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REVIEW ARTICLE

Crosstalk between Alzheimer's disease and diabetes: a focus on anti-diabetic drugs

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Abstract

Alzheimer's disease (AD) and Type 2 diabetes mellitus (T2DM) are two of the most common age-related diseases. There is accumulating evidence of an overlap in the pathophysiological mechanisms of these two diseases. Studies have demonstrated insulin pathway alternation may interact with amyloid-β protein deposition and tau protein phosphorylation, two essential factors in AD. So attention to the use of anti-diabetic drugs in AD treatment has increased in recent years. In vitro, in vivo, and clinical studies have evaluated possible neuroprotective effects of anti-diabetic different medicines in AD, with some promising results. Here we review the evidence on the therapeutic potential of insulin, metformin, Glucagon-like peptide-1 receptor agonist (GLP1R), thiazolidinediones (TZDs), Dipeptidyl Peptidase IV (DPP IV) Inhibitors, Sulfonylureas, Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors, Alpha-glucosidase inhibitors, and Amylin analog against AD. Given that many questions remain unanswered, further studies are required to confirm the positive effects of anti-diabetic drugs in AD treatment. So to date, no particular anti-diabetic drugs can be recommended to treat AD.

Keywords Type 2 diabetes mellitus (T2DM) · Alzheimer's disease (AD) · Anti-diabetic drugs · Amyloid-β protein · Tau protein · Insulin resistance

Introduction

Alzheimer's disease (AD) is the most common age-related neurological disorder. More than 30 million people worldwide suffer from dementia, of whom about two-third have AD (Patterson 2018). AD is characterized by a gradual decline in memory and cognitive function, leading to premature death several years after diagnosis. The main pathological features of AD are an abnormal accumulation of amyloid-β (Aβ), misfolded and aggregated forms of tau protein, and severe loss of neurons in brain tissue called brain atrophy (Meng et al. 2020; Shieh et al. 2020). Although more than a century has passed since the first case of AD was diagnosed, there is no definitive cure for the disease. For this reason, to identify the treatment of AD, its relationship with other diseases has been investigated. It has been reported that Type 2 diabetes mellitus (T2DM) and its consequences, including hyperinsulinemia, hyperglycemia, vascular lesions, and inflammation, are independent risk factors for AD (Haan 2006; Kandimalla et al. 2017; Boccardi et al. 2019).

T2DM is a chronic metabolic disease that can damage blood vessels, nerves, eyes, and kidneys (Goodarzi et al. 2016), is characterized by insulin resistance and relative insulin deficiency (Ramos-Rodriguez et al. 2017). Further studies have shown that diabetic patients often show cognitive impairment similar to the early stages of AD

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(Gorska-Ciebiada et al. 2014). A survey of AD patients showed that 80% of people with AD had impaired glucose tolerance or were diabetic (Janson et al. 2004). Epidemiological, clinical, and molecular evidence also suggests that there is a significant overlap in the pathophysiological mechanisms of T2DM and AD and that people with diabetes are at higher risk for AD, so the term "type 3 diabetes" has been introduced to describe these patients (Stoeckel et al. 2016; Arnold et al. 2018). Brain atrophy, impaired glucose metabolism, insulin signaling pathway, inflammation, mitochondrial dysfunction, and oxidative stress are common pathophysiological features in AD and T2DM (De la Monte and Wands 2008; de Matoset al. 2018; Meng et al. 2020; Shieh et al. 2020).

On the other hand, many studies support the relationship between AD and T2DM at the genetic level (Hao et al. 2015; Gao et al. 2016). Although there is no definitive conclusion on how AD and T2DM are related, their similar pathogenesis has provided convincing evidence that AD could be considered a metabolic disorder, which glucose metabolism and insulin signaling are impaired in the brain. Thus, several studies and clinical trials have been conducted to assess the neuroprotective effects of anti-diabetic drugs. This review discusses the main anti-diabetic drugs that are suitable treatment candidates for AD.

Insulin as a bridge between T2DM and AD

Insulin is the primary regulator of energy homeostasis and appetite, and it modulates brain activity. With its neurotrophic, neuromodulatory, and neuroprotective effects, insulin in the brain helps to control nutrient homeostasis and cognitive function (Blázquez et al. 2014). Therefore, insulin and its signaling pathway can affect many neuronal activities. Insulin is involved in maintaining nerve function by inducing the expression of the genes that are involved in acetylcholine synthesis. Consequently, suboptimal insulin values and hyposensitivity to the insulin receptor can be a biochemical link between diabetes and AD (Li and Hölscher 2007; Stanciu et al. 2020). Under normal conditions, insulin signaling can inhibit the production of Aβ and Tau phosphorylation by reducing BACE1 (Beta-Secretase 1) mRNA expression and activity, reducing Amyloid Precursor Protein (APP), and inhibiting Glycogen synthase kinase-3(GSK3β) phosphorylation (Ly et al. 2012). The insulin signaling pathway, including PI3K/AKT, is disrupted in the insulin resistance state. The PI3K / Akt pathway regulates downstream factors such as apoptotic pathway proteins, GSK3β, mTORC1, and forkhead box transcription factor (FOX) (Gabbouj et al. 2019; Hölscher 2019). Increased activation of GSK-3β in insulin resistance conditions may lead to Tau hyperphosphorylation, an important event in the formation of Neurofibrillary tangle (NFTs). Changes in Aβ production and clearance play an important role in AD. Increasing the activity of GSK3β lead to activation of presenilin 1 and finally Aβ accumulation (5). The insulin-degrading enzyme (IDE) plays an important role in clearing insulin and Aβ, and reducing its function can be important in developing both AD and diabetes. In addition to reducing IDE production in an insulin resistance state, insulin is elevated and competes with Aβ for binding to the IDE resulting in slower clearance of Aβ in the brain (Fig. 1) (Farris et al. 2003). Receptors for Advanced Glycation End Products (RAGE) have an important role in Aβ clearance. Bothe the AGEs and Aβ could bind to RAGE. Under insulin resistance conditions, AGEs compete with Aβ for binding to the RAGE. Therefore, the clearance rate of Aβ is reduced. In addition, the binding of AGEs and Aβ to RAGE increase inflammatory cytokines expression such as tumor necrosis factor (TNFα), Interleukin 6 (IL6), which accelerate the development of AD (Kong et al. 2020). Insulin Receptor Substrate 1 (IRS1), an adapter protein in the insulin signaling pathway, has been shown to be involved in the pathogenesis of AD. A recent study showed that abnormal IRS1-pS (616) phosphorylation is a pathological feature of AD (Yarchoan et al. 2014).

Therapeutic potential of type 2 diabetes drugs against AD

Although it is not clear how AD and T2DM are related, similar pathogenesis and common pathophysiological pathways in both diseases have led to an exponential increase in the number of studies examining the therapeutic effects of anti-diabetic drugs against AD (Cao et al. 2018). These studies may lead to the discovery of an effective drug against AD. Therefore, reviewing previous studies can provide valuable clues for future studies. In this review, we will discuss the therapeutic potential of several anti-diabetic drugs such as insulin, metformin, Glucagon-like peptide-1 receptor (GLP1R) agonist, thiazolidinediones (TZDs), Dipeptidyl Peptidase IV (DPP IV) inhibitors, Sulfonylureas, Sodium-glucose Cotransporter-2 (SGLT2) inhibitors, Alpha-glucosidase inhibitors and Amylin analog against AD. We will also discuss the mechanism of the action of these anti-diabetic drugs in AD pathology and analyze the results of different studies from animal and human studies.

Insulin

Insulin is a peptide hormone that affects the metabolism of carbohydrates, fats, and proteins. The expression of the insulin receptor and insulin-sensitive transmitters such as GLUT4 on the surface of the hypothalamus and hippocampus indicates insulin's role in the brain's physiological

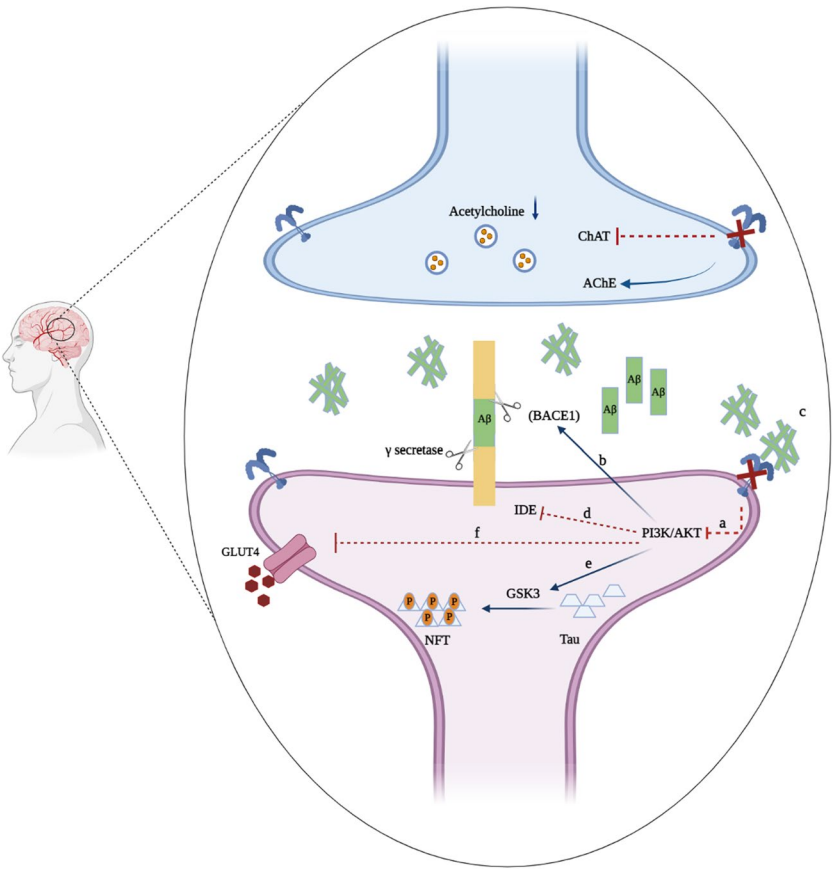

Fig. 1 Insulin as a bridge between T2DM and AD. Schematic outline of neuronal insulin signaling in the AD brain. Insulin is involved in maintaining nerve function by inducing acetylcholine synthesis gene expression. Under normal conditions, insulin signaling can inhibit the production of Aβ and Tau phosphorylation by reducing BACE1 mRNA expression and activity, reducing APP, and inhibiting GSK3β phosphorylation. Under insulin resistance conditions, APP cleavage by γ secretase in trance membrane domain and release insoluble Aβ into extracellular space that can further intensify insulin resistance (a, b, c). insulin resistance leads to inhibition of IDE and decreased Aβ clearance (d). Increased activation of GSK-3β in insulin resistance conditions may lead to Tau hyperphosphorylation (e)

function (Reger et al. 2006). For example, by inducing the expression of N-methyl-D-aspartate (NMDA) receptors, insulin induces long-term potentiation (LTP) (Skeberdis et al. 2001), and by modulating neurotransmitters such as acetylcholine and norepinephrine, it improves cognitive-behavioral performance (Figlewicz et al. 1993; Reger et al. 2006). Therefore, given the increasing AD prevalence in insulin resistance and diabetes patients, there has been a rise in studies on the effects of insulin on AD. In these studies, the effects of insulin on improving AD, intravenously and intranasal, were investigated. Studies on a 3xTg-AD mouse model fed a high-fat diet showed that obesity and insulin resistance reduced memory and cognitive function and improved memory following intravenous insulin treatment. Insulin reduced the production of Aβ in mice through mechanisms such as the reduction of BCAE1. This finding has also been confirmed by in vitro studies (Pandini et al. 2013). Insulin also decreased Aβ production and improved AD disorders by increasing x11α and decreasing the LC3I / LC3II ratio (Vandal et al. 2014). In addition to Aβ, insulin affects the amount of tau-phosphorylated protein in the brain. In a model of diabetic mice with high and low doses of Streptozotocin (STZ), intravenous injection of insulin led to a decrease in phosphatase 2A protein and a decrease in the amount of tau-phosphorylated protein (Gratuze et al. 2017). Despite the evident effects of intravenous insulin on cognitive, functional, and memory behaviors of patients with AD disease, due to the long-term hypoglycemic effects and limitation in crossing the blood–brain barrier (Craft et al. 1996; Kern et al. 2001; Morris and Burns 2012), intranasal use of the insulin has been recently introduced.

In Alzheimer's rodent models, intranasal insulin use improves the pathological features of AD, as well as the short-term and long-term memory (Barone et al. 2019). In a study, 6 weeks of intranasal insulin treatment improved cognitive function and decreased tau-phosphorylated protein (Thr205, Ser262, and Ser396) by reducing the kinases of GSK-3, extracellular signal-regulated protein kinase (ERK1 / 2), and Ca2 + /Calmodulin protein kinase II (CaMKII) in the hippocampus of Alzheimer's rats (Guo et al. 2017). Neuritis characterized by activation of Astroglia and Microglia is a pathological feature of AD that occurs before the formation of amyloid plaques and NFTs (Prickaerts et al. 1999; Mrak and Griffin 2001). Intranasal insulin treatment also decreases the activation markers of astrocytes (Glial fibrillary acidic protein) and microglia (Ionized calcium-binding adaptor molecule 1 (Iba1) in the hippocampus of rats with the intraventricular injection of STZ. Insulin can also be an effective treatment for AD by increasing the doublecortin (DCX) neurogenesis marker and inducing insulin signaling

by increasing AKT expression (Guo et al. 2017). In addition to improving learning and memory, insulin has been shown to increase IRS-1-PI3K-Akt-GSK3β pathway activity through the olfactory bulb – subventricular zone – subgranular zone (OB-SVZ-SGZ) in the hippocampus and subclavian region (Lv et al. 2020). Long-term treatment with insulin and GLP1 agonist (Exenatide) has been reported to reduce IRSP gene expression, improve insulin signaling pathway, and reduce Aβ by 30–30% in the Tg2576 model of AD mice (Robinson et al. 2019). It has also been observed that daily intranasal insulin administration improves cognitive and memory impairments after decreasing the level of consciousness caused by propofol (Zhang et al. 2016). The results of these studies are inconsistent with those of Elizabeth M, et al. as intranasal administration of insulin to SAMP8 mice had no effects on the expression of insulin signaling pathway but it could be a candidate in treatment of AD disease by modulating the other pathways including inflammatory pathways (Rhea et al. 2019).

Human studies have provided evidence regarding the effectiveness of insulin in the treatment of AD. Investigations using functional magnetic resonance imaging (MRI), electroencephalogram (EEG), magnetoencephalography (MEG) have shown the positive effects of intranasal insulin on the improvement of central nervous system function (Kullmann et al. 2016). A study on healthy individuals found that 8 weeks of intranasal insulin administration reduced anger thresholds, increased mood and self-esteem, and improved memory. In addition, receiving insulin in this way did not affect systemic insulin and blood glucose levels. (Benedict et al. 2004, 2007). Two studies on the elderly with AD showed that short-term (21 days) intranasal insulin administration improved memory function, decreased cortisol levels, and increased Aβ 40 solution form (Reger et al. 2008; Claxton et al. 2015). In another randomized, double-blind, placebo-controlled trial, the effects of intranasal insulin at doses of 20 and 40 IU for 4 months on 104 patients with cognitive impairment and AD were investigated. This study showed that insulin in both amounts of 20 and 40 IU improves AD by improving the Scale-Cognitive subscale (ADAS-Cog12) (Craft et al. 2012). Another study showed that insulin's effects on memory function occur at high doses, and the APOE-ε4 genotype enhances the effects of insulin (Claxton et al. 2015). In this regard, additional studies showed that the effects of intranasal insulin might be improved by gender and ApoE ε4 genotype (Claxton et al. 2013). A placebo-controlled double-blind, randomized trial showed improved memory and decreased tau-P181 / Aβ42 ratio following regular insulin therapy for 2 and 4 months (Craft et al. 2017). Although it is difficult to demonstrate the therapeutic activity of Large molecular weight compounds like proteins and peptides due to some physiological barriers such as BBB, enzymatic degradation, and clearance, numerous studies have shown successful impacts of insulin in the preclinical and clinical stages of AD treatment. However, none of them has been approved for AD treatment to date. Therefore, it appears that more data are required to establish the actual value of insulin appropriately in the treatment of AD.

Metformin

Metformin has recently attracted considerable scholarly attention in the treatment of AD. In the mice model of AD, metformin causes memory improvement and reduces the pathological factors of Aβ and tau phosphorylation (Chen et al. 2021). Low-dose metformin has been reported to reduce scopolamine-induced cognitive impairment and significantly reduce inflammation and oxidative stress in rats (Mostafa et al. 2016). Also, the administration of metformin in the Senescence Accelerated Mouse (SAMP8) mouse model improves learning ability and memory by reducing APPc99 and pTau levels (Farr et al. 2019). These effects of metformin may be mediated through activating the AMPK, inhibiting the P65 NF-κB pathways, and reducing the expression of BACE1 protein (Ou et al. 2018). In addition, metformin protects neurons against apoptosis by reducing JNK hyperphosphorylation (Chen et al. 2016; Chenet al. 2019). A study on the AD mouse model reported conflicting results despite the above data. Activating the AMPK by metformin increases the severity of memory impairment in males, whereas it has protective effects in females (DiTacchio et al. 2015). In a placebo-controlled randomized trial, 80 non-diabetic participants with mild cognitive impairment received metformin or placebo daily for 12 months. Although promising results were obtained for the memory, no differences were observed for ADAS-Cog12, CSF, Aβ42, and cerebral glucose metabolism (Luchsinger et al. 2016). A placebo-controlled clinical trial study showed that metformin is safe and tolerable in patients with AD. This drug didn't have significant effects on, Aβ42, total tau, and p-tau in CSF and language and motor speed but improved learning/memory and attention (Koenig et al. 2017).

In contrast to the above reports, a cohort study of 4651 diabetic patients showed that long-term metformin administration increased the risk of all-cause dementia, vascular dementia, and AD (HR: 2.13, 95% CI = 1.20–3.79) (Kuan et al. 2017). These findings are in line with previous results indicating that long-term use of metformin increases the risk of AD (Moore et al. 2013). One study has examined the effects of anti-diabetic drugs on the brain and the risk of AD. The results of the research showed that compared to metformin, glyburide had the highest score, whereas GLP-1 receptor agonists and rosiglitazone had the lowest score for risk of AD (Akimoto et al. 2020). Furthermore, long-term use of sulfonylureas, thiazolidinediones, or insulin has a

lower AD risk than metformin (Imfeld et al. 2012). The paradoxical effect of metformin on the risk of AD was studied in a transgenic mouse model with tauopathy. Although metformin decreases tau phosphorylation in the cerebral cortex and hippocampus through AMPK / mTOR and PP2A, it also increases the insoluble form of tau and Aβ plates in the brain. Metformin also stimulates caspase-3 to increase the cleavage of Tau proteins and disrupts synaptic communication (Barini et al. 2016). Metformin-induced accumulation of autophagosomes leads to increased γ-secretase activity and Aβ generation (Son et al. 2016). Although most of the data on the use of metformin in dementia / AD with or without T2DM are promising, it should be noted that the effect of metformin might depend on complex underlying pathological processes. In some cases, metformin has even been shown to have harmful effects. Some studies have failed to provide convincing evidence of the effect of metformin on mild cognitive impairment or AD, which may be due to a short period of use or duration of studies. Therefore, to determine the effects of metformin in the control and treatment of dementia/AD, it is necessary to define broader cohort studies with long-term use of metformin and larger study groups.

Thiazolidinediones

Thiazolidinediones (glitazones) are an important family of anti-diabetic drugs that exert their anti-inflammatory and insulin-sensitizing effects by stimulating peroxisome proliferator-activated receptor gamma (PPARγ). At the molecular level, PPAR-γ plays a critical role in regulating glucose and lipid metabolism and inflammatory responses. The Thiazolidinediones family improves insulin resistance in adipose and muscle tissues via activating PPAR-γ. Thiazolidinediones also inhibit hepatic gluconeogenesis, a process involved in regulating blood glucose (Hurren and Dunham 2021; Long et al. 2021). In recent years, various studies have demonstrated that thiazolidinediones can effectively treat neurodegenerative diseases, especially AD, by reducing and delaying the risk of neurodegeneration (Miller et al. 2011; Pérez and Quintanilla 2015; Galimberti and Scarpini 2017; Meng et al. 2020). Thiazolidinediones have been reported to treat AD by decreasing inflammatory cytokines, oxidative stress, Aβ deposits, glial activation, and Tau protein phosphorylation (Pérez and Quintanilla 2015). In the following section, we will discuss the effects of pioglitazone and rosiglitazone on the treatment of AD in-vivo and in-vitro and clinical trial studies.

Pioglitazone

Pioglitazone has been approved since 1999 as a supplement to control blood glucose in T2DM patients (Al-Majed et al. 2016). In animal models, the preventive effects of pioglitazone on AD have been identified. *Chen* et al. observed that pioglitazone suppressed hyper-activation of cyclin-dependent kinase 5 (Cdk5) in the hippocampus of mice with the mutated APP / PS1 gene by reducing P35 protein expression (Chen et al. 2015). Pioglitazone reduced astroglial activation and cortical cholinergic innervation. It also reversed cerebral blood flow (CBF) and cerebral glucose uptake (CGU) responses to increased neural activity but failed to improve spatial memory. Hence, chronic administration of pioglitazone overcomes cerebrovascular dysfunction and alters neurometabolic coupling, and counteracts oxidative stress in the brain, glial activation, and to some extent, cholinergic denervation (Nicolakakis et al. 2008). It has also been indicated that 7-day oral treatment of APPV717I mice with pioglitazone reduced the number of active microglia and reactive astrocytes in the hippocampus and cortex. Moreover, pioglitazone decreased the expression of the proinflammatory genes such as cyclooxygenase 2 (COX2) and nitric oxide synthase (iNOS) and reduced mRNA and protein BACE1(Heneka et al. 2005). In the mouse model of AD treated with pioglitazone, a remarkable decrease in the level of soluble and insoluble Aβ was observed in the brain, which was associated with the loss of both diffuse and dense-core plaques within the brain cortex (Mandrekar-Colucci et al. 2012). Furthermore, due to the anti-inflammatory effects of pioglitazone, treatment with this drug resulted in a phenotypic change of microglial cells from proinflammatory M1 to an M2 anti-inflammatory state, a phenomenon correlated with increased phagocytosis of deposited Aβ (Mandrekar-Colucci et al. 2012; Galimberti and Scarpini 2017). Recently, it has been reported that the levels of collapsin response mediator protein-2 (CRMP-2) and p35 protein were increased in the cerebellum of APP / PS1 mice with AD. Pioglitazone normalized the levels of these proteins in the cerebellum and attenuated impaired motor coordination ability and long-term depression in the pre-Aβ accumulation stage (Toba et al. 2016). *Yang* et al. illustrated that pioglitazone improves insulin sensitivity and attenuates Aβ42 accumulation in rats with diet-induced insulin resistance by modulation of AKT/GSK3β activation(Yang et al. 2017). In another study, four months of treatment with pioglitazone at 18 mg/Kg/day in the triple transgenic mouse model of AD (3xTg-AD) led to improving learning on the active avoidance task, lower Aβ and tau deposits in the hippocampus, and increase of short- and long-term plasticity. (Searcy et al. 2012). Meanwhile, *Xiang* et al. found that pioglitazone had a neuroprotective effect against scopolamine-induced cholinergic system deficit and cognitive impairment by decreased acetylcholine levels and reduced choline acetyltransferase activity, and elevated acetylcholinesterase activity in the hippocampus or cortex (Xiang et al. 2012). Recently, a study investigated the effects

of chronic administration of pioglitazone on learning and memory in an STZ-induced AD rat model. The findings elucidated that pioglitazone impaired spatial learning and memory in normal rats but improved learning and memory in STZ-induced AD rats(Aali et al. 2020).

There is clinical evidence for the effects of pioglitazone on AD. For instance, in clinical trials, a pilot prospective randomized, open-controlled study revealed that pioglitazone improved metabolism and cognition in AD and mild cognitive impairment (MCI) patients (Hanyu et al. 2009). A further randomized, open-controlled trial indicated that cognitive improvement was correlated with the decline of TNF-α status after pioglitazone therapy (Hanyu et al. 2010). Additionally, it was reported that pioglitazone treatment improved cognition and regional cerebral blood flow (rCBF) in the parietal lobe and displayed stabilization of the disease in mild AD accompanied with T2DM patients compared with control (Hanyu et al. 2010). Another double-blind, placebo-controlled, randomized controlled trial demonstrated that pioglitazone was well tolerated, and no unanticipated safety problems in AD patients without DM were observed via an 18-month treatment duration (Geldmacher et al. 2011).

Taken together, although this drug helps improve the cognition of diabetic patients with AD and mild Cognitive Impairment (MCI), contradictory results have been reported from in-vivo and clinical trials studies. The discrepancies between the studies could be due to the different length of treatment, sample size, inclusion and exclusion criteria, and patient selection methods. Therefore, more basic and clinical investigations are needed in this regard.

Rosiglitazone

Rosiglitazone is another important insulin-sensitizing drug in the treatment of T2DM. Evidence from in-vitro and in-vivo studies suggests that rosiglitazone may improve cognition and the pathology of Aβ in AD patients. For example, rosiglitazone enhanced learning and memory impairments in Tg2576 mice by affecting brain levels of IDE and Aβ42 (Pedersen et al. 2006). In addition, Aβ accumulation was decreased in 7-month-old APP / PS1 mice following 4 weeks of treatment with rosiglitazone (O'Reilly and Lynch 2012). Treatment of APPswe / PSEN1DE9 mice with rosiglitazone reduced spatial memory impairment induced by amyloid burden; Aβ aggregates and Aβ oligomers; and astrocytic and microglia activation. Besides, rosiglitazone treatment prevents changes in presynaptic and postsynaptic markers (Toledo and Inestrosa 2010). One of the important pathways in AD is the Wnt signaling (Inestrosa et al. 2021). Rosiglitazone was shown to increase β-catenin and inhibit GSK3β resulting in reducing various neuropathological markers of AD (Toledo and Inestrosa 2010).

Interestingly, in mice with T2DM and AD, treatment with rosiglitazone increased IDE expression levels, reduced Aβ40 and Aβ42 accumulation, and learning and spatial cognition disorders by activating the PPARγ / AMPK signaling pathway (Zhou et al. 2018). Rosiglitazone has been elucidated to improve cognitive ability, learning, and memory impairment through modulating the insulin-dependent signaling pathway Akt-GSK3β followed by reducing hyper-phosphorylation of Tau and neurofilament proteins (Tokutake et al. 2012).

Clinical trials have reported conflicting results regarding the effect of rosiglitazone on AD. In a preliminary study, 30 subjects with mild AD or amnestic mild cognitive impairment were randomly selected, with 20 treated with rosiglitazone (4 mg daily) and 10 treated with placebo for 6 months. Rosiglitazone exhibited better delayed recall (months 4 and 6) and selective attention (month 6) than those in the placebo group. At the 6th month, plasma Aβ levels remained unchanged in subjects receiving rosiglitazone, but it decreased in those receiving placebo (Watson et al. 2005). Another study using three different doses of rosiglitazone (2, 4, or 8 mg for 6 months) indicated a significant improvement in the primary endpoint (change of ADASCog from the beginning) only in APOE4 patients receiving 8 mg of rosiglitazone (Risner et al. 2006). However, the clinical trial results were inconsistent with the evidence from the previous two studies. This discrepancy seems to be due to the duration of rosiglitazone treatment and the type of subjects included in the study regarding APOE positive or negative. Although rosiglitazone has beneficial effects on insulin resistance, glucose and lipid metabolism, its weak penetration into the brain and its association with severe cardiotoxicity limit its clinical applications. Today, only pioglitazone is approved for the treatment of T2DM, while rosiglitazone is not prescribed due to the high incidence of cardiovascular complications.

Sulfonylureas

Sulfonylureas (e.g., glimepiride, tolbutamide, glyburide) are commonly used to treat diabetes. Their molecular mechanism is to stimulate endogenous insulin secretion by binding to specific receptors on pancreatic β cells, leading to closing ATP-sensitive potassium channels and increasing intracellular calcium levels (Costello and Shivkumar 2020). These channels are expressed in the pituitary, microglia, and nerve cells in various brain areas, including the hippocampus, frontal cortex, amygdala, and hypothalamus. Molecular studies have shown that ATP-sensitive potassium channels consist of four kir pore-forming subunits and four sulfonylurea regulatory subunits. Three sulfonylurea receptors (SUR) isoforms (SUR1, SUR2A, SUR2B) have been identified in the pancreas, heart, and arteries, respectively. The Kir subunit can also exist in two forms, Kir6.1 and Kir6.2 (Lefer et al.

2009; Principalli et al. 2015). Recent studies have shown that potassium ATP channels of the central nervous system play an essential role in neuroprotection, synaptic transmission, neuroplasticity, and neurobehavioral disorders such as anxiety, depression, learning, and memory loss. In addition, these channels have been documented to play an important role in the pathogenesis of AD (Zubov et al. 2020). Therefore, targeting these channels could be potentially a strategy to treat AD.

The SUR1 subunit can interact with the transient receptor potential cation channel subfamily M member 4 (TRPM4) channels. The expression of SUR1-TRPM4 increases following the damage or inflammation in nerve cells. It also activates microglia cells in the CNS following inflammation and causes cognitive decline. Opening of SUR1-TRPM4 channels due to edema and cell death causes a cytotoxic effect. It has been suggested that glibenclamide inhibited the SUR1-TRPM4 channel by binding directly to the SUR1 subunit and thus preventing CNS cell death (Simard et al. 2006; Kurland et al. 2016). Glibenclamide is a known K-ATP channel blocker that can cross blood–brain barrier systems and affects brain nerve cells (Wen et al. 2021).

Moreover, it has been demonstrated that Aβ25-35 leads to over activation of the hypothalamic–pituitary–adrenal-(HPA) axis and an increase of the symptoms of depression and anxiety in rats. The blockage of K-ATP channels with glibenclamide reduces behaviors related to depression and anxiety in Aβ25-treated rats by normalizing HPA axis activity (Esmaeili et al. 2018). In addition, improvement in anxiety-like symptoms following treatment with glyburide was observed in high-fat-diet-induced obesity mice (Gainey et al. 2016). Recent studies in animal models of AD have shown evidence for a two-way pathway between Aβ and the K-ATP channel. For example, Aβ was found to increase the expression of KATP channel subunits in primary neurons (Ma et al. 2009). In contrast, the K-ATP channel modulates Aβ production (Kong et al. 2015). Tolbutamide inhibits Aβ1-42-induced memory impairment and synaptic plasticity alterations in the hippocampus (105), a K-ATP channel blocker.

Sulfonylureas affect ABC transporters, especially ABCA1. ABCA1 is expressed in various nerve cells and is involved in regulating cholesterol levels. Impairment of ABC1 leads to increased inflammatory responses and impaired synaptic transmission. In a mice model of AD, inactivation of ABCA1 increased soluble and insoluble forms of amyloid and produced amyloid plaques and Lewy bodies. On the other hand, due to the interaction of glibenclamide with ABCA1, it can also be involved in the processes described (Koldamova et al. 2014; van Deijk et al. 2017).

Although in vitro and in vivo studies have reported the preventive effects of sulfonylurea drugs against AD, clinical studies have reported conflicting results. One study reported that long-term use of sulfonylureas was not associated with a changed risk of developing AD (Imfeld et al. 2012). In another study by Hsu et al., combined treatment of metformin with sulfonylurea reduced the risk of dementia by 35% over 8 years (Hsu et al. 2011). Interestingly, in a meta-analysis of 5 cohort studies, it was found that there was no significant relationship between the use of metformin or sulfonylurea and brain function and structure outcomes (Weinstein et al. 2019). From the results of these studies, it can be concluded that more clinical studies using larger sample sizes are needed to accurately investigate the mechanism of the action of sulfonylurea in AD.

DPP4 inhibitors

DPP4, as a serine exopeptidase, is ubiquitously expressed on the surface of a variety of cells. This exopeptidase selectively cleaves N-terminal dipeptides from various substrates, including cytokines, growth factors, neuropeptides, and the incretin hormones. Accordingly, DPP4 exerts multifunctional effects on different signaling pathways such as inflammation, glucose metabolism, neurophysiological and neuroendocrine processes, food intake, pain, and vascular modulation. It has been suggested that the suppression of DPP-4 activity may increase the anti-inflammatory and neuroprotective effects in the brain (Cheng et al. 2020). Studies have reported that DPP4 inhibitors improve mitochondrial dysfunction and neuroinflammation, prevent Aβ deposition and inhibit total tau protein formation and phosphorylation (Chalichem et al. 2018; Wu et al. 2020). Commonly available DPP-4 inhibitors include linagliptin, vildagliptin, and saxagliptin. In this section, we summarize in-vivo, in-vitro, and clinical studies on the effects of DPP4 inhibitor family drugs on the neuropathophysiology of AD.

Linagliptin

Linagliptin is one of the most potent inhibitors of DPP-4, which shows greater selectivity for DPP-4 than the other DPPs and related proteases (e.g., DPP8 and DPP9). Approved by the FDA in 2011, this drug does not pass through the BBB, but by peripherally inhibiting DPP-4 triples the incretin level so that it can pass through the BBB (Röhrborn et al. 2015; Cheng et al. 2020). Recent in vitro and in vivo studies have shown that linagliptin can significantly inhibit the neurodegeneration process observed in AD through several molecular mechanisms. For example, Aβ disrupts insulin signaling and kills SK-N-MC cells. Linagliptin protects SK-N-MC cells against Aβ-induced toxicity, and restoring insulin signaling inhibits GSK3b activation and Tau protein hyperphosphorylation. In addition, it reduces Aβ-induced mitochondrial dysfunction and

intracellular ROS production, which may be due to the activation of AMPK-Sirt1 signaling (Kornelius et al. 2015). In another study, linagliptin was reported to improve behavioral abnormalities, oxidative stress, inflammation, and cuprizone-induced demyelination by modulating the AMPK / SIRT1 and JAK2 / STAT3 / NF-κB signaling pathways (Elbaz et al. 2018). In addition, 8-week administration of linagliptin has been shown to reduce cognitive deficits, brain incretin levels, Aβ deposition, tau protein phosphorylation, and neuroinflammation in 3xTg-AD mice (Kosaraju et al. 2017). *Nakaoka* et al. observed that PS19 mice treated with linagliptin have higher levels of GLP1 and lower fasting blood glucose than the controls. They reported that linagliptin significantly restored spatial reference memory and increased CBF without affecting the rate of tau or eNOS protein phosphorylation in the brain. In fact, it improves cognitive deterioration caused by a high-fat diet in tauopathy by increasing brain perfusion through an eNOS-independent pathway (Nakaoku et al. 2019). It has been found that linagliptin improved cognitive impairment in STZ-induced diabetic mice by inhibiting oxidative stress, reducing NADPH oxidase and TNF-α expression, and microglial activation (Ide et al. 2020). It is of note that to date no experimental study has been performed to evaluate the effects of linagliptin on improving the neurophysiopathological conditions of AD, and such studies are necessary.

Saxagliptin

Saxagliptin is one of the oral drugs from the DPP4 family of inhibitors that is well tolerated with minimal side effects and is used to treat diabetic patients (Men et al. 2018). To date, only one study has examined the efficacy of saxagliptin in a rat model of AD. Three months after the onset of AD, these rats were treated orally with saxagliptin (0.25, 0.5, and 1 mg/kg) for 60 days. This study showed a reduction in Aβ deposition, tau phosphorylation, and inflammatory markers following treatment with saxagliptin. Saxagliptin also improved hippocampal GLP-1 and memory retention (Kosaraju et al. 2013). Due to the small number of studies on the effect of saxagliptin on neurological processes in AD, more cellular, animal, and clinical trials are needed to determine the beneficial effects and the exact mechanism of this drug.

Vildagliptin

Vildagliptin under the chemical name (1-[[3-hydroxy-1-adamantyl) amino] acetyl]-2-cyano-(S)-pyrrolidine) and the Galvus proprietary name was introduced in 2007 as one of the key drugs in the DPP4 inhibitor family for treatment T2DM (De Oliveira et al. 2017). In terms of the mechanism of the action, cellular and animal studies have demonstrated that vildagliptin has positive effects on neurological processes and cognitive functions in AD by increasing the expression and the activity of GLP-1 in peripheral blood and reducing Aβ deposition, phosphorylated tau protein, and inflammation in brain tissue (Ma et al. 2018; Khalaf et al. 2019; Yossef et al. 2020). For example, in a study, it was reported that vildagliptin reduced GSK3b and Tau phosphorylation levels by reducing apoptosis-related proteins (caspase-3 and caspase-9) in SH-SY5Y cells. Decreased expression of PSEN1 and PSEN2 also exerts a protective effect against Aβ (Dokumacı and Aycan 2019). *Khalaf* et al. observed that vildagliptin alone and combined with memantine, a subfamily of glutamate receptors involved in brain function, decreased blood glucose, HOMA-IR, lipid profile, homocysteine, malondialdehyde, acetylcholinesterase, and increased apolipoprotein E. In addition, treatment of mice with combined diabetes AD using vildagliptin, alone and in combination with memantine, reduces the expression of amyloid precursor protein and phosphorylated tau protein (Khalaf et al. 2019). Treatment with vildagliptin has been reported to improve memory deficits and reduce neuronal apoptosis in the hippocampus. In addition, treating Alzheimer's rats with Vildagliptin increased BCL2 expression levels, while the expression levels of caspase-3, Bcl-2-associated protein (Bcl - 2 associated X protein), and AD-associated proteins in the hippocampus were reduced (Ma et al. 2018). Moreover, vildagliptin was able to reduce the levels of tau phosphorylated proteins, amyloid precursor protein (APPs), and p-GSKs, and increase the expression levels of the PSD 95 proteins, synaptophysin, and p-Akt, with positive effects on AD recovery (Ma et al. 2018). *Pipatpiboon* et al. observed that vildagliptin prevented neuronal insulin resistance by restoring long-term insulin-induced depression, neuronal IR phosphorylation, IRS-1 phosphorylation, and Akt / PKB-ser phosphorylation. It also improved mitochondrial dysfunction and cognitive function (Pipatpiboon et al. 2013). In a recent study, vildagliptin was shown to reduce inflammatory markers (TNF-α), apoptosis (caspase 3), and oxidative stress (FOXO1) in the hippocampus, BCL2 associated X (BAX), and inhibit JAK2 / STAT3 signaling pathway along with restoration of metabolic disorders (Yossef et al. 2020). Apart from in-vivo and in vitro studies, only one clinical study investigated the effects of vildagliptin on cognitive function in elderly patients with T2DM. This study showed that the addition of vildagliptin to the treatment of diabetic patients improves cognitive function and metabolic control in elderly patients with T2DM(Bulut et al. 2020). Overall, all cell and animal studies have confirmed that vildagliptin has beneficial effects on cognitive function and neurological processes in AD models. However, more studies are needed to confirm this.

GLP-1 agonists

Reports have shown that stimulation of Glucagon-like peptide-1 receptor (GLP-1) can play neurotrophic and neuroprotective roles in many types of cellular and animal neurodegeneration models (Salcedo et al. 2012). Therefore, synthetic analogs of GLP-1 can have beneficial effects in neurodegenerative diseases such as AD (Meng et al. 2020). In the following, we will focus on the drugs of the GLP-1 agonists family.

Liraglutide

Liraglutide is a synthetic analog of GLP-1 with 97% homology. This drug has various effects on AD by crossing the blood–brain barrier (Hunter and Hölscher 2012), including reducing the amount of Aβ plaques, attenuating insulin receptor and synaptic pathology, and reducing cognitive disorders (Long-Smith et al. 2013; Batista et al. 2018; Holubová et al. 2019). Different signaling pathways have been proposed for these effects, addressed below.

Synaptic plasticity acts as a link in the brain between type 2 diabetes and AD. Liraglutide in amyloid precursor protein (APP) / PS1 mice regulates synaptic plasticity and can increase neuron proliferation and differentiation (Parthsarathy and Hölscher 2013). This was confirmed by a recent study by Hamilton et al. They found that Liraglutide increased the number of progenitor cells or doublecortin-positive young neurons in the dentate gyrus of diabetic mice (Hamilton et al. 2011). In the studies of McClean et al., Liraglutide has been shown to improve spatial learning and memory and prevent impairment in synaptic plasticity in the CA1 area of the hippocampus (Llorens-Martín et al. 2014). It also reduces chronic inflammation and increases long-term potentiation (LTP) in Alzheimer's mice model (McClean et al. 2010, 2011, 2015). In addition, treatment with Liraglutide significantly increases memory retention and total hippocampal CA1 pyramidal neuron numbers (Hansen et al. 2015). In the hyperhomocysteinemia rat model, Liraglutide reduced tau hyperphosphorylation and Aβ overproduction, which may alleviate AD-like cognitive impairment (Zhang et al. 2019). Different groups have shown that Liraglutide can reduce the level of hyperphosphorylation of tau and neurofilaments through the glycogen synthase kinase-3β (GSK-3β) c-Jun N terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and cAMP signaling pathways (Hunter and Hölscher 2012; Han et al. 2013; Xiong et al. 2013; Yang et al. 2013; Qi et al. 2016, 2017; Chen et al. 2017).

The effects of this drug have also been observed in clinical trial studies. It has been observed that 12 weeks of this drug in diabetic patients with a family history of AD led to a significant improvement in connectivity between bilateral hippocampal and anterior medial frontal structure (Watson et al. 2019). A clinical pilot study has also shown that Liraglutide improves chronic depression and brain volume on magnetic resonance imaging (MRI) scans (Mansur et al. 2017). Another study found that six months of Liraglutide administration inhibited the reduction of glucose metabolism in the brain according to [(18) F] FDG positron electron tomography (FDG-PET) scans. However, no change in amyloid plaque was observed (Gejl et al. 2016). On the other hand, in their animal studies on APP / PS1 mouse models of AD, Hansen et al. found that long-term use of Liraglutide did not affect amyloid plaque levels (Hansen et al. 2016).

Exenatide

Exenatide is another drug in the GLP-1 agonists family that has been shown to have potential therapeutic effects in AD. Exenatide can increase progenitor cells or doublecortin-positive young neurons in the dentate gyrus (Hamilton et al. 2011). Studies have also suggested the influential role of this drug in neuroprotective pathways. Accordingly, Exenatide has protective effects against tau hyperphosphorylation in mice model of AD through downregulation of GSK-3β activity (Chen et al. 2012; Xu et al. 2015). Four-weeks treatment with this drug in APP / PS1 mice can rescue memory deficits and neuropathological changes and reduce acetylglucosaminyltransferase III (GnT-III) expression through Akt / GSK-3β / β-catenin pathway in neurons (Wang et al. 2018). It has been shown that the Exenatide could reduce hippocampal IRS-1pSer and reduce JNK / TNF-α pathway activity and TNF-α levels. It also improves memory and cognitive behaviors (Bomfim et al. 2012; Solmaz et al. 2015). Studies have also reported that the improvement in cognitive function of the brain caused by treatment with Exenatide may be due to increased anaerobic glycolysis of the brain. However, these results were observed only in PS1-KI mice and not in 3xTg-AD mice (Bomba et al. 2013). In addition, Exenatide can reduce the harmful induction of Aβ42 in the rat hippocampal CA1 region and increase the cAMP signaling pathway (Wang et al. 2016). Clinical trial studies for further investigation about Exenatide in this issue are suggested.

Lixisenatide

Lixisenatide enhances neuronal progenitor proliferation in the dentate gyrus, neurogenesis in the brain, and increases cAMP levels in the brain. Lixisenatide can cross the blood–brain barrier easily and even at lower concentrations than Liraglutide (Hunter and Hölscher 2012). In the meantime, it has been reported that lixisenatide brings about cognitive and pathological improvements in AD at lower doses compared to Liraglutide. It also increases long-term

potentiation, prevents synaptic number reduction in APP / PS1 mice, and decreases the load of amyloid plaque and chronic inflammation (McClean and Hölscher 2014). The results of Cai et al., study have shown that this drug can prevent reducing spatial learning and memory ability by injecting Aβ25-35 into the hippocampus of rats, and this effect is mediated through the PI3K-Akt-GSK3β pathway (Cai et al. 2014).

Dulaglutide

Dulaglutide is another member of this family of drugs that have shown effects against AD. Dulaglutide has a beneficial impact on cognitive ability and memory impairment in the streptozocin-induced AD mouse model. In addition, it reduces the phosphorylation of tau proteins and neurofilament. These results suggest that the neuroprotective role of dulaglutide may be through the PI3K / Akt / GSK3β signaling pathway (Zhou et al. 2019).

SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin)

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are oral anti-hyperglycemic drugs approved to treat type 2 diabetes. Some studies point to their potential effects on the central nervous system's neuroprotective properties.

The study by Hierro-Bujalance et al. has shown that empagliflozin can reduce amyloid β (Aβ) levels, reduce the density of senile plaques in the cortex, and hypothalamus and cause positive cognitive effects (Hierro-Bujalance et al. 2020). Lin et al. also obtained confirmatory results in this regard. They observed that treatment with empagliflozin in db/db mice inhibited cognitive dysfunction associated with a reduction in cerebral oxidative stress and increased cerebral brain-derived neurotrophic factor (BDNF) (Lin et al. 2014). BDNF has important and different roles in the nervous system, including differentiation, maturation, and survival of nerve cells and neuroprotective effects in glutamatergic stimulation, cerebral ischemia, neurotoxicity, and hypoglycemia situations (Wiciński et al. 2020). The protective effect of empagliflozin has also been suggested to be through inhibition of apoptosis. According to a study by Abdel et al., empagliflozin reduced caspase-3 and infarct size and increased HIF-1α / VEGF level in rats with cerebral ischemia / reperfusion (I / R) (Abdel-latif et al. 2020). Interestingly, elderly diabetic rats treated with empagliflozin experienced positive effects on their brain structure and demonstrated protection against abnormalities in the neurovascular units (Hayden et al. 2019).

Canagliflozin from the SGLTi family had favorable effects in scopolamine-induced memory impairment rats. This effect can be attributed to the potential inhibitory properties of its acetylcholine esterase activity (Arafa et al. 2017). These results appear to be consistent with another study that confirms that canagliflozin has dual inhibitor properties for both AChE and SGLT2 (Syed et al. 2014).

Other drugs in this class dapagliflozin, has been shown to have inhibitory effects on acetylcholinesterase. Based on molecular docking, it has been shown that this drug can bind to the AChE receptor with low binding energy, similar to the energy required to bind to SGLT2 (Shaikh et al. 2016). Other drugs in this family, such as ertugliflozin and sotagliflozin, show similar properties (Shakil 2017). Another study on mice receiving a high-fat diet leading to insulin resistance and cognitive decline showed that dapagliflozin could improve hippocampal synaptic plasticity and prevent cognitive decline (Sa-nguanmoo et al. 2017). In addition, SGLT2 inhibitors can enhance angiogenesis and neurogenesis and prevent ischemia-related cerebral damage (Wiciński et al. 2020). Eventually, despite the positive effects of SGLT2 inhibitors on AD, there is still insufficient evidence in this area and various in-vitro and in-vivo studies are required.

Meglitinides (repaglinide, nateglinide, mitiglinide)

Meglitinides are oral non-sulfonylurea drugs for type 2 diabetes that facilitate insulin secretion, and their primary function is inhibiting ATP-sensitive potassium channels in pancreatic beta cells. One of the most common manifestations of neurodegenerative diseases, including AD, is a disorder in the regulation of intracellular calcium concentrations in neurons. Downstream Regulatory Element Antagonist Modulator (DREAM) is a calcium-binding protein in neurons that has a specific function in protein–protein and DNA–protein reactions. Studies have shown that rapaglinide can reduce the half-life of DREAM and disrupt the PS-2 and DREAM reactions, suggesting that rapaglinide may be involved in pathways associated with AD (Naranjo et al. 2018; Santiago et al. 2019). Another manifestation of these drugs is their neuroprotective effects, which may not be directly related to AD. Rapaglinide has been shown to reduce the destructive effects of Kanic acid, in the CA3 region of the hypothalamus, whereas nateglinide does not show such effects (Kim et al. 2014a, b). In addition, Xiao et al., showed that rapaglinide can inhibit the proliferation and migration of Glioblastoma multiforme cells and inhibit the expression of Bcl-2, Beclin-1 and PD-L1 in orthotopic glioma cells (Xiao et al. 2017). On the other hand, it has been shown that nateglinide can also exert its neuroprotective effects in different ways. According to Saad et al. study, nateglinide have different effects such as inhibition of motor activity deterioration through Cav-1, anti-inflammatory property through JAK2 / STAT3 pathway and anti-apoptotic and antioxidant actions by inhibition of Caspase3 and NO and MPO, respectively in the hypothalamus of rats treated with this drug (Saad et al.

Table 1 Therapeutic potential of anti-diabetic drugs against AD

Drug type	Drug name	Study design	intervention	Findings	References
Hypoglycemic agents	Insulin	Rat	2 mU/day porcine insulin	Insulin may play a regulatory role in the synthesis of norepinephrine transporter protein, thereby modulating activity in CNS noradrenergic pathways	Figlewicz et al. (1993)
Hypoglycemic agents	Insulin	3xTg-AD	Intravenous injection of insulin (3.8 units/kg of human insulin	Insulin therapy improves Insulin production, memory deficits, and caspase-3 in pancreatic islets and decreased insoluble AB40 and AB42 in the cerebral cortex in 3xTg-AD mice feeding with HFD	Vandal et al. (2014)
Hypoglycemic agents	Insulin	STZ induced diabetes in hTau mice	insulin injection (4 IU/kg)	Insulin injection 30 min before scarify diabetic mice inhibited phosphatase 2 and restored tau phosphorylation to control levels	Gratuze et al. (2017)
Hypoglycemic agents	Insulin	3×Tg-AD mice	2 UI total, 4 µL/nostril	Intranasal insulin administration improves short-term learning, memory and brain insulin resistance Ameliorates the depressive-like behavior Prevents the impairment of BVR-A and the early dysfunction of the insulin signaling cascade Reduced oxidative stress levels and AD neuropathological markers in the hippocampus and cortex	Barone et al. (2019)
Hypoglycemic agents	Insulin	STZ induced Alzheimer's rat model	2 U/50 µl insulin or saline	Improved cognitive function, neurogenesis and microglial activation Attenuated the level of tau hyperphosphorylation through the down-regulation of ERK1/2 and CaMKII in the brains of ICV-STZ rats	Guo et al. (2017)
Hypoglycemic agents	Insulin	STZ induced Alzheimer's C57 mice model	I.C.V. injection insulin (20 µl per side)	Intranasal insulin administration improves learning and memory function, p-IRS-1 protein level in the hippocampus, and PI3K-Akt-GSK3β pathway Recovered the neurogenesis and neurogenesis markers doublecortin (DCX), NeuroD and BrdU Decreased Aβ and brain insulin resistance	Lv et al. (2020)
Hypoglycemic agents	Insulin	C57BL/6 J wild type (WT) and Tg2576 male mice	Intranasal administration of insulin and GLP-1 agonist, Exenatide 6 days a week for 8 months	Combination therapy intranasal of insulin and exenatide improve learning function and decreased reduced expression of IRSP genes and AB in brain	Robinson et al. (2019)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
Hypoglycemic agents	Insulin	C57BL6/129 mice	Intranasal administration of insulin (1.75 U/day) for one week before anesthesia	intranasal of insulin administration prevent memory deficits Reduce hyperphosphorylation of tau in the mouse brain Improve synaptic proteins, and insulin signaling	Zhang et al. (2016)
Hypoglycemic agents	Insulin	SAMP8 mouse	0.1 g, 1 g, or 10 g human insulin dissolved in 0.25 M phosphate buffer	Intranasal administration of insulin did not alter the genes and protein expression which involved in insulin signaling pathway	Rhea et al. (2019)
Hypoglycemic agents	Insulin	AMCI	Intranasal insulin (20 or 40 IU)	Insulin and glucose level didn't different between AD and MCI subjects and Intranasal insulin administration had no effect on plasma insulin or glucose levels, improve verbal memory in memory-impaired ε4 − adults than for memory-impaired ε4 + subjects and normal adults	Reger et al. (2006)
Hypoglycemic agents	Insulin	Healthy male	Intravenous insulin 1.5 mU/kg / min	Following low and high administration of intravenous insulin despite increased plasma insulin concentration but the glucose levels didn't change Improve cognitive and memory function	Kern et al. (2001)
Hypoglycemic agents	Insulin	Healthy and normal subject	8 weeks of intranasal insulin 0.4 ml insulin (containing 40 IU)	Blood glucose and plasma insulin levels did not differ between the placebo and insulin conditions Improve mood, memory function, self-confidence	Benedict et al. (2004)
Hypoglycemic agents	Insulin	Healthy and normal subject	4 × 40 IU/day over 8 weeks insulin Aspart (ASP-I), insulin RH-I intranasal	Insulin Aspart (ASP-I), improve memory function rather than insulin RH-I	Benedict et al. (2007)
Hypoglycemic agents	Insulin	MCI or mild to moderate AD subjects	20 IU, or 40 IU of insulin detemir for 21 days,	Daily treatment of adults AD patients with 40 IU insulin detemir modulate cognition	Claxton et al. (2015)
Hypoglycemic agents	Insulin	early AD and mild cognitive impairment (MCI)	20 IU intranasal insulin treatment	Intranasal insulin improved cognition function Fasting AB40 levels were elevated, while AB42 was unchanged, AB40/AB42 ratio increased	Reger et al. (2008)
Hypoglycemic agents	Insulin	mild to moderate AD mild cognitive impairment	20 and 40 IU of intranasal insulin 4 months	20 IU of intranasal administration of insulin have better effects on memory and cognitive function than 40 IU. Insulin in two dose didn't change CSF biomarkers	Craft et al. (2012)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
Hypoglycemic agents	Insulin	AD and mild cognitive impairment (MCI)	20 and 40 IU of intranasal insulin 4 months	Low dose of insulin improves cognitive function in both men and women, but high dose just improves in men ApoE ε4 negative males not females benefited from the high dose of insulin Intranasal insulin therapy didn't effects on BMI and weight	Claxton et al. (2013)
Hypoglycemic agents	Insulin	AD and mild cognitive impairment (MCI)	40 IU of intranasal insulin 4 months	Insulin treatment had improved memory especially in ε4 carriers, preserved brain volume on MRI, and reduction in the tau-P181/$A\beta_{42}$ ratio	Craft et al. (2017)
Biguanides	Metformin	APP/PS1 transgenic mice	Metformin (4 mg/ml)was administrated in the drinking water for 2 months	Metformin ameliorated the microglial autophagy impairment, increased the number of microglia around Aβ plaques, promoted the phagocytosis of NP tau, and reduced Aβ load and NP tau pathology in APP/PS1 mice	Chen et al. (2021)
Biguanides	Metformin	Scopolamine-induced memory deficit in rats	Oral metformin (100 and 300 mg/kg/day)	Metformin (low dose) improve cognitive behaviors tests, reduced brain oxidative and inflammatory markers, total AKT while increasing its phosphorylated AKT	Mostafa et al. (2016)
Biguanides	Metformin	11-month-old SAMP8 mice	Injections of metformin at 20 mg/kg/sc or 200 mg/kg/sc for eight weeks	Metformin improved memory, increased pGSK-3βser9 at 200 mg/kg, and decreased Aβ at 20 mg/kg and pTau404 and APPc99 at both 20 mg/kg and 200 mg/kg	Farr et al. (2019)
Biguanides	Metformin	n APP/PS1 female mice	Intraperitoneal injection of 200 mg/kg/d metformin	Metformin attenuated spatial memory deficit, neuron loss in the hippocampus and enhanced neurogenesis, decreased Aβ plaque load and chronic inflammation in the hippocampus and cortex, enhanced cerebral AMPK activation, suppressed the activation of P65 NF-κB, mTOR and S6K, reduced BACE1 protein expression	Ou et al. (2018)
Biguanides	Metformin	db/db mice	Intraperitoneal injection of 200 mg/kg/d metformin	Metformin ameliorates spatial cognitive impairment and hippocampal structure abnormalities, promote autophagy, reduced hyperphosphorylated tau proteins, restored the impaired autophagy in the hippocampi and promotes autophagy in an AMPK-dependent manner in HT22 cells	Chen et al. (2019)
Biguanides	Metformin	Hippocampal Neurons Culture	100 mM	Metformin induced hyperphosphorylation of MAPK JNK, decreased Aβ-Induced Cytotoxicity, and suppresses apoptosis	Chen et al. (2016)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
Biguanides	Metformin	Amnestic mild cognitive impairment (AMCI)	500, 1000,1500,2000 mg twice a day for 12 months	Metformin decreased inflammatory marker hsCRP and HbA1c, Improved selective remaining test (SRT) in a dose-dependent manner without serious adverse effects	Luchsinger et al. (2016)
Biguanides	Metformin	MCI or early dementia due to AD	Metformin (2000 mg/d) for 8 weeks	Metformin decreased BMI and improved learning/memory and attention, and significant changes in CSF glucose, Aβ42, total tau were not observed	Koenig et al. (2017)
Biguanides	Metformin	T2DM	Metformin	Long-term metformin exposure in patients with T2DM increased risk of Parkinson, all cause of dementia and vascular dementia than non-metformin group	Kuan et al. (2017)
Biguanides	Metformin	MCI and AD	Metformin	Among patients with T2DM cognitive performance was worse in metformin consumers	Moore et al. (2013)
Biguanides	Metformin	T2DM	Anti-diabetic drugs	Metformin has a significantly higher associated risk of AD than GLP-1 receptor agonists and rosiglitazone	Akimoto et al. (2020)
Biguanides	Metformin	AD	Anti-diabetic drugs	Metformin In contrast of other anti-diabetic drugs increased risk of developing AD	Imfeld et al. (2012)
Biguanides	Metformin	P301S transgenic mice	2 mg/ml metformin in the drinking water for 4 months	Chronic administration metformin decreased p-tau via AMPK/mTOR and PP2A in cortex and hippocampus, Increased insoluble tau species, β-sheet aggregates, caspase 3 and disrupts synaptic structures	Barini et al. (2016)
Biguanides	Metformin	Tg6799 mice and SH-SY5Y cells	Intraperitoneal Metformin (final dose 200 mg/kg) for 9 days	Metformin increased Aβ plaques, Aβ42 in brain tissue Increased β- and γ-secretase, autophagy via AMPK signaling in SH-SY5Y cells	Son et al. (2016)
Thiazolidinediones	Pioglitazone	APP/PS1 (APPSWE + PSEN1dE9) transgenic mice	Pioglitazone (10 mg/kg) per day for 7 days	Pioglitazone could inhibit Cdk5 activity by decreasing p35 protein level. pioglitazone treatment corrected long-term potentiation (LTP) deficit caused by Aβ exposure in cultured slices and pioglitazone administration rescued impaired LTP and spatial memory in AD mouse models	Chen et al. (2015)
Thiazolidinediones	Pioglitazone	APP transgenic mice	Pioglitazone (20 mg/kg/d) in Teklad Rodent chow diet	Pioglitazone reduced astroglial activation and cortical cholinergic innervation. It reversed CBF and CGU responses to increased neural activity, but failed to improve spatial memory	Nicolakakis et al. (2008)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
Thiazolidinediones	Pioglitazone	APPV717I mice	Pioglitazone (40 mg/kg/d) per day for 7 days	Pioglitazone reduced the number of active microglia and reactive astrocytes in the hippocampus and cortex, as well as decreased the COX2, iNOS, and BACE1 expression	Heneka et al. (2005)
Thiazolidinediones	Pioglitazone	APPswe/PS1Δe9	Pioglitazone (80 mg/kg) gavage for 9 days	Pioglitazone decrease in the level of soluble and insoluble Aβ and increase the microglia uptake of Aβ by PPARγ	Mandrekar-Colucci et al. (2012)
Thiazolidinediones	Pioglitazone	Rat	Pioglitazone (20 mg/kg) was administered intragastrically for 4 weeks	Pioglitazone improve of insulin sensitivity and attenuation Aβ42 accumulation by modulation of AKT/GSK3β activation	Yang et al. (2017)
Thiazolidinediones	Pioglitazone	3xTg-AD	Pioglitazone at 18 mg/Kg/day for 14 weeks	Pioglitazone improved learning, short- and long-term plasticity, and reduce serum cholesterol, Aβ and tau deposits in the hippocampus	Searcy et al. (2012)
Thiazolidinediones	Pioglitazone	Scopolamine-induced memory deficit in mice	9 mg/kg, and 18 mg/kg orally for 9 days	Pioglitazone attenuated scopolamine-induced memory deficits by the enhancement of the cholinergic nerve system, indicated by the elevation of ACh levels, which result from the decreased AChE activity and increased ChAT activity in hippocampus	Xiang et al. (2012)
Thiazolidinediones	Pioglitazone	STZ-induced AD rat model	Intraperitoneal pioglitazone 10 mg/kg for 21 days	Chronic administration of Pioglitazone prevents the STZ-induced memory and learning impairments	Aali et al. (2020)
Thiazolidinediones	Pioglitazone	Mild Alzheimer disease (AD) accompanied with T2DM	15–30 mg per daily	Pioglitazone treatment resulted in improvements of FPG, HbA1c, FIRI, HOMA-R, insulin sensitivity and cognition function	Sato et al. (2011)
Thiazolidinediones	Pioglitazone	Non-diabetic patients with AD	15 mg per daily	Peripheral edema was the principal adverse effect occurring more frequently in subjects taking pioglitazone than placebo. No group differences in laboratory measures were identified. No significant treatment effect was observed on exploratory analysis of clinical efficacy	Geldmacher et al. (2011)
Thiazolidinediones	Rosiglitazone	Tg2576 mice	30 mg/kg of food	Rosiglitazone attenuates learning and memory deficits, brain IDE, and Aβ42 levels	Pedersen et al. (2006)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
Thiazolidinediones	Rosiglitazone	Mild-to-moderate AD patients	2, 4 and 8 mg/once daily	*APOE ε4* non-carriers exhibited cognitive and functional improvement in response to rosiglitazone, whereas *APOE ε4* allele carriers showed no improvement and some decline was noted	Risner et al. (2006)
Thiazolidinediones	Rosiglitazone	APOE-negative subjects	8 mg rosiglitazone XR, 2 mg rosiglitazone XR	No evidence of efficacy of 2 mg or 8 mg RSG XR monotherapy in cognition or global function was detected in the APOE-4—negative or other analysis populations	Gold et al. (2010)
Sulfonylureas	Glibenclamide	Rats	6 mg/kg/day	Aβ25-35 microinjection increased corticosterone and HPA axis activity in rats. Glibenclamide decreased Aβ25-35-induced behavioral abnormalities in rats Glibenclamide reduced Aβ25-35-induced HPA axis hyperactivity in rats	Esmaeili et al. (2018)
Sulfonylureas	Glyburide	Mice with Short-Term High-Fat Diet	Intraperitoneal (6.6 mg/kg)	Administration of glyburide ameliorated hippocampal-independent brain function in HFD-mice	Gainey et al. (2016)
Sulfonylureas	Tolbutamide, glyburide and Glipizide	ICR mice	1 g, in 0.5 ml of ethanol plus 0.5 ml of polyethylene glycol 400	tolbutamide, glyburide and glipizide exert a protective effect against kainic acid-induced neuronal cells death in CA3 region of the hippocampus	Kim et al. (2014ab)
Sulfonylureas	Glibenclamide	C57Bl/6 mice	intraperitoneally (10 µg right after intracerebral hemorrhage	Glibenclamide ameliorates the disrupted blood–brain barrier in experimental intracerebral hemorrhage by inhibiting the activation of NLRP3 inflammasome	Xu et al. (2019)
Sulfonylureas	Glimepiride	N/A	N/A	Glimepiride modified the membrane microenvironments in which Aβ-induced signaling leads to synapse damage. soluble PrP^{C}, released from neurons by glimepiride, neutralized Aβ-induced synapse damage	Osborne et al. (2016)
Sulfonylureas	Glibenclamide	5XFAD mice	Oral administrated 5 mg/kg of glibenclamide in 5% tween per day for eight weeks	Glibenclamide was able to inhibit microglial activation and decrease excessive neuroinflammation both the BV2 microglial cells and 5XFAD mouse. Glibenclamide alleviates Aβ levels in the 5XFAD mouse	Ju et al. 2020
Sulfonylureas	N/A	Diabetes patients with Sulfonylureas or metformin treatment	N/A	sulfonylureas may decrease the risk of dementia, as does metformin	Hsu et al. (2011)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
sulfonylurea	N/A	Meta-analysis	N/A	there was no significant relationship between the use of metformin or sulfonylurea and brain function and structure outcomes	Weinstein et al. (2019)
DPP4 inhibitor	Linagliptin	SK-N-MC human neuronal cells	10 to 100 µM of Linagliptin for 24 h	Linagliptin protected against Aβ-induced cytotoxicity, and prevented the activation of glycogen synthase kinase 3β (GSK3β) and tau hyper-phosphorylation by restoring insulin downstream signaling. Linagliptin alleviated Aβ-induced mitochondrial dysfunction and intracellular ROS generation, which may be due to the activation of 5′ AMP-activated protein kinase (AMPK)-Sirt1 signaling	Kornelius et al. (2015)
DPP4 inhibitor	Linagliptin	C57Bl/6 mice	10 mg/kg/day orally for 3 weeks	Linagliptin exerted a neuroprotective effect in mice with cuprizone-induced demyelination possibly by modulating AMPK/SIRT1 and JAK2/STAT3/NF-κB signaling pathways	Elbaz et al. (2018)
DPP4 inhibitor	Linagliptin	3xTg-AD	Linagliptin orally (5, 10, and 20 mg/kg) for 8 weeks	Linagliptin treatment mitigates the cognitive deficits present in 3xTg-AD mice, and improves brain incretin levels and attenuates amyloid beta, tau phosphorylation as well as neuroinflammation	Kosaraju et al. (2017)
DPP4 inhibitor	Linagliptin	High-fat Induced Cognitive Decline in PS19 transgenic mice	Linagliptin (100 mg/L) in their drinking water, at 10 mg/kg BW/day	Linagliptin-treated mice exhibited higher levels of GLP-1 and decreased fasting blood glucose, compared with the vehicle-treated mice at 8 months. Linagliptin treatment restored spatial reference memory and increased cerebral blood flow without affecting phosphorylation levels of tau or endothelial nitric oxide synthase (eNOS) in the brain	Nakaoku et al. (2019)
DPP4 inhibitor	Linagliptin	STZ-induced diabetic mice	(3 mg/kg/24 h) for 17 weeks	Linagliptin, improved cognitive dysfunction, by decreasing oxidative stress and inhibiting microglial activation in a diabetes model mouse	Ide et al. (2020)
DPP4 inhibitor	Saxagliptin	STZ- induced rat model of AD	orally administered Saxagliptin (0.25, 0.5 and 1 mg/kg) for 60 days	Saxagliptin exerts complete reversal of cognitive deficits that may be attributed to its effect of lowering amyloid load, tau phosphorylation and inflammation in the brain	Kosaraju et al. (2013)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
DPP4 inhibitor	Vildagliptin	SH-SY5Y human neuron-like cells	vildagliptin (50, 100, 250 μM) in the presence of Aβ (5 μM)	vildagliptin exerts a protective effect against Aβ by decreasing apoptosis related proteins, lowering GSK3β and tau phosphorylation levels in addition to expression of PSEN1 and PSEN2 mRNA downregulation effect	Dokumacı and Aycan (2019)
DPP4 inhibitor	Vildagliptin	Rat	10 mg/kg/day, 30 days	Vildagliptin can ameliorate AD-induced biochemical changes in experimental rats, where vildagliptin administration enhanced levels of AChE, Hcy, MDA, and ApoE in a rat model of combined T2DM and AD. Combined vildagliptin and memantine treatment down-regulated APP and phosphorylated tau protein expression in brain tissue of Alzheimer diabetic rats	Khalaf et al. (2019)
DPP4 inhibitor	Vildagliptin	Rat	5 and 10 mg/kg, 4 weeks	vildagliptin improved learning and memory deficits induced in an AD rat model, through an increase in the expression of proteins associated with synaptic plasticity, and a decrease in the expression of apoptosis and AD-associated proteins	Ma et al. (2018)
DPP4 inhibitor	Vildagliptin	Rat	2 mL/kg/day, 21 days	vildagliptin, improved both the peripheral and neuronal insulin resistance caused by HFD consumption. vildagliptin attenuated the impairment of brain IR signaling, and improved the learning and memory deficit caused by HFD consumption	Pipatpiboon et al. (2013)
DPP4 inhibitor	Vildagliptin	Rat	10 mg/kg, oral gavage, 60 days	The neuroprotective properties of vildagliptin are not only through improving metabolic performance, but also through its strong antioxidant, anti-inflammatory and anti-apoptotic potential	Yossef et al. (2020)
DPP4 inhibitor	Vildagliptin	T2DM	N/A	The addition of vildagliptin to treatment improved the copying subdomain of cognitive function and metabolic control of the older patients with type 2 DM within 6 months	Bulut et al. (2020)
GLP-1 agonists	Liraglutide	C57/BL mice	Intraperitoneal 2.5, 25, or 250 nmol/kg/day	Liraglutide could cross the BBB and show physiological activity and neurogenesis in the brain, which may be of use as a treatment of neurodegenerative diseases	Hunter and Hölscher (2012)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
GLP-1 agonists	Liraglutide	AD induced by amyloid-β oligomers in male swiss mice	Daily i.p.[1] injections of 25 nmol/kg For 7 days	Showed that liraglutide prevented the loss of brain insulin receptors and synapses, and reversed memory impairment induced by AD-linked amyloid-β oligomers (aβos) in mice	Batista et al. (2018)
GLP-1 agonists	Liraglutide	Appswe/PSEN1dE9 (APP/PS1) male mice with a C57Bl/6 background	S.c.[2] injected with 0.2 mg/kg of bw (once daily for 2 months)	Liraglutide reduced the Aβ plaque load in the hippocampus and reduced cortical astrocytosis. Moreover, a significant decrease in Tau phosphorylation at Thr231. Also l reduced the levels of caspase 3, which has multiple roles in the pathogenesis of AD	Holubová et al. (2019)
GLP-1 agonists	Liraglutide	Appswe/PS1dE9 mice with a C57BL/6 background	Treated for 8 weeks With 25 nm/kg bw, i.p once daily	Ameliorated of insulin receptor aberrations and attenuated of IRS-1 ps616 upregulation, plaque and glial activation in APPSWE/PS1dE9 mice	Long-Smith et al. (2013)
GLP-1 agonists	Liraglutide	APPSWE/PS1DE9 mice	I.p. Once daily with 25 nmol/Kg bw for 7 days (acute treatment) and 37 days (chronic treatment)	Showed liraglutide improves cell proliferation in subgranular zone and increases differentiation of progenitor cells to neurons	Parthsarathy and Hölscher (2013)
GLP-1 agonists	Liraglutide	Three mouse models of diabetes: ob/ob, db/db, or high-fat-diet-fed mice	S.c., once daily with 25 nmol/kg, 25 nmol/kg and 200 µg/kg bw Respectively, for 4, 6, or 10 weeks	Showed progenitor cell division was enhanced compared with nondiabetic controls after chronic injection. ($P < 0.001$). Also found an increase in young neurons in the DG of high-fat-diet-fed mice after drug treatment ($P < 0.001$)	Hamilton et al. (2011)
GLP-1 agonists	Liraglutide	Male Wistar rats	15 nmol Liraglutide in 5 µl i.c.v.[3]	Demonstrated that Liraglutide and other GLP-1 analogues elicit effects on neurotransmission in the brain. Furthermore, they are also effective in modulating synaptic plasticity	McClean et al. (2010)
GLP-1 agonists	Liraglutide	Appswe/PS1DE9mice with a C57Bl/6 background	25 nm/kg bw (i.p.) Once daily for 8 month	Showed that memory formation were normalised and synapse loss and the loss of synaptic plasticity was prevented. In addition, amyloid plaque load, including dense core congophilic plaques, was much reduced. Chronic inflammation (activated microglia) was also reduced in the cortex, and neurogenesis was enhanced in the dentate gyrus	McClean et al. (2015)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
GLP-1 agonists	Liraglutide	Appswe/PS1DE9mice with a C57Bl/6 background	Injected for 8 weeks at 25 nmol/kg bw (i.p.) Once daily	Prevented memory impairments and prevented synapse loss and deterioration of synaptic plasticity in the hippocampus. Overall β-amyloid plaque count in the cortex and dense-core plaque numbers were reduced by 40–50%, while levels of soluble amyloid oligomers were reduced by 25%. The inflammation response as measured by activated microglia numbers was halved in liraglutide treated APP/PS1 mice. Also numbers of young neurons in the dentate gyrus were increased	McClean et al. (2011)
GLP-1 agonists	Liraglutide	SAMP8 mice	S.c. Once daily With 100 or 500 µg/kg/day; equivalent to 26 or 133 nmol/kg/day For 4 months	Liraglutide delayed or partially halted the progressive decline in memory function associated with hippocampal neuronal loss in a mouse model of pathological aging with characteristics of neurobehavioral and neuropathological impairments observed in early-stage sporadic AD	Hansen et al. (2015)
GLP-1 agonists	Liraglutide	Male Sprague–Dawley rats induced with the vena caudalis with homocysteine	150 µg/kg, 300 µg/kg, or 450 µg/kg per 12 h with s.c. injection for 14 days	Ameliorated the Hyperhomocysteinemia (Hhcy)-induced memory deficit, along with increased density of dendritic spines and up-regulation of synaptic proteins. Also attenuated the Hhcy-induced tau hyperphosphorylation and Aβ overproduction, and the molecular mechanisms involved the restoration of protein phosphatase-2A activity and inhibition of β- and γ-secretases. Phosphorylated insulin receptor substrate-1 also decreased after treatment with Liraglutide	Zhang et al. (2019)
GLP-1 agonists	Liraglutide	APP/PS1/Tau triple transgenic (3 × Tg) AD model mice with a C57Bl/6 background	8 weeks with 300 µg/kg/day, s.c. Injection	Reduced hyperphosphorylation of tau and nurofilamentss and reduced neuronal degeneration, apparently through alterations in JNK and ERK signaling	Chen et al. (2017)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
GLP-1 agonists	Liraglutide	Male C57/BL6 mice induced i.c.v. By Aβ1–42 to produce AD mice	S.c. Injection 25 nmol/bw/day, once daily for 8 weeks	Demonstrated that liraglutide can improve cognitive dysfunction induced by Aβ1–42 and can protect against Aβ1–42-induced ultra-structural changes in neurons and synapses in mice. Hyper phosphorylation of tau at several phosphorylation sites in the brain of AD model mice could be ameliorated by liraglutide via increasing phosphorylation of AKT and decreasing the activity of GSK-3β	Qi et al. (2016)
GLP-1 agonists	Liraglutide	Male C57/BL6 mice induced i.c.v. By methylglyoxal to produce AD mice	S.c. Injection 25 nmol/bw/day, once daily for 8 weeks	Liraglutide reduced methylglyoxal -induced hyper phosphorylation of tau in the brain at several phosphorylation sites by increasing Akt phosphorylation and decreasing GSK-3β activity	Qi et al. (2017)
GLP-1 agonists	Liraglutide	Male Kunming mice	S.c. Injection 300 μg/kg for 30 days	Liraglutide decreased the hyperphosphorylation of tau and neurofilament proteins by enhancing O-glycosylation of neuronal cytoskeleton protein, improving the JNK and ERK signaling pathway, and reduced neural degeneration may be related to its protective effects on AD-like learning and memory impairment induced by i.c.v. Injection of STZ	Xiong et al. (2013)
GLP-1 agonists	Liraglutide	Male Wistar rats	S.c. 0.2 mg/kg/bw twice a day for up to four weeks	Demonstrated decreased phosphorylation of AKT at Ser308 and GSK-3β at Ser9, indicating decreased insulin signaling and the consequent activation ofgsk-3β, and hyperphosphorylation of tau at several AD-associated phosphorylation sites in the brain of a rat model of type 2 diabetes induced by HF-diet and intraperitoneal injection of STZ. Subcutaneous administration of liraglutide reversed these brain abnormalities in a time-dependent manner	Yang et al. (2013)
GLP-1 agonists	Liraglutide	Male Sprague–Dawley rats induced by Aβ25–35	0.05–5 nmol liraglutide injected into the bilateral hippocampus with a rate of 0.2 μl/min	Pretreatment with liraglutide effectively and dose-dependently protected against the Aβ25–35-induced impairment of spatial memory and deficit of late-phase long-term potentiation and also activated camp signal pathway in the brain	Han et al. (2013)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
GLP-1 agonists	Liraglutide	Double-blinded, placebo-controlled study	S.c. Injection W^4 1: 0.6 mg W 2: 1.2 mg, W 3–12: 1.8 mg per day	At baseline (time point 1), higher fasting plasma glucose (FPG) was associated with decreased connectivity between bilateral hippocampal and anterior medial frontal structures. At time point 2, we observed significant improvement in intrinsic connectivity within the default mode network (DMN) in the active group relative to placebo. There were no detectable cognitive differences between study groups after this duration of treatment	Watson et al. (2019)
GLP-1 agonists	Liraglutide	4-week pilot, open-label trial	Adjunctive therapy W 1: 0.6 mg, W 2: 1.2 mg, W 3,4: 1.8 mg per day	Adjunctive liraglutide promoted significant weight loss and weight loss- moderated changes in brain morphometry, which were correlated with improvement in cognitive function	Mansur et al. (2017)
GLP-1 agonists	Liraglutide	26-week, randomized, placebo-controlled, double-blinded intervention	S.c. Injection W 1: 0.6 mg W 2: 1.2 mg W 3–26: 1.8 mg per day	Liraglutide treatment prevented the expected decline of glucose metabolism that reflects disease progression, as observed in the placebo group. Also they found no differences between the groups treated with liraglutide and Placebo with respect to amyloid deposition or cognition	Gejl et al. (2016)
GLP-1 agonists	Liraglutide	Transgenic happlon/PS1A246E mice in FVB/N x C57Bl/6 J (F1) background and Transgenic happswe/hps1δe9 mice in C57Bl/6 J background	Happlon/PS1A246E mice for 3 Months (100 or 500 ng/kg/day, s.c.), and happswe/PS1ΔE9 mice for 5 months (500 ng/kg/day, s.c.)	Long-term liraglutide treatment exhibited no effect on cerebral plaque load in two transgenic mouse models of low- and high-grade amyloidosis, which suggests differential sensitivity to long-term liraglutide treatment in various transgenic mouse models mimicking distinct pathological hallmarks of AD	Hansen et al. (2016)
GLP-1 agonists	Exenatide	Three mouse models of diabetes: ob/ob, db/db, or high-fat-diet-fed mice	S.c., once daily with 25 nmol/kg, 25 nmol/kg and 200 µg/kg bw respectively, for 4, 6, or 10 weeks	Showed progenitor cell division was enhanced compared with nondiabetic controls after chronic injection. Also found an increase in young neurons in the DG of high-fat-diet-fed mice after drug treatment	Hamilton et al. (2011)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
GLP-1 agonists	Exenatide	Male Wistar rats induced with I.C.V injection of STZ[5], PC12 cell lines	S.c. Twice-daily with 10 μg/kg/bw for 14 days	Exenatide could increase the viability of neuronal cells under either high glucose or oxidative stress conditions in vitro, and in vivo treatment led to improved memory and cognitive performance. Also, Exenatide has potential effects in the treatment of neurodegenerative diseases such as AD especially DM-related AD, and probably is related to a decrease of tau hyperphosphorylation levels and GSK-3β activity	Chen et al. (2015)
GLP-1 agonists	Exenatide	Male Sprague–Dawley rats induced with high fat diet and i.p. Injection of STZ	I.p., twice-daily with 3.2 μg/kg/bw for 28 days	Results demonstrate that multiple days with Exenatide appears to prevent the hyperphosphorylation of AD-associated tau protein due to increased insulin signaling pathway in the brain	Xu et al. (2015)
GLP-1 agonists	Exenatide	Male APP/PS1 double-transgenic mice and PC12 cell lines	S.c. Twice-daily with 25 nmol/kg/bw for 4 weeks	Results showed that the levels of gnt-III were increased in APP/PS1 mice and Aβ25-35-incubated neurons, which suggested that gnt-III was affected in progression AD and aberrant gnt-III expression might accelerate the progression of AD through affecting glycoproteins. Exenatide could down-regulate the aberrant gnt-III expression possibly through the Akt/GSK-3β/β-catenin signaling	Wang et al. (2018)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
GLP-1 agonists	Exenatide	APP/PS1 mice on a C57BL/6 background, cynomolgus monkeys induced with amyloid-β peptide oligomers	I.p. Once-daily with 25 nmol/kg/bw for 3 weeks, i.c.v. Canula every three days with 100 µg for 24 days	They show that serine phosphorylation of IRS-1 (IRS-1pser) is common to both diseases. Brain tissue from humans with AD had elevated levels of IRS-1pser and activated JNK, analogous to what occurs in peripheral tissue in patients with diabetes. We found that amyloid-β peptide (Aβ) oligomers, synaptotoxins that accumulate in the brains of AD patients, activated the JNK/TNF-α pathway, induced IRS-1 phosphorylation at multiple serine residues, and inhibited physiological IRS-1ptyr in mature cultured hippocampal neurons. Impaired IRS-1 signaling was also present in the hippocampi of Tg mice with a brain condition that models AD. Importantly, intracerebroventricular injection of Aβ oligomers triggered hippocampal IRS-1pser and JNK activation in cynomolgus monkeys. The oligomer-induced neuronal pathologies observed in vitro, including impaired axonal transport, were prevented by exposure to exendin-4 (exenatide), an anti-diabetes agent. In Tg mice, exendin-4 decreased levels of hippocampal IRS-1pser and activated JNK and improved behavioral measures of cognition	Bomfim et al. (2012)
GLP-1 agonists	Exenatide	Male Sprague Dawley rats induced with I.C.V injection of STZ	I.p. Once-daily with 20 µg/ kg/bw for 2 weeks	Showed that exenatide could increase the viability of hippocampal neurons and improve the cognitive performance in ICV-STZ treated rats by suppressing the inflammation response and increasing cholinergic activity	Solmaz et al. (2015)
GLP-1 agonists	Exenatide	PS1-KI and 3xtg-AD mice	I.p. 5 days a with 500 µg/kg/bw for 9 month	Exenatide promoted beneficial effects on short and long-term memory performances in PS1-KI. In PS1-KI mice, the drug increased brain lactate dehydrogenase activity leading to a net increase in lactate levels, and no effects on mitochondrial respiration. Although, exenatide had no effects on brain metabolism of 3xtg-AD mice	Bomba et al. (2013)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
GLP-1 agonists	Exenatide	Male C57BL/6 mice induced with 15 nmol of Aβ31–35	Intranasal injection with 0.5 or 0.05 nmol	Showed that Aβ31–35 given by intrahippocampal injection disrupted circadian rhythm and impaired learning and memory in mice, and Exendin-4 ameliorated Aβ31–35-induced circadian rhythm disturbance of locomotor activity and impairment of learning and memory	Wang et al. (2016)
GLP-1 agonists	Lixisenatide	C57/BL model of AD[6]	I.p. Once daily with 2.5, 25, or 250 nmol/kg bw[7]	Lixisenatide could cross the BBB[8]. Enhanced neurogenesis and also enhanced camp levels in the brain which may be of use as a treatment of neurodegenerative diseases	Hunter and Hölscher (2012)
GLP-1 agonists	Lixisenatide	Appswe/PS1DE9 mice with a C57Bl/6 background	I.p. Once daily with 1 or 10 nmol/kg/bw for 10 weeks	Lixisenatide improved cognition and long-term potentiation of synaptic transmission. The reduction of synapse numbers and the amyloid plaque load was prevented. The chronic inflammation response (microglial activation) was also reduced by all treatments	McClean and Hölscher (2014)
GLP-1 agonists	Lixisenatide	Male Sprague–Dawley rats induced with 5 nmol/μl of Aβ25–35	Lixisenatide (5 nmol/μl) were twice injected into the bilateral hippocampi with an injected rate of 0.2 μl/ min	Lixisenatide treatment effectively prevented the Ab25–35-induced impairments; and inhibited activation of glycogen synthase kinase 3b (GSK3b), with a significant increase in the phosphorylation of ser9 and a significant decrease in the phosphorylation of Y216	Cai et al. (2014)
GLP-1 agonists	Dulaglutide	C57/BL6 male mice induced with I.C.V injection of STZ	I.p. With 0.6 mg/kg/week/bw for 5 weeks	Dulaglutide significantly shortened the escape latency and increased the number of hidden platform crossings in MWM test and also decreasing the hyperphosphorylation of tau and nfs proteins through improving the PI3K/AKT/GSK3b signaling pathway	Zhou et al. (2019)
SGLT2 inhibitors	Canagliflozin	Male Wistar rats	10 mg/5 ml/kg two times	Canagliflozin improve memory dysfunction induced by scopolamine hydrobromide via cholinergic and monoamines system	Arafa et al. (2017)
SGLT2 inhibitors	Dapagliflozin	Male Wistar rats	Intragastric gavage with 1 mg/kg/day for 4 weeks	Suggested that dapagliflozin prevented cognitive decline in the obese-insulin resistance and could preserving synaptic plasticity	Sa-nguanmoo et al. (2017)

Table 1 (continued)

Drug type	Drug name	Study design	intervention	Findings	References
SGLT2 inhibitors	Empagliflozin	APP/PS1xdb/db mice	Administered in the diet with 10 mg /kg/ week from 4 to 26 weeks of age	EMP treatment helped to maintain insulin levels in diabetic mice. At the central level, EMP limited cortical thinning and reduced neuronal loss in treated mice. Hemorrhage and microglia burdens were also reduced. Senile plaque burden was lower, and these effects were accompanied by an amelioration of cognitive deficits in APP/PS1xdb/db mice	Hierro-Bujalance et al. (2020)
SGLT2 inhibitors	Empagliflozin	Male db/db mice (C57BLKS/J-leprdb/ leprdb)	Administered in the diet with 0.03% for 10 weeks	Empagliflozin significantly prevented the impairment of cognitive function in, which was associated with the attenuation of cerebral oxidative stress and the increase in cerebral brain-derived neurotrophic factor	Lin et al. (2014)
SGLT2 inhibitors	Empagliflozin	Female db/db (BKS.Cg-Dock7m+/+Leprdb/J; DBC)	Administered in the diet with 10 mg/kg/ day for 10 weeks	Findings suggest neuroprotection by empagliflozin via protection of the NVU, blood–brain barrier, US morphology of constituent NVU mural EC, and Pcs/neuroglia AC and mgcs and oligodendrocyte/myelin remodeling in the obese, insulin resistant model of T2DM	Hayden et al. (2019)

[1] Intraperitoneal

[2] Subcutaneously

[3] Intracerebroventricular

[4] Week

[5] streptozotocin

[6] Alzheimer disease

[7] Body weight

[8] Blood brain barrier

2019). According to our search of literature, no study was found on mitiglinide in this area. In general, more studies in the meglitinides family are required to establish the actual mechanism of these medicines on AD.

Conclusion

Based on accumulating evidence that indicates strong association and similar pathological mechanisms between AD and T2DM we discussed the potential of anti-diabetic drugs against AD in currently available animal and clinical studies. Based on data collection in Table 1, the use of intranasal insulin, rosiglitazone, glibenclamide, and GLP-1 agonists was found to have positive effects in AD treatment. In addition, although pioglitazone and sulfonylureas improved diabetic conditions and cognitive impairment, but contradictory results have been seen in the in-vivo and clinical studies. Rosiglitazone has beneficial effects on insulin resistance, glucose, and lipid metabolism, but due to weak penetration in the brain and cardiotoxicity association, it is not recommended for AD treatment. GLP1 agonist (Exenatide) and DPP4 inhibitors (Vidagliptin) have neuroprotective effects. However, more studies are needed to confirm it. Since that metformin is the first line of treatment in diabetes and the most widely used drug in the treatment of diabetes, it is necessary to study its effects on AD. Although most of the data on the use of metformin in AD with or without T2DM are promising, it should be noted that the effect of metformin might depend on complex underlying pathological processes. In some cases, metformin has even been shown to have harmful effects. Therefore, to determine the effects of metformin in the control and treatment of dementia/AD, it is necessary to define broader cohort studies with long-term use of metformin and larger study groups.

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Mahmood Maniatie: edit the English language

Ghodratollah Panahi: completed the review and editing

Reza meshkani: supervised and approved the final manuscript

Data availability The data used to support the findings of this study are included in the article.

Declarations

Ethics approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication All of the authors consent for publication.

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