizzi, G., Palumbo, L., Amato, A., Conigliaro, A., Nuzzo, D., Terzo, S., Caruana, L., Picone, P., Alessandro, R., Mulè, F., et al., 2021. Altered insulin pathway compromises mitochondrial function and quality control both in in vitro and in vivo model systems. Mitochondrion 60, 178–188. https://doi.org/10.1016/j.mito.2021.08.014.

Gaur, A., Pal, G.K., Ananthanarayanan, P.H., Pal, P., 2014. Role of ventromedial hypothalamus in high fat diet induced obesity in male rats: association with lipid profile, thyroid profile and insulin resistance. Ann. Neurosci. 21, 104–107. https://doi.org/10.5214/ans.0972.7531.210306.

Gil-Campos, M., Cañete, R., Gil, A., 2004. Adiponectin, the missing link in insulin resistance and obesity. Clin. Nutr. 23, 963–974. https://doi.org/10.1016/j.clnu.2004.04.010.

González-Ortiz, M., Méndez-Del Villar, M., Martínez-Abundis, E., Ramírez-Rodríguez, A. M., 2018. Effect of dapagliflozin administration on metabolic syndrome, insulin sensitivity, and insulin secretion. Minerva Endocrinol. 43, 229–235. https://doi.org/10.23736/S0391-1977.16.02550-5.

Growth factors in cultured fetal neurons, 1991, 379–380..

Gyimesi, G., Pujol-Giménez, J., Kanai, Y., Hediger, M.A., 2020. Sodium-coupled glucose transport, the SLC5 family, and therapeutically relevant inhibitors: from molecular discovery to clinical application. Pflug. Arch. Eur. J. Physiol. 472, 1177–1206. https://doi.org/10.1007/s00424-020-02433-x.

Haider, K., Pathak, A., Rohilla, A., Haider, M.R., Ahmad, K., Yar, M.S., 2019. Synthetic Strategy and SAR Studies of C-Glucoside Heteroaryls as SGLT2 Inhibitor: A Review. Eur. J. Med. Chem. 184. https://doi.org/10.1016/j.ejmech.2019.111773.

Hassanein, E.H.M., Saleh, F.M., Ali, F.E.M., Rashwan, E.K., Atwa, A.M., Abd El-Ghafar, O.A.M., 2023. Neuroprotective Effect of Canagliflozin against Cisplatin-Induced Cerebral Cortex Injury Is Mediated by Regulation of HO-1/PPAR-γ, SIRT1/FOXO-3, JNK/AP-1, TLR4/INOS, and Ang II/Ang 1–7 Signals. Immunopharmacol. Immunotoxicol. 45, 304–316. https://doi.org/10.1080/08923973.2022.2143371.

Hasselbalch, S.G., Knudsen, G.M., Videbaek, C., Pinborg, L.H., Schmidt, J.F., Holm, S., Paulson, O.B., 1999. No effect of insulin on glucose blood-brain barrier transport and cerebral metabolism in humans. Diabetes 48, 1915–1921. https://doi.org/10.2337/diabetes.48.10.1915.

Hattori, S., 2018. Anti-Inflammatory effects of empagliflozin in patients with type 2 diabetes and insulin resistance UMIN000021552 UMIN. Diabetol. Metab. Syndr. 10, 1–7. https://doi.org/10.1186/s13098-018-0395-5.

Havrankova, J., Schmechel, D., Roth, J., Brownstein, M., 1978. Identification of insulin in rat brain. Proc. Natl. Acad. Sci. U. S. A. 75, 5737–5741. https://doi.org/10.1073/pnas.75.11.5737.

Heimke, M., Lenz, F., Rickert, U., Lucius, R., Cossais, F., 2022. Anti-inflammatory properties of the SGLT2 inhibitor empagliflozin in activated primary microglia. Cells 11. https://doi.org/10.3390/cells11193107.

Hesp, A.C., Schaub, J.A., Prasad, P.V., Vallon, V., Laverman, G.D., Bjornstad, P., van Raalte, D.H., 2020. The role of renal hypoxia in the pathogenesis of diabetic kidney disease: a promising target for newer renoprotective agents including SGLT2 inhibitors? Kidney Int 98, 579–589. https://doi.org/10.1016/j.kint.2020.02.041.

Hirota, Y., Kakei, Y., Imai, J., Katagiri, H., Ebihara, K., Wada, J., Suzuki, J., Urakami, T., Omori, T., Ogawa, W., 2024. A multicenter, open-label, single-arm trial of the efficacy and safety of empagliflozin treatment for refractory diabetes mellitus with insulin resistance (EMPIRE-01). Diabetes Ther. 15, 533–545. https://doi.org/10.1007/s13300-023-01526-x.

Holman, G.D., 2020. Structure, function and regulation of mammalian glucose transporters of the SLC2 family. Pflug. Arch. Eur. J. Physiol. 472, 1155–1175. https://doi.org/10.1007/s00424-020-02411-3.

Holtzman, D.M., Morris, J.C., Goate, A.M., 2011. Alzheimer's disease: the challenge of the second century. Sci. Transl. Med. 3. https://doi.org/10.1126/scitranslmed.3002369.

Hom, F.G., Goodner, C.J., Berrie, M.A.N.N., 1984. Frederick g. Hom. Charles J. Goodner, Mary Ann. Berrie 33, 141–152.

Ibáñez, C., Simó, C., Martín-Álvarez, P.J., Kivipelto, M., Winblad, B., Cedazo-Mínguez, A., Cifuentes, A., 2012. Toward a predictive model of Alzheimer's disease progression using capillary electrophoresis-mass spectrometry metabolomics. Anal. Chem. 84, 8532–8540. https://doi.org/10.1021/ac301243k.

Janson, J., Laedtke, T., Parisi, J.E., O'Brien, P., Petersen, R.C., Butler, P.C., 2004. Increased risk of type 2 diabetes in Alzheimer disease. Diabetes 53, 474–481. https://doi.org/10.2337/diabetes.53.2.474.

Jojima, T., Sakurai, S., Kishi, H., Kato, K., Iijima, T., Tomaru, T., Usui, I., Aso, Y., 2024. Empagliflozin Increases Plasma Levels of Citrulline, Histidine, and α-Aminobutyric Acid in Patients with Type 2 Diabetes: Effects of a Sodium-Glucose Co-Transporter 2 Inhibitor on the Plasma Amino Acid Profile. Expert Opin. Pharm. 25, 937–944. https://doi.org/10.1080/14656566.2024.2362265.

Jurcovicova, J., 2014. Glucose transport in brain – effect of inflammation. Endocr. Regul. 48, 35–48. https://doi.org/10.4149/endo_2014_01_35.

Kao, C.C., Parulekar, A.D., 2019. Spotlight on fevipiprant and its potential in the treatment of asthma: evidence to date. J. Asthma Allergy 12, 1–5. https://doi.org/10.2147/JAA.S167973.

Katusic, Z.S., Austin, S.A., 2014. Endothelial nitric oxide: protector of a healthy mind. Eur. Heart J. 35, 888–894. https://doi.org/10.1093/eurheartj/eht544.

Khamies, S.M., El-Yamany, M.F., Ibrahim, S.M., 2024. Canagliflozin Mitigated Cognitive Impairment in Streptozotocin-Induced Sporadic Alzheimer's Disease in Mice: Role of AMPK/SIRT-1 Signaling Pathway in Modulating Neuroinflammation. J. Neuroimmune Pharm. 19, 39. https://doi.org/10.1007/s11481-024-10140-y.

Khan, T., Khan, S., Akhtar, M., Ali, J., Najmi, A.K., 2021. Empagliflozin nanoparticles attenuates type2 diabetes induced cognitive impairment via oxidative stress and inflammatory pathway in high fructose diet induced hyperglycemic mice. Neurochem. Int. 150, 105158. https://doi.org/10.1016/j.neuint.2021.105158.

Khedr, L.H., Eladawy, R.M., Nassar, N.N., Saad, M.A.E., 2023. Canagliflozin attenuates chronic unpredictable mild stress induced neuroinflammation via modulating AMPK/MTOR autophagic signaling. Neuropharmacology 223, 109293. https://doi.org/10.1016/j.neuropharm.2022.109293.

Koekkoek, L.L., Mul, J.D., la Fleur, S.E., 2017. Glucose-sensing in the reward system. Front. Neurosci. 11, 1–11. https://doi.org/10.3389/fnins.2017.00716.

Kullmann, S., Hummel, J., Wagner, R., Dannecker, C., Vosseler, A., Fritsche, L., Veit, R., Kantartzis, K., Machann, J., Birkenfeld, A.L., et al., 2022. Empagliflozin improves insulin sensitivity of the hypothalamus in humans with prediabetes: a randomized, double-blind, placebo-controlled, phase 2 trial. Diabetes Care 45, 398–406. https://doi.org/10.2337/dc21-1136.

Lardaro, A., Quarta, L., Pagnotta, S., Sodero, G., Mariani, S., Del Ben, M., Desideri, G., Ettorre, E., Baratta, F., 2024. Impact of Sodium Glucose Cotransporter 2 Inhibitors (SGLT2i) Therapy on Dementia and Cognitive Decline. Biomedicines 12. https://doi.org/10.3390/biomedicines12081750.

Lee, C.C., Huang, C.C., Wu, M.Y., Hsu, K.Sen, 2005. Insulin Stimulates Postsynaptic Density-95 Protein Translation via the Phosphoinositide 3-Kinase-Akt-Mammalian Target of Rapamycin Signaling Pathway. J. Biol. Chem. 280, 18543–18550. https://doi.org/10.1074/jbc.M414112200.

Lee, C.T., Lin, K.Der, Hsieh, C.F., Wang, J.Y., 2024. SGLT2 inhibitor canagliflozin alleviates high glucose-induced inflammatory toxicity in BV-2 microglia. Biomedicines 12. https://doi.org/10.3390/biomedicines12010036.

Lin, B., Koibuchi, N., Hasegawa, Y., Sueta, D., Toyama, K., Uekawa, K., Ma, M.J., Nakagawa, T., Kusaka, H., Kim-Mitsuyama, S., 2014. Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. Cardiovasc. Diabetol. 13, 1–15. https://doi.org/10.1186/s12933-014-0148-1.

Liu, Z., Ma, X., Ilyas, I., Zheng, X., Luo, S., Little, P.J., Kamato, D., Sahebkar, A., Wu, W., Weng, J., et al., 2021. Impact of Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors on Atherosclerosis: From Pharmacology to Pre-Clinical and Clinical Therapeutics. Theranostics 11, 4502–4515. https://doi.org/10.7150/THNO.54498.

Liy, P.M., Puzi, N.N.A., Jose, S., Vidyadaran, S., 2021. Nitric oxide modulation in neuroinflammation and the role of mesenchymal stem cells. Exp. Biol. Med. 246, 2399–2406. https://doi.org/10.1177/15353702219970052.

Lorin, J., Zeller, M., Guilland, J.C., Cottin, Y., Vergely, C., Rochette, L., 2014. Arginine and nitric oxide synthase: regulatory mechanisms and cardiovascular aspects. Mol. Nutr. Food Res. 58, 101–116. https://doi.org/10.1002/mnfr.201300033.

Lull, M.E., Block, M.L., 2010. Microglial activation and chronic neurodegeneration. Neurotherapeutics 7, 354–365. https://doi.org/10.1016/j.nurt.2010.05.014.

Lundkvist, P., Sjöström, C.D., Amini, S., Pereira, M.J., Johnsson, E., Eriksson, J.W., 2017. Dapagliflozin Once-Daily and Exenatide Once-Weekly Dual Therapy: A 24-Week Randomized, Placebo-Controlled, Phase II Study Examining Effects on Body Weight and Prediabetes in Obese Adults without Diabetes. Diabetes, Obes. Metab. 19, 49–60. https://doi.org/10.1111/dom.12779.

Maciejczyk, M., Żebrowska, E., Chabowski, A., 2019. Insulin resistance and oxidative stress in the brain: what's new? Int. J. Mol. Sci. 20. https://doi.org/10.3390/ijms20040874.

Maekawa, F., Toyoda, Y., Torii, N., Miwa, I., Thompson, R.C., Foster, D.L., Tsukahara, S., Tsukamura, H., Maeda, K.I., 2000. Localization of glucokinase-like immunoreactivity in the rat lower brain stem: for possible location of brain glucose-

sensing mechanisms. Endocrinology 141, 375–384. https://doi.org/10.1210/endo.141.1.7234.
Malhotra, A., Kudyar, S., Gupta, A., Kudyar, R., Malhotra, P., 2015. Sodium glucose co-transporter inhibitors – a new class of old drugs. Int. J. Appl. Basic Med. Res. 5, 161. https://doi.org/10.4103/2229-516x.165363.
Mancinetti, F., Xenos, D., De Fano, M., Mazzieri, A., Porcellati, F., Boccardi, V., Mecocci, P., 2023. Diabetes-Alzheimer's connection in older age: SGLT2 inhibitors as promising modulators of disease pathways. Ageing Res. Rev. 90, 102018. https://doi.org/10.1016/j.arr.2023.102018.
Markham, A., Elkinson, S., 2014. Luseogliflozin: first global approval. Drugs 74, 945–950. https://doi.org/10.1007/s40265-014-0230-8.
Marquet-De Rougé, P., Clamagirand, C., Facchinetti, P., Rose, C., Sargueil, F., Guihenneuc-Jouyaux, C., Cynober, L., Moinard, C., Allinquant, B., 2013. Citrulline diet supplementation improves specific age-related raft changes in wild-type rodent hippocampus. Age (Omaha) (35), 1589–1606. https://doi.org/10.1007/s11357-012-9462-2.
Martínez-González, K., Serrano-Cuevas, L., Almeida-Gutiérrez, E., Flores-Chavez, S., Mejía-Aranguré, J.M., Garcia-delaTorre, P., 2021. Citrulline supplementation improves spatial memory in a murine model for Alzheimer's disease. Nutrition 90. https://doi.org/10.1016/j.nut.2021.111248.
Mastro, A., Caputo, J.B., Vagula, M.C., 2014. Cognitive impairment and dementia in type 2 diabetes mellitus. U. S. Pharm. *39*.
McGill, J.B., 2014. The SGLT2 inhibitor empagliflozin for the treatment of type 2 diabetes mellitus: a bench to bedside review. Diabetes Ther. 5, 43–63. https://doi.org/10.1007/s13300-014-0063-1.
Medina, M., Avila, J., 2014. The role of extracellular tau in the spreading of neurofibrillary pathology. Front. Cell. Neurosci. 8, 1–7. https://doi.org/10.3389/fncel.2014.00113.
Melnick, I.V., Price, C.J., Colmers, W.F., 2011. Glucosensing in parvocellular neurons of the rat hypothalamic paraventricular nucleus. Eur. J. Neurosci. 34, 272–282. https://doi.org/10.1111/j.1460-9568.2011.07742.x.
Michailidis, M., Moraitou, D., Tata, D.A., Kalinderi, K., Papamitsou, T., Papaliagkas, V., 2022. Alzheimer's disease as type 3 diabetes: common pathophysiological mechanisms between Alzheimer's disease and type 2 diabetes. Int. J. Mol. Sci. 23. https://doi.org/10.3390/ijms23052687.
Miklossy, J., Qing, H., Radenovic, A., Kis, A., Vileno, B., Làszló, F., Miller, L., Martins, R. N., Waeber, G., Mooser, V., et al., 2010. Beta amyloid and hyperphosphorylated tau deposits in the pancreas in type 2 diabetes. Neurobiol. Aging 31, 1503–1515. https://doi.org/10.1016/j.neurobiolaging.2008.08.019.
Milstein, J.L., Ferris, H.A., 2021. The brain as an insulin-sensitive metabolic organ. Mol. Metab. 52, 101234. https://doi.org/10.1016/j.molmet.2021.101234.
Mui, J.V., Zhou, J., Lee, S., Leung, K.S.K., Lee, T.T.L., Chou, O.H.I., Tsang, S.L., Wai, A.K. C., Liu, T., Wong, W.T., et al., 2021. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors vs. Dipeptidyl Peptidase-4 (DPP4) Inhibitors for New-Onset Dementia: A Propensity Score-Matched Population-Based Study With Competing Risk Analysis. Front. Cardiovasc. Med. 8. https://doi.org/10.3389/fcvm.2021.747620.
Mulder, C., Wahlund, L.O., Blomberg, M., De Jong, S., Van Kamp, G.J., Scheltens, P., Teerlink, T., 2002. Alzheimer's disease is not associated with altered concentrations of the nitric oxide synthase inhibitor asymmetric dimethylarginine in cerebrospinal fluid. J. Neural Transm. 109, 1203–1208. https://doi.org/10.1007/s00702-002-0760-1.
Mullins, R.J., Diehl, T.C., Chia, C.W., Kapogiannis, D., 2017. Insulin Resistance as a Link between Amyloid-Beta and Tau Pathologies in Alzheimer's Disease. Front. Aging Neurosci. 9, 1–16. https://doi.org/10.3389/fnagi.2017.00118.
Munshi, M., Grande, L., Hayes, M., Ayres, D., Suhl, E., Capelson, R., Lin, S., Milberg, W., Weinger, Katie, 2006. E. Cognitive Dysfunction Is Associated with Poor Diabetes Control in Older Adults. Diabetes Care 29, 1794–1799. https://doi.org/10.2337/dc06-0506.
Navale, A.M., Paranjape, A.N., 2016. Glucose transporters: physiological and pathological roles. Biophys. Rev. 8, 5–9. https://doi.org/10.1007/s12551-015-0186-2.
Neeland, I.J., McGuire, D.K., Chilton, R., Crowe, S., Lund, S.S., Woerle, H.J., Broedl, U.C., Johansen, O.E., 2016. Empagliflozin reduces body weight and indices of adipose distribution in patients with type 2 diabetes mellitus. Diabetes Vasc. Dis. Res. 13, 119–126. https://doi.org/10.1177/1479164115616901.
Nguyen, T., Wen, S., Gong, M., Yuan, X., Xu, D., Wang, C., Jin, J., Zhou, L., 2020. Dapagliflozin activates neurons in the central nervous system and regulates cardiovascular activity by inhibiting Sglt-2 in mice. Diabetes, Metab. Syndr. Obes. 13, 2781–2799. https://doi.org/10.2147/DMSO.S258593.
Ni, L., Yuan, C., Chen, G., Chen, G., Zhang, C., Zhang, C., Zhang, C., Zhang, C., Wu, X., 2020. SGLT2i: beyond the glucose-lowering effect. Cardiovasc. Diabetol. 19, 1–10. https://doi.org/10.1186/s12933-020-01071-y.
Nijenhuis, W.A.J., Oosterom, J., Adan, R.A.H., 2001. AgRP(83-132) acts as an inverse agonist on the human-melanocortin-4 receptor. Mol. Endocrinol. 15, 164–171. https://doi.org/10.1210/me.15.1.164.
O'Malley, D., Reimann, F., Simpson, A.K., Gribble, F.M., 2006. Sodium-coupled glucose cotransporters contribute to hypothalamic glucose sensing. Diabetes 55, 3381–3386. https://doi.org/10.2337/db06-0531.
Oomura, Y., Yoshimatsu, H., 1984. Neural network of glucose monitoring system. J. Auton. Nerv. Syst. 10, 359–372. https://doi.org/10.1016/0165-1838(84)90033-X.
Pang, B., Zhang, L.L., Li, B., Sun, F.X., Wang, Z.Da, 2023. The Sodium Glucose Co-Transporter 2 Inhibitor Ertugliflozin for Alzheimer's Disease: Inhibition of Brain Insulin Signaling Disruption-Induced Tau Hyperphosphorylation. Physiol. Behav. 263, 114134. https://doi.org/10.1016/j.physbeh.2023.114134.
Patching, S.G., 2017. Glucose transporters at the blood-brain barrier: function, regulation and gateways for drug delivery. Mol. Neurobiol. 54, 1046–1077. https://doi.org/10.1007/s12035-015-9672-6.
Pawlos, A., Broncel, M., Woźniak, E., Gorzelak-Pabiś, P., 2021. Neuroprotective effect of SGLT2 inhibitors. Molecules 26. https://doi.org/10.3390/molecules26237213.
Pearson, A., Ajoy, R., Crynen, G., Reed, J.M., Algamal, M., Mullan, M., Purohit, D., Crawford, F., Ojo, J.O., 2020. Molecular abnormalities in autopsied brain tissue from the inferior horn of the lateral ventricles of nonagenarians and Alzheimer disease patients. BMC Neurol. 20, 1–20. https://doi.org/10.1186/s12883-020-01849-3.
Pereira, M.J., Eriksson, J.W., 2019. Emerging role of SGLT-2 inhibitors for the treatment of obesity. Drugs 79, 219–230. https://doi.org/10.1007/s40265-019-1057-0.
Perna, S., Mainardi, M., Astrone, P., Gozzer, C., Biava, A., Bacchio, R., Spadaccini, D., Solerte, S.B., Rondanelli, M., 2018. 12-Month Effects of Incretins versus SGLT2-Inhibitors on Cognitive Performance and Metabolic Profile. A Randomized Clinical Trial in the Elderly with Type-2 Diabetes Mellitus. Clin. Pharmacol. Adv. Appl. 10, 141–151. https://doi.org/10.2147/CPAA.S164785.
Poole, R.M., Dungo, R.T., 2014. Ipragliflozin: first global approval. Drugs 74, 611–617. https://doi.org/10.1007/s40265-014-0204-x.
Poppe, R., Karbach, U., Gambaryan, S., Wiesinger, H., Lutzenburg, M., Kraemer, M., Witte, O.W., Koepsell, H., 1997. Expression of the Na+ -D-Glucose Cotransporter SGLT1 in Neurons. J. Neurochem. 69, 84–94. https://doi.org/10.1046/j.1471-4159.1997.69010084.x.
Poznyak, A., Grechko, A.V., Poggio, P., Myasoedova, V.A., Alfieri, V., Orekhov, A.N., 2020. The diabetes mellitus–atherosclerosis connection: the role of lipid and glucose metabolism and chronic inflammation. Int. J. Mol. Sci. 21, 1–13. https://doi.org/10.3390/ijms21051835.
Prakash, A., Kumar, A., 2014. Role of nuclear receptor on regulation of BDNF and neuroinflammation in hippocampus of β-amyloid animal model of Alzheimer's disease. Neurotox. Res. 25, 335–347. https://doi.org/10.1007/s12640-013-9437-9.
Ramnanan, C.J., Kraft, G., Smith, M.S., Farmer, B., Neal, D., Williams, P.E., Lautz, M., Farmer, T., Donahue, E.P., Cherrington, A.D., et al., 2013. Interaction between the central and peripheral effects of insulin in controlling hepatic glucose metabolism in the conscious dog. Diabetes 62, 74–84. https://doi.org/10.2337/db12-0148.
Rizvi, S., Shakil, S., Biswas, D., Shakil, S., Shaikh, S., Bagga, P., Kamal, M., 2014. Invokana (Canagliflozin) as a Dual Inhibitor of Acetylcholinesterase and Sodium Glucose Co-Transporter 2: Advancement in Alzheimer's Disease- Diabetes Type 2 Linkage via an Enzoinformatics Study. CNS Neurol. Disord. - Drug Targets 13, 447–451. https://doi.org/10.2174/18715273113126660160.
Rizzo, M.R., Di Meo, I., Polito, R., Auriemma, M.C., Gambardella, A., di Mauro, G., Capuano, A., Paolisso, G., 2022. Cognitive Impairment and Type 2 Diabetes Mellitus: Focus of SGLT2 Inhibitors Treatment. Pharmacol. Res. 176, 106062. https://doi.org/10.1016/j.phrs.2022.106062.
Roden, M., Price, T.B., Perseghin, G., Petersen, K.F., Rothman, D.L., Cline, G.W., Shulman, G.I., 1996. Mechanism of free fatty acid-induced insulin resistance in humans. J. Clin. Invest 97, 2859–2865. https://doi.org/10.1172/JCI118742.
Roden, M., Weng, J., Eilbracht, J., Delafont, B., Kim, G., Woerle, H.J., Broedl, U.C., 2013. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 1, 208–219. https://doi.org/10.1016/S2213-8587(13)70084-6.
Routh, V.H., 2010. Glucose sensing neurons in the ventromedial hypothalamus. Sens. (Switz. ) 10, 9002–9025. https://doi.org/10.3390/s101009002.
Salkovic-Petrisic, M., Osmanovic, J., Grünblatt, E., Riederer, P., Hoyer, S., 2009. Modeling sporadic Alzheimer's disease: the insulin resistant brain state generates multiple long-term morphobiological abnormalities including hyperphosphorylated tau protein and amyloid-β. J. Alzheimer'S. Dis. 18, 729–750. https://doi.org/10.3233/JAD-2009-1184.
Salvatore, T., Carbonara, O., Cozzolino, D., Torella, R., Nasti, R., Lascar, N., Carlo Sasso, F., 2011. Kidney in diabetes: from organ damage target to therapeutic target. Curr. Drug Metab. 12, 658–666. https://doi.org/10.2174/138920011796504509.
Samman, W.A., Selim, S.M., El Fayoumi, H.M., El-Sayed, N.M., Mehanna, E.T., Hazem, R. M., 2023. Dapagliflozin ameliorates cognitive impairment in aluminum-chloride-induced Alzheimer's disease via modulation of AMPK/MTOR, oxidative stress and glucose metabolism. Pharmaceuticals 16. https://doi.org/10.3390/ph16050753.
Sa-nguanmoo, P., Tanajak, P., Kerdphoo, S., Jaiwongkam, T., Pratchayasakul, W., Chattipakorn, N., Chattipakorn, S.C., 2017. SGLT2-inhibitor and DPP-4 inhibitor improve brain function via attenuating mitochondrial dysfunction, insulin resistance, inflammation, and apoptosis in HFD-induced obese rats. Toxicol. Appl. Pharm. 333, 43–50. https://doi.org/10.1016/j.taap.2017.08.005.
Scheen, A.J., 2015. Pharmacodynamics, Efficacy and Safety of Sodium-Glucose Co-Transporter Type 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes Mellitus. Drugs 75, 33–59. https://doi.org/10.1007/s40265-014-0337-y.
Schur, E.A., Melhorn, S.J., Oh, S.K., Lacy, J.M., Berkseth, K.E., Guyenet, S.J., Sonnen, J. A., Tyagi, V., Rosalynn, M., De Leon, B., et al., 2015. Radiologic evidence that hypothalamic gliosis is associated with obesity and insulin resistance in humans. Obesity 23, 2142–2148. https://doi.org/10.1002/oby.21248.
Sebastiani, A., Greve, F., Gölz, C., Förster, C.Y., Koepsell, H., Thal, S.C., 2018. RS1 (Rsc1A1) Deficiency Limits Cerebral SGLT1 Expression and Delays Brain Damage after Experimental Traumatic Brain Injury. J. Neurochem. 147, 190–203. https://doi.org/10.1111/jnc.14551.
Sergi, D., Naumovski, N., Heilbronn, L.K., Abeywardena, M., O'Callaghan, N., Lionetti, L., Luscombe-Marsh, N., 2019. Mitochondrial (dys)function and insulin resistance: from pathophysiological molecular mechanisms to the impact of diet. Front. Physiol. 10. https://doi.org/10.3389/fphys.2019.00532.
SGLT2inhibitors the Statins of the 21st Century 2. 2016.

Shah, K., DeSilva, S., Abbruscato, T., 2012. The role of glucose transporters in brain disease: diabetes and Alzheimer's disease. Int. J. Mol. Sci. 13, 12629–12655. https://doi.org/10.3390/ijms131012629.

Shaikh, S., Rizvi, S.M.D., Shakil, S., Riyaz, S., Biswas, D., Jahan, R., 2016. Forxiga (dapagliflozin): plausible role in the treatment of diabetes-associated neurological disorders. Biotechnol. Appl. Biochem 63, 145–150. https://doi.org/10.1002/bab.1319.

Shakil, S., 2017. Molecular interaction of anti-diabetic drugs with acetylcholinesterase and sodium glucose co-transporter 2. J. Cell. Biochem 118, 3855–3865. https://doi.org/10.1002/jcb.26036.

Sim, A.Y., Barua, S., Kim, J.Y., Lee, Y.H., Lee, J.E., 2021. Role of DPP-4 and SGLT2 Inhibitors Connected to Alzheimer Disease in Type 2 Diabetes Mellitus. Front. Neurosci. 15, 1–11. https://doi.org/10.3389/fnins.2021.708547.

Sim, A.Y., Choi, D.H., Kim, J.Y., Kim, E.R., Goh, A. ra, Lee, Y. ho, Lee, J.E., 2023. SGLT2 and DPP4 Inhibitors Improve Alzheimer's Disease–like Pathology and Cognitive Function through Distinct Mechanisms in a T2D–AD Mouse Model. Biomed. Pharm. 168, 115755. https://doi.org/10.1016/j.biopha.2023.115755.

Smith, G.E., Pankratz, V.S., Negash, S., Machulda, M.M., Petersen, R.C., Boeve, B.F., Knopman, D.S., Lucas, J.A., Ferman, T.J., Graff-Radford, N., et al., 2007. A plateau in pre-alzheimer memory decline: evidence for compensatory mechanisms? Neurology 69, 133–139. https://doi.org/10.1212/01.wnl.0000265594.23511.16.

Song, J., Kang, S.M., Kim, E., Kim, C.H., Song, H.T., Lee, J.E., 2015. Impairment of insulin receptor substrate 1 signaling by insulin resistance inhibits neurite outgrowth and aggravates neuronal cell death. Neuroscience 301, 26–38. https://doi.org/10.1016/j.neuroscience.2015.05.072.

Spinelli, M., Fusco, S., Grassi, C., 2019. Brain insulin resistance and hippocampal plasticity: mechanisms and biomarkers of cognitive decline. Front. Neurosci. 10, 1–13. https://doi.org/10.3389/fnins.2019.00788.

Srikanth, V., Sinclair, A.J., Hill-Briggs, F., Moran, C., Biessels, G.J., 2020. Type 2 diabetes and cognitive dysfunction—towards effective management of both comorbidities. Lancet Diabetes Endocrinol. 8, 535–545. https://doi.org/10.1016/S2213-8587(20)30118-2.

Stanciu, G.D., Bild, V., Ababei, D.C., Rusu, R.N., Cobzaru, A., Paduraru, L., Bulea, D., 2020. Link between Diabetes and Alzheimer's Disease Due to the Shared Amyloid Aggregation and Deposition Involving Both Neurodegenerative Changes and Neurovascular Damages. J. Clin. Med. 9, 1–25. https://doi.org/10.3390/jcm9061713.

Stanciu, G.D., Rusu, R.N., Bild, V., Filipiuc, L.E., Tamba, B.I., Ababei, D.C., 2021. Systemic actions of Sglt2 inhibition on chronic mtor activation as a shared pathogenic mechanism between Alzheimer's disease and diabetes. Biomedicines 9. https://doi.org/10.3390/biomedicines9050576.

Stanciu, G.D., Ababei, D.C., Solcan, C., Bild, V., Ciobica, A., Beschea Chiriac, S.I., Ciobanu, L.M., Tamba, B.I., 2023. Preclinical studies of canagliflozin, a sodium-glucose co-transporter 2 inhibitor, and donepezil combined therapy in Alzheimer's disease. Pharmaceuticals 16, 1–18. https://doi.org/10.3390/ph16111620.

Steen, E., Terry, B.M., Rivera, E.J., Cannon, J.L., Neely, T.R., Tavares, R., Xu, X.J., Wands, J.R., De La Monte, S.M., 2005. Impaired Insulin and Insulin-like Growth Factor Expression and Signaling Mechanisms in Alzheimer's Disease - Is This Type 3 Diabetes? J. Alzheimer'S. Dis. 7, 63–80. https://doi.org/10.3233/JAD-2005-7107.

Steiner, S., 2016. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. Z. fur Gefass (13), 17–18. https://doi.org/10.1056/nejmoa1504720.

Szekeres, Z., Toth, K., Szabados, E., 2021. The effects of Sglt2 inhibitors on lipid metabolism. Metabolites 11, 1–9. https://doi.org/10.3390/metabo11020087.

Tobita, H., Sato, S., Miyake, T., Ishihara, S., Kinoshita, Y., 2017. Effects of dapagliflozin on body composition and liver tests in patients with nonalcoholic steatohepatitis associated with type 2 diabetes mellitus: a prospective, open-label, uncontrolled study. Curr. Ther. Res. - Clin. Exp. 87, 13–19. https://doi.org/10.1016/j.curtheres.2017.07.002.

Tsujii, S., Bray, G.A., 1990. Effects of glucose, 2-deoxyglucose, phlorizin, and insulin on food intake of lean and fatty rats. Am. J. Physiol. - Endocrinol. Metab. 258. https://doi.org/10.1152/ajpendo.1990.258.3.e476.

Vallon, V., Thomson, S.C., 2017. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia 60, 215–225. https://doi.org/10.1007/s00125-016-4157-3.

Verma, M., Howard, R.J., 2012. Semantic memory and language dysfunction in early Alzheimer's disease: a review. Int. J. Geriatr. Psychiatry 27, 1209–1217. https://doi.org/10.1002/gps.3766.

Vinuesa, A., Pomilio, C., Gregosa, A., Bentivegna, M., Presa, J., Bellotto, M., Saravia, F., Beauquis, J., 2021. Inflammation and insulin resistance as risk factors and potential therapeutic targets for Alzheimer's disease. Front. Neurosci. 15, 1–25. https://doi.org/10.3389/fnins.2021.653651.

Wang, R., Liu, X., Hentges, S.T., Dunn-Meynell, A.A., Levin, B.E., Wang, W., Routh, V.H., 2004. The regulation of glucose-excited neurons in the hypothalamic arcuate nucleus by glucose and feeding-relevant peptides. Diabetes 53, 1959–1965. https://doi.org/10.2337/diabetes.53.8.1959.

Wanner, C., Inzucchi, S.E., Lachin, J.M., Fitchett, D., von Eynatten, M., Mattheus, M., Johansen, O.E., Woerle, H.J., Broedl, U.C., Zinman, B., 2016. Empagliflozin and progression of kidney disease in type 2 diabetes. N. Engl. J. Med. 375, 323–334. https://doi.org/10.1056/nejmoa1515920.

Wiciński, M., Wódkiewicz, E., Górski, K., Walczak, M., Malinowski, B., 2020. Perspective of Sglt2 inhibition in treatment of conditions connected to neuronal loss: focus on Alzheimer's disease and ischemia-related brain injury. Pharmaceuticals 13, 1–12. https://doi.org/10.3390/ph13110379.

Wright, E.M., LOO, D.D.F.L., Hirayama, B.A., 2011. Biology of human sodium glucose transporters. Physiol. Rev. 91, 733–794. https://doi.org/10.1152/physrev.00055.2009.

Xu, H., Tartaglia, L.A., Chen, H., Xu, H., Barnes, G.T., Yang, Q., Tan, G., Yang, D., Chou, C.J., Sole, J., et al., 2003. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance find the latest version: chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J. Clin. Invest 112, 1821–1830. https://doi.org/10.1172/JCI200319451.Introduction.

Yu, A.S., Hirayama, B.A., Timbol, G., Liu, J., Basarah, E., Kepe, V., Satyamurthy, N., Huang, S.C., Wright, E.M., Barrio, J.R., 2010. Functional Expression of SGLTs in Rat Brain. Am. J. Physiol. - Cell Physiol. 299, 1277–1284. https://doi.org/10.1152/ajpcell.00296.2010.

Yu, A.S., Hirayama, B.A., Timbol, G., Liu, J., Diez-Sampedro, A., Kepe, V., Satyamurthy, N., Huang, S.C., Wright, E.M., Barrio, J.R., 2013. Regional Distribution of SGLT Activity in Rat Brain in Vivo. Am. J. Physiol. - Cell Physiol. 304. https://doi.org/10.1152/ajpcell.00317.2012.

Zhao, W.Q., Alkon, D.L., 2001. Role of insulin and insulin receptor in learning and memory. Mol. Cell. Endocrinol. 177, 125–134. https://doi.org/10.1016/S0303-7207(01)00455-5.

Zheng, Y., Ley, S.H., Hu, F.B., 2018. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat. Rev. Endocrinol. 14, 88–98. https://doi.org/10.1038/nrendo.2017.151.