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REVIEW

Alzheimer's disease and type 2 diabetes mellitus: Pathophysiologic and pharmacotherapeutics links

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Abstract

At present, Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) are two highly prevalent disorders worldwide, especially among elderly individuals. T2DM appears to be associated with cognitive dysfunction, with a higher risk of developing neurocognitive disorders, including AD. These diseases have been observed to share various pathophysiological mechanisms, including alterations in insulin signaling, defects in glucose transporters (GLUTs), and mitochondrial dysfunctions in the brain. Therefore, the aim of this review is to summarize the current knowledge regarding the molecular mechanisms implicated in the association of these pathologies as well as recent therapeutic alternatives. In this context, the hyperphosphorylation of tau and the formation of neurofibrillary tangles have been associated with the dysfunction of the phosphatidylinositol 3-kinase and mitogen-activated protein kinase pathways in the nervous tissues as well as the decrease in the expression of GLUT-1 and GLUT-3 in the different areas of the brain, increase in reactive oxygen species, and production of mitochondrial alterations that occur in T2DM. These findings have contributed to the implementation of overlapping pharmacological interventions based on the use of insulin and antidiabetic drugs, or, more recently, azeliragon, amylin, among others, which have shown possible beneficial effects in diabetic patients diagnosed with AD.

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Core Tip: Alzheimer's disease and type 2 diabetes mellitus are highly prevalent chronic diseases that have shown a significant association. Important pathways have shown to be involved in this relationship, including the phosphatidylinositol 3-kinase and mitogen-activated protein kinase pathways, among others. This has led to the development of therapeutic approaches that can overlap and address both diseases. Some of the most promising interventions include the use of azeliragon, amylin, and glucagon-like peptide-1.

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INTRODUCTION

Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) are highly prevalent diseases in elderly patients[1,2]. According to the International Diabetes Federation, 1 in 11 people had DM in 2019, amounting to approximately 463 million cases worldwide, of which 90% is attributed to T2DM. These alarming numbers have quadrupled since 1990, with a prevalence of 9.3% in adults[3-5]. Moreover, numerous complications have been associated with this disorder, among which are renal disease [6], retinopathy[7], dermopathy[8], peripheral vasculopathy[9], and cognitive alterations[10]. The latter have been investigated recently, due to the prominent link between T2DM and any type of neurocognitive disorder, especially AD.

As a progressive, degenerative, and irreversible disorder, AD is characterized by neuronal loss, the formation of senile plaques composed of extracellular deposits of amyloid beta, and the presence of neurofibrillary tangles (NT) in neuronal microtubules [11]. Recent studies have demonstrated a higher incidence of AD in patients with T2DM in comparison to those without comorbidities. This epidemiologic association has spawned various hypothetical pathophysiological links between both diseases[12]. These studies focus on the role of insulin as a necessary hormone for glucose metabolism in the central nervous system (CNS), with receptors widely localized in the hippocampus, frontal area, and entorhinal cortex, which are all structures involved in memory and learning[13].

Insulin resistance (IR) is a key alteration of this hormone's signaling and is the pathogenic cornerstone of T2DM, where it promotes a chronic state of hyperinsulinemia and hyperglycemia[14]. IR has been associated with the disruption of amyloid protein metabolism in the brain, tau phosphorylation in microtubules[15], and the formation of reactive oxygen species (ROS) in the mitochondria. Thus, these conditions may contribute to the pathogenesis and development of AD.

Therefore, the aim of this narrative review is to summarize the current knowledge on the molecular mechanisms linking T2DM with the development of AD, along with possible emerging therapeutic strategies.

MOLECULAR BASIS OF GLUCOSE METABOLISM IN THE BRAIN

Of all organs, the brain requires the largest energetic demand[16] (Figure 1). Under physiological conditions, a constant supply of glucose, which is the main substrate, is necessary for a normal metabolic functionality. Glucose traffic to the brain is regulated in the endothelial wall of the capillaries by the blood-brain barrier (BBB), a structure composed of two semipermeable membranes, one luminal and one abluminal[17].

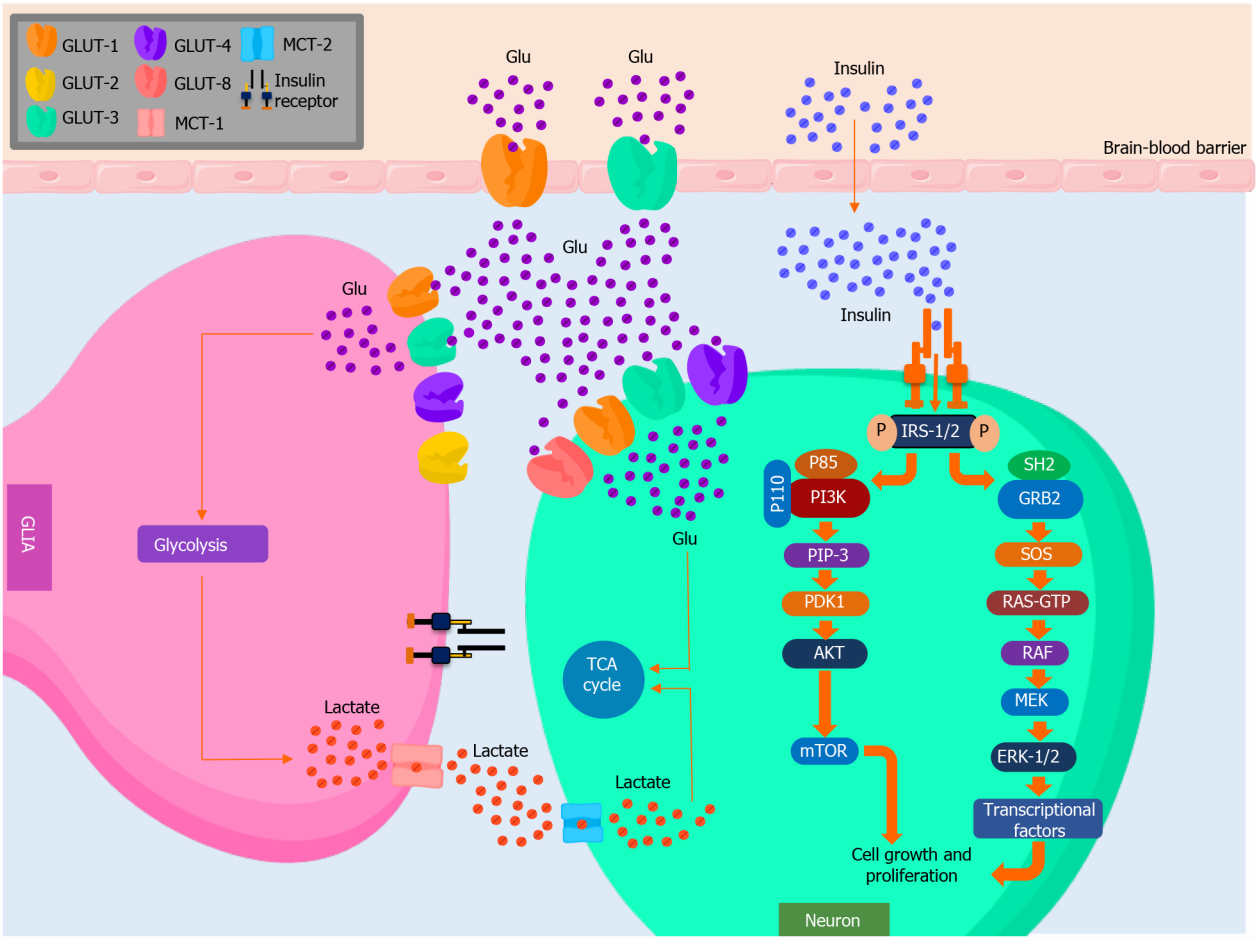

Figure 1 Molecular basis of brain glucose and insulin metabolism. Glucose transporter (GLUT)-1 and GLUT-3 are widely expressed in the brain blood barrier (BBB), allowing glucose transport. Likewise, GLUT-1, GLUT-2, GLUT-3, and GLUT-4 are present in the membrane of glial cells, whereas GLUT-1, GLUT-3, GLUT-4, and GLUT-8 are expressed in neurons. These allow the transport of glucose to the intracellular environment, ready for energetic metabolism. On the other hand, it has been proposed that insulin crosses the BBB through a saturable transporter and then couples to the insulin receptor substrate (IRS) in the neuronal membrane, causing a conformational change that phosphorylates IRS-1/2, which mainly activates the AKT and extracellular signal-regulated kinase (ERK)-1/2 pathways. After a phosphorylation cascade, this activates mTOR and various transcriptional factors involved in the growth and cellular differentiation of the nervous system. Glu: Glucose; GLUT: Glucose transporters; IR: Insulin receptor; MCT: Monocarboxylate transporter; IRS: Insulin receptor substrate; GRB2: Growth factor receptor-bound protein 2; SOS: Son of Sevenless homolog; RAF: Rapidly accelerated fibrosarcoma kinase; MEK: Mitogen-activated protein kinases; ERK: Extracellular signal-regulated kinase; PI3K: Phosphatidylinositol 3-kinase; PIP-3: Phosphatidylinositol (3,4,5)-trisphosphate; PDK1: Phosphoinositide-dependent kinase-1; AKT: Protein kinase B; TCA cycle: Tricarboxylic acid cycle.

Both are aligned next to endothelial cells, regulating the transportation of hydrophilic metabolic substrates, such as carbohydrates and amino acids, in the CNS[18].

Glucose is a polar and hydrophilic molecule, preventing its diffusion through the blood capillaries. Thus, it needs a system of specific transporters[16]. Glucose transporters (GLUTs) in the cells of superior organisms are classified into two large families: the family of facilitated diffusion GLUTs and the family of sodium and glucose co-transporters. GLUTs are glycoproteins located in the plasmatic membrane. They have a range between 45 and 55 kDa and their N- and C-terminal ends are both located in the cytoplasm[19].

GLUTs in the nervous system: GLUT-1 and GLUT-3

GLUT-1 and GLUT-3 isoforms display the highest affinity for glucose. Therefore, their presence in tissues that exclusively depend on glucose for their metabolic requirements is extremely important[16]. They are expressed in the endothelial cells of the BBB as well as the plasma membranes of neurons and glial cells[20].

The GLUT-1 gene is located in the 1p35.31.3 chromosome, which is widely expressed in numerous tissues, and is considered the main GLUT of the BBB[16]. It is 3-4 times more abundant in the luminal membrane than the abluminal membrane and mediates the transport of glucose from the blood to astrocytes. GLUT-1 isoforms vary on molecular weight. 55-kD GLUT-1 is expressed in the endothelial cells of the brain blood vessels, whereas 45-kD GLUT-1 is mainly expressed in astrocytes. GLUT-1 is

highly hydrophobic, and its high glucose affinity (Km = 1-2 mmol/L) allows it to transport glucose into cells at virtually any concentration[17], with selectivity for D-glucose. Therefore, it is thought to act as a basal GLUT that maintains stable glucose levels in the CNS[20].

GLUT-3 works in harmony with GLUT-1, allowing the vectorial transport of glucose to neurons[16]. It is a high-affinity GLUT (Km = 1-2 mmol/L) found primarily in the brain, although low levels of GLUT-3 have been detected in the myocardium, placenta, liver, and muscle. Regarding its kinetic properties, it appears to alternate between the intake and release of glucose[21]. Current hypotheses suggest the facilitated transport of glucose involves conformational changes in the tertiary structure of the transporter. This is triggered by the presence of glucose in its binding site on the extracellular portion of the transporter and its progressive movement to the intracellular portion of it, where another binding site is found[19].

The expression of GLUT in the nervous system varies across different cells. Astrocytes express different isoforms of the GLUT family, including GLUT-1, GLUT-2, and GLUT-4. These cells cover 99% of the BBB and it is through these GLUT isoforms that glucose is able to cross this barrier[18]. Meanwhile, neurons express GLUT-3, GLUT-4, and GLUT-8. Despite the expression of these GLUT isoforms, it has been investigated whether astrocytes, which take glucose and release lactate, are a necessary mediator between glucose and neurons or, as the conventional hypothesis proposes, neurons receive glucose directly from the interstitial fluid of the brain in aerobic conditions[21]. Through this process, glucose would enter the glycolytic pathway and the tricarboxylic acid pathway for its later oxidation, which provides the cell with the necessary energy to maintain cellular function[17]. The aforementioned glucose transportation mechanism can become the limiting step in certain situations, including the development of hypoglycemia and other conditions, such as AD, mainly limiting blood flow, BBB permeability, and changes in GLUT-1 expression[18].

Role of insulin in the brain

Insulin is a peptide hormone necessary for maintaining glucose homeostasis[22]. In the brain, it has important neuroprotective and neuromodulatory functions, such as regulating its growth, repairing dendritic cells and neurons, and having anorexigenic effects on the hypothalamus, among other effects[23]. It is chiefly synthesized in the pancreas[24], although the presence of insulin mRNA in neurons suggests that it may be locally produced in the nervous tissues, especially in the hypothalamus, cerebral cortex, olfactory bulb, substantia nigra, and pituitary gland[16]. Insulin may also intervene in learning and memory brain functions, especially verbal memory, as evidence shows this hormone modulates the secretion of neurotransmitters, such as acetylcholine, and favors synaptic plasticity[22].

Once in the plasma, insulin can cross the BBB *via* active transportation mediated by its receptor, which is abundantly expressed in neurons and, in lower quantities, in glial cells[22]. After binding to its receptor, insulin promotes the autophosphorylation of tyrosine residues, triggering its intrinsic tyrosine kinase activity and phosphorylating the insulin receptor substrate (IRS) coupling protein in the tyrosine residue[24]. The majority of this response is coupled to IRS-1 and IRS-2, which are ubiquitously expressed and the main mediators of insulin-dependent mitogenesis, and the regulation of glucose metabolism in the majority of cell types[21]. Historically, IRS-1 was the first insulin substrate to be identified and represents the prototype of IRS family proteins, whereas IRS-2 is mainly involved in the regulation of brain growth. The phosphorylation of tyrosine residues on IRS activates Akt, which phosphorylates substrates, such as the mammalian target of rapamycin (mTOR) and the glycogen synthase kinase-3 (GSK3), among other targets[25]. Insulin also activates the extracellular signal receptor kinase (ERK) pathway by activating type 1 and type 2 ERKs[24]. These molecules can modify the expression of certain genes (c-fos, Elk-1) involved in cell growth and differentiation[22].

PATHOGENESIS OF AD: NEUROBIOLOGICAL PRINCIPLES

AD is a neurogenerative disorder that results in a gradual and irreversible deterioration of memory and other cognitive functions. It can also be frequently accompanied by other manifestations, such as psychosis, depression, and behavioral alterations[26]. Various environmental, genetic, and biologic factors participate in its pathogenesis[27,28]. Genetic data suggest that AD may be the result of the dysfunction in the amyloid protein precursor pathway, where the production of presenilin 1

(PSEN1) and presenilin 2 (PSEN2) takes place. The *PSEN1* gene is located in chromosome 14, whereas the *PSEN2* gene is located in chromosome 1[29]. Although mutations in these genes lead to the familiar autosomal presentations of AD, the presence of the E4 allele of the E apolipoprotein (APOE) is the main genetic susceptibility factor that has been identified. People with E4/4 homozygotes are eight times more likely to suffer AD compared to those who do not have these alleles[30].

Amyloid metabolism: Senile plaques

Physiologically, neuronal cells release soluble amyloid beta, which is a peptide with a molecular weight of 4 kD and a length of 42-43 amino acids. The main types of amyloid (Aβ40 and Aβ42) emerge as a product of the normal secretion of the transmembrane amyloid protein precursor after a proteolytic process that requires the participation of secretases (α β γ). α-Secretase acts on the amyloid beta peptide, promoting its breakdown in two segments, which are nexin II and soluble amyloid beta peptide, which has 16 amino acids[31].

Afterward, the α-2-macroglobulin acts forming the BA-A2M complex, which will couple to a protease enzyme to reenter the neuron[32]. During this process, the secretases cleave the BA peptide from 40 to 42 amino acids. Such enzymes include the beta secretase (acting on amino acid 1) and gamma secretase (40-42 activity). The accumulation in the interstitial tissue of insoluble 1-42 beta amyloid fragments goes through various transformations in relation to its protein structure until it acquires a folded shape that is difficult to break down. Furthermore, other stable proteins are associated with this process, such as the serum amyloid P component[33]. The presence of these structures leads to the activation of the immune system, especially the phagocytic cells of the CNS (microglia), which perpetuate the lesion due to pseudoinflammation and the release of ROS. However, recent studies have suggested that the participation of amyloid beta is attributed to its deposit on the brain blood vessels, which leads to degeneration and hemorrhages, which are important events in the physiopathology of AD[34].

Neurofibrillary metabolism: NT

Tau is a protein that is highly associated with neuronal microtubules[35]. Through its isoforms and phosphorylation, tau protein interacts with tubulin to stabilize the structure of neuronal microtubules, allowing for an efficient synaptic activity[36]. The tau hypothesis indicates that an excessive or abnormal phosphorylation of this protein results in the transformation to a paired helical filament conformation (PHF-tau). This leads to its precipitation and autoaggregation, which slows the axonal transport and causes neurodegeneration due to possible apoptosis[37]. NT can be intracellular and extracellular. Intracellular NT are hyperphosphorylated and usually found in abundance in the neuritic component of the neuritic plaque. Meanwhile, extracellular NT are the result of neuronal death and the denomination of the insoluble fibrillar skeleton and is characterized by insoluble neurofibrillary components that are difficult to proteolyze. These persist even after neuronal death as remains in the extracellular medium[38].

AD, IR, AND T2DM: PHYSIOPATHOLOGICAL LINKS

General glucose metabolism involves various intracellular processes, including glycolysis, the Krebs cycle, and oxidative phosphorylation. Likewise, it requires extracellular factors, such as its transportation from the circulation to the intracellular environment, in which insulin has a key regulating role[12]. T2DM is associated with the progressive loss of sensitivity to this hormone in a growing IR state, which is also present in AD. This outlines a possible overlap in the pathogenesis of both condi-tions [39].

T2DM has been associated with changes in cognition and cognitive dysfunction, reporting a higher risk of developing any type of neurocognitive disorder, including AD[40]. Indeed, various clinical and preclinical studies suggest that these disorders may share multiple biochemical characteristics and signaling pathways[41] (Figure 2).

Different studies have demonstrated the association between IR and AD, even in the absence of hyperglycemia or DM. In this sense, it has been found that neurocognitive functions dependent on insulin in patients with sporadic AD could play an important role in the physiopathology of this disease, causing disruptions of insulin signaling in the brains of these individuals[42]. Similarly, a second study examining AD patients non-homozygous for the APOE-ε4 allele reported the presence of fasting insulinemia

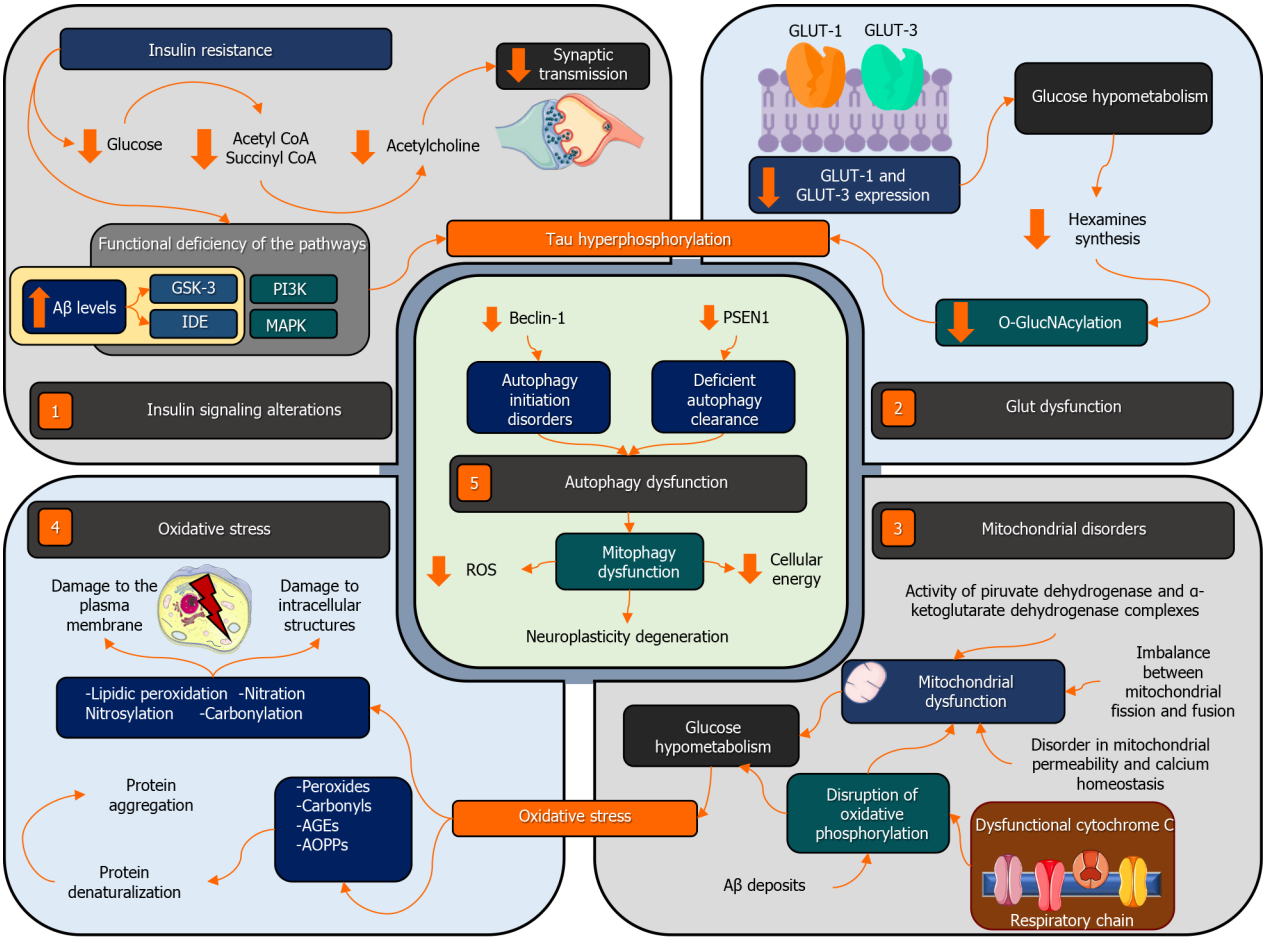

Figure 2 Pathophysiological links between Alzheimer's disease and type 2 diabetes mellitus. Alterations in insulin signaling (1), particularly insulin resistance (IR), decrease the bioavailability of intracellular glucose, altering the synthesis of acetylcholine precursors, which affects synaptic transmissions related to cognition. Likewise, IR alters the intracellular signaling cascade of the PI3K (phosphoinositide 3-kinase), MAPK (mitogen-activated protein kinase), GSK-3 (glycogen synthase kinase-3), and IDE (insulin-degrading enzyme) pathways. This increases tau hyperphosphorylation. On the other hand, the low expression of glucose transporter (GLUT)-1 and GLUT-3 in the different brain regions (2) is related to the downregulation of hexosamines, which decreases O-GlcNAcylation and increases tau hyperphosphorylation. Moreover, mitochondrial dysfunction (3) caused by functional and structural changes in mitochondria and the production of ROS (4) increase protein aggregation and compromise both the intracellular and membrane components of the neurons. Moreover, mitophagy and autophagy dysfunction (5) also contribute to the development and progression of Alzheimer's disease in type 2 diabetes mellitus. PI3K: Phosphoinositide 3-kinase; MAPK: Mitogen-activated protein kinase; IDE: Insulin-degrading enzyme; GSK-3: Glycogen synthase kinase-3; PSEN1: Presenilin 1; ROS: Reactive oxygen species.

and a lower concentration of insulin in the cerebrospinal fluid (CSF), which shows decreased brain insulin uptake[43]. These findings together with those reported by other studies[44,45], suggest that insulin signaling disruption can be particularly important in the physiopathology of AD in those individuals who are not homozygous for the APOE-ε4 allele.

More recent studies point out that due to its effects on neurodegeneration, brain glucose metabolism, and cognitive performance, peripheral IR could be associated with the pathophysiology of AD in pre-diabetic[46] and non-diabetic patients[47,48]. A study that included 130 non-diabetic patients with AD reported that IR was independently associated with decreased glucose metabolism in the hippocampus and with a lower volume of gray matter[47]. Likewise, a second study reported that high serum insulin levels were significantly associated with severe AD presentations. This significance persisted when non-diabetic patients were excluded[48]. In fact, different studies have shown a decrease in AD incidence[49] and improvement of cognitive performance and brain insulin metabolism in patients with AD that have been treated with insulin or insulin-sensitizing drugs. This provides further evidence of the role of IR in the pathogenesis of AD[15,50,51].

Abnormalities in insulin signaling: Phosphatidylinositol 3-kinase and mitogen-activated protein kinase pathways

The terms "type 3 diabetes mellitus" or "brain insulin resistance" have been coined to describe the dysfunction of insulin signaling seen in AD[52]. IR decreases the

availability of glucose needed for neuronal synaptic transmissions due to the deficiency of certain metabolites produced in the glycolytic pathway, such as coenzyme A and succinyl coenzyme A. These are key precursors for the synthesis of acetylcholine, the main neurotransmitter related to cognition[53]. Similarly, it has been proposed that IR induces a series of changes in molecular mechanisms that promote the synthesis and degradation of the amyloid beta peptide and the hyperphosphorylation of the tau protein[54].

Dysfunction in insulin signaling mainly affects the efficiency of the phosphatidylinositol 3-kinase (PI3K). Studies have reported that the brains of patients suffering from AD and T2DM have decreased levels of PI3K, which leads to nervous tissue degeneration. Furthermore, deficient insulin signaling leads to hypoglycemia, which is characteristically found in AD. A decrease in the O-GlcN-acylation of tau has also been observed in the brains of these patients, which is a consequence of hypoglycemia as O-GlcN-acylation is a glucose-dependent process[55,56]. However, this is not the only pathway involved in the pathogenesis of AD. Other factors, such as the mitogen-activated protein kinase (MAPK) pathway, GSK-3, insulin-degrading enzyme (IDE), and microvascular dysfunction, also play an important role in tau hyperphosphorylation. In this sense, a decrease in GSK-3 phosphorylation and increase of its activity can facilitate γ-secretase activities and the processing of the amyloid precursor protein, resulting in higher levels of intracellular amyloid beta peptide[57]. Alternatively, IDE is a zinc metalloprotease that participates in the degradation of different extracellular substrates, such as insulin and amyloid beta. Therefore, its low quantities contribute to an increase in brain amyloid beta levels, especially in the hippocampus [58].

Abnormalities in GLUT-1 and GLUT 3

In regard to GLUTs, clinical studies have revealed that part of the brain hypometabolism in individuals with AD and T2DM may be attributed to a decrease in the expression of GLUT-1 and GLUT-3 in the different areas of the brain[59,60]. Possible causes appear to be post-translational, as no changes have been found in the GLUT-1 ARNm levels in the cerebral cortex[61]. Alterations in glucose transport lead to a reduction in its metabolism, which is associated with the down-regulation of the hexosamine biosynthesis pathway. This involves a decrease in the O-glycosylation of the Ser/Thr residues of tau protein by the β-N-acetylglucosamine (or O-GlcNA cylation), which leads to its abnormal hyperphosphorylation and the formation of NT, contributing to the progression to AD[62].

Moreover, reduced neuronal levels of GLUT-3 have also been identified in patients with T2DM[63]. Likewise, this decrease in the O-GlcNAcylation and hyperphosphorylation of tau has been correlated with decreased levels of GLUT-1 and GLUT-3 in the brain tissue samples of patients with AD[64]. Similarly, other research groups have found a decreased expression of GLUT-1 and/or GLUT-3 in the brain cortex[65] and the dentate gyrus of the hippocampus[66], which were related to the formation of NT. However, the decrease in the expression of these GLUTs, rather than being the main cause of the hypometabolism observed in patients with AD, is more likely to be the result of a decrease in energy demand[64]. Further studies are needed to confirm the direct link between the alterations of GLUTs and neurodegeneration.

Oxidative stress and mitochondrial dysfunction in AD and T2DM

The brain is particularly vulnerable to oxidative damage and mitochondrial dysfunction because of the neurons' high metabolic rate, their dependence on mitochondria to obtain energy, and their low antioxidant defenses[67,68]. Numerous findings have indicated that mitochondrial dysfunction and oxidative stress are implicated in the physiopathology of AD and T2DM[69,70].

Regarding mitochondrial disorders, a decrease in the activity of the pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes has been found in the brains of patients with AD. Both complexes are involved in the Krebs cycle, which can lead to mitochondrial dysfunction, glucose hypometabolism, and neuronal oxidative stress[71,72]. Similarly, brain hypometabolism in individuals with AD is related to a disruption in mitochondrial oxidative phosphorylation[73]. Cytochrome c oxidase is the complex with greater alterations in the respiratory chain in neurons from different cortical regions[74-76]. Moreover, mitochondrial dysfunction in AD is associated with an imbalance in mitochondrial fusion and fission, alterations in mitochondrial permeability, calcium homeostasis, and the release of proapoptotic factors[77,78]. Furthermore, the accumulation of amyloid beta deposits in the mitochondria of individuals with AD alters the functions of the respiratory chain and other mitochondrial components, which impacts multiple neuronal properties and activities[79-82].

On the other hand, the increase in ROS and their effects on biomolecules have been associated with the development of cell disorders related to age in AD and DM. Therefore, oxidative stress is one of the main mediators in the processes underlying both diseases[83,84]. Oxidative damage to structural components of the neuronal membrane affects enzymes, ionic channels, and receptors anchored to it. Likewise, it also affects intracellular structures, such as organelles (mitochondria) and DNA or RNA, be it through lipidic peroxidation, nitration, nitrosylation, or carbonylation[85]. Likewise, oxidative stress can lead to the formation of peroxides, carbonyls, advanced glycation end products (AGEs), and advanced oxidation protein products. Furthermore, this results in the denaturalization and aggregation of proteins[86].

The increase in ROS inhibits the cellular production of energy and decreases insulin secretion and sensitivity[87]. Similarly, oxidative damage affects a variety of signaling pathways related to the unfolded protein response and protein degradation, which could lead to IR[88]. Finally, studies have found that mitochondrial disorders related to age increase the oxidative stress in individuals with T2DM, contributing to the development and progression of AD[89-91].

Autophagy in AD and T2DM

Autophagy is a catabolic process which is both constitutive and inducible, wherein a cell uses the liposomal machinery to degrade components or cellular organelles that are damaged or senescent. This process can also recycle biomolecules that are then available for the ensemble of new cell structures[92]. Different studies have reported that autophagy is a crucial deleterious process in AD and T2DM[93-95]. Furthermore, evidence suggests autophagic dysfunction in β-pancreatic cells and other peripheral tissues could contribute to IR[96,97]. This can occur through the deposit of amyloid in the islets, mitochondrial dysfunction, or disorders in regulatory mechanisms, such as the AMPK pathway and the mTOR pathway[69,97-99]. All of these factors are involved in the regulation of autophagy, glucose homeostasis, and peripheral insulin sensitivity.

Moreover, autophagy also intervenes in synaptic plasticity, axonal myelinization, and inflammatory modulation by glial cells. Therefore, alterations in this process contribute to the occurrence and development of neurodegenerative disorders, such as AD[100-102]. This association has been supported by animal and human studies related to AD, reporting alterations in genes and proteins associated with autophagy [95]. Transgenic mice studies have focused on the role of defective lysosomal degradation in the pathogenesis of this condition[103,104]. Studies in patients with AD have reported that mutations in PSEN1 contribute to the defective proteolysis of autophagy substrates[105]. Furthermore, it has been suggested that the excess of autophagy vacuoles reported in dystrophic neurons in such patients is the result of a defective clearance of the autophagosome[106]. Likewise, a significant reduction in the expression of Beclin-1 has been observed in AD patients, which is a fundamental protein in the stages of initiation and maintenance of autophagy, interfering with autophagy activities[107]. Furthermore, dysfunctions in mitophagy have also been identified. This mechanism participates in the detection and elimination of damaged mitochondria. It has also been associated with AD as it induces the deterioration of neuroplasticity by increasing the levels of ROS and decreasing the levels of cellular energy[108,109]. Alterations at the beginning of autophagy, deficient clearance of autophagy substrates, and dysfunction in mitophagy constitute the physiopathological processes important in AD[110].

In synthesis, various associations between T2DM and the development of neurocognitive disorders, specifically AD, have been reported over the years. However, some authors suggest that this association may be confounded by factors, such as smoking, hypertension, APOE E ε4, or brain infarctions, which could explain the progressive emergence of cognitive deterioration and clinical diagnosis of AD in patients with T2DM[111]. At any rate, various epidemiological and postmortem studies (Table 1) have observed the high frequency of AD in patients with T2DM, which could be explained by the different common pathophysiological mechanisms explained in the previous section[112-120].

NEW STRATEGIES FOR THE TREATMENT OF AD

Concerning the multiple pathophysiological links between T2DM and AD, the neuroprotective effects of lifestyle interventions, antidiabetic drugs, and other molecules have gained interest in the scientific community in the past years (Table 2).

Table 1 Epidemiological studies on the link between Alzheimer's disease and type 2 diabetes mellitus

Ref.	Methodology	Results
Gudala *et al*[112]	Meta-analysis with 28 prospective observational studies which evaluated the association between diabetes and the risk of developing AD	A 56% risk of developing AD [RR = 1.56 (95%CI: 1.41-1.73), $P < 0.05$] was reported in patients with diabetes
Profenno *et al*[113]	Meta-analysis of 16 cross-sectional studies evaluating the relationship between diabetes and AD	The presence of diabetes significantly and independently increased the risk of AD [OR = 1.54 (95%CI: 1.33-1.79; $P < 0.001$]
Ohara *et al* [114]	Prospective study that evaluated the association between glucose tolerance status and the development of neurocognitive disorders in 1017 individuals ≥ 60 yr	AD incidence was significantly higher in subjects with T2DM compared to subjects with normal tolerance to glucose [HR = 2.05 (95%CI: 1.18 to 3.57), $P = 0.01$]
Xu *et al* [115]	Prospective study that examined the association between diabetes and the different types of neurocognitive disorders in 1248 older adults. Diagnoses were based on the DSM-III-R criteria	Individuals with non-diagnosed diabetes had a HR of 3.29 (95%CI: 1.20-9.01) $P < 0.05$ for AD diagnosis
Xu *et al* [116]	Prospective study that evaluated the association between T2DM and neurocognitive disorders and AD in 1301 older adults	T2DM diagnosis was significantly associated with neurocognitive disorders [HR = 1.5 (95%CI: 1.0-2.1) $P = 0.04$] and AD [HR = 1.3 (95%CI: 0.9-2.1) $P < 0.05$]
Peila *et al* [117]	Prospective study that examines the association between T2DM and neurocognitive disorder incidence in 2574 Japanese-American men. Diagnosis of neurocognitive disorder was performed through physical exam and MRI according to the NINCDS-ADRDA and DSM-IV criteria	T2DM was significantly associated with AD diagnosis [RR = 1.8 (95%CI: 1.1-2.9) $P < 0.05$]
McIntosh *et al*[118]	Prospective study that examined the relationship between T2DM, biomarkers, and the risk for suffering from neurocognitive disorders in 1289 dementia-free participants. AD biomarker levels were measured from the CSF. Neurocognitive disorders were evaluated through the CDRSB	Untreated diabetic individuals had higher levels of p-tau, p-tau/Aβ1-42, and t-tau/Aβ1-42 in their CSF than normoglycemic or prediabetic individuals ($P < 0.05$). The untreated group did not progress to neurocognitive disorder in higher rates than normoglycemic individuals [HR = 1.602 (95%CI: 1.057-2.429); $P = 0.026$]

AD: Alzheimer's disease; T2DM: Type 2 diabetes mellitus; RR: Relative risk; HR: Hazard ratio; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, revised third edition; CSF: Cerebrospinal fluid; CDRSB: Clinical Dementia Rating Sum of Boxes; p-tau: Phosphorylated tau; t-tau: Total tau; Aβ1-42: β-amyloid 1-42; MRI: Magnetic resonance imaging; NINCDS: National Institute of Neurological and Communicative Disorders and Stroke; ADRDA: Alzheimer's Disease and Related Disorders Association; CI: Confidence interval; OR: Odds ratio.

Lifestyle interventions such as nutritional counseling and physical activity are among the first indications made to diabetic and insulin-resistant patients as established by international guidelines[121]. A systematic review by Dunkley *et al*[122] reported the efficacy of these interventions in diabetes prevention, similar to what was observed by a second systematic review in which high-risk T2DM patients participated in lifestyle interventions, observing that there was a lower incidence of T2DM among these subjects[123].

Numerous benefits have also been observed in the context of lifestyle interventions and cognitive decline. As it has been reported, nutritional behaviors such as calorie restriction and the inclusion of an antioxidant-rich diet have shown a beneficial effect in slowing the progression of neurodegenerative illnesses[124]. In addition, dietary interventions with meals characterized by low saturated fat and low glycemic index have shown improvement not only in insulin sensitivity but also in molecular markers of AD, such as an increase of Aβ42 in the CSF, which normally shows reduced levels in patients with AD[125].

Furthermore, when examining the impact of healthy lifestyle behaviors in AD incidence, two longitudinal studies found that there is an additive effect. In consequence, those individuals who practiced two to three behaviors such as following the Mediterranean diet, performing physical activity, and having a low consumption of alcohol showed a lower incidence of AD than those performing only one or none of these behaviors[126]. Overall, lifestyle interventions for diabetic patients, patients with IR, and patients with AD show benefits at the metabolic and cognitive levels and are recommended as part of non-pharmacological treatment and preventive interventions for these conditions.

There are numerous pharmacological interventions for the treatment of T2DM and AD. The systematic administration of insulin has been widely associated with a decrease in the pathological accumulation of amyloid beta as well as with cognitive improvement[127], especially in declarative memory[128,129] and attention[127]. Nevertheless, the use of insulin has not yet proven to be a safe and effective treatment for AD. Furthermore, there are adverse effects such as hypoglycemia[130], which is one of the main issues associated with insulin therapy, related in some cases to higher cardiovascular risk and, subsequently, death[131,132]. Likewise, repeated episodes of

Table 2 Summary of key evidence and ongoing trials on Alzheimer's disease and type 2 diabetes mellitus

Ref.	Antidiabetic drug	Methodology	Results
Craft *et al*[137]	Intranasal insulin	Randomized, double-blind, placebo-controlled trial which evaluated the effects of intranasal insulin administration in 104 adults with amnestic mild cognitive impairment or mild to moderate AD	Treatment with 20 UI of insulin improved delayed memory ($P \leq 0.05$). According to caretakers, a functional improvement was observed in the groups receiving 20 and 40 UI of insulin, respectively ($P \leq 0.01$)
Alp *et al*[164]	Beta-glucan and gliclazide	Preclinical assay including mice with induced diabetes. These were subdivided into six groups among which two groups received treatment with beta-glucan or gliclazide. Different parameters were used to determine the level of oxidative stress, including paraoxonase-1, total antioxidative status, and malondialdehyde	Mice with induced diabetes with no treatment presented high levels of malondialdehyde with a decrease in paraoxonase-1. Groups treated with beta-glucan and gliclazide presented a return of these values to normal levels after treatment, showing a decrease in brain oxidative stress ($P \leq 0.05$)
Mostafa *et al* [174]	Metformin	Preclinical study in mice in which a group received scopolamine and metformin at and the other group received scopolamine and rivastigmine. Malondialdehyde, Akt, phosphorylated Akt, phosphorylated tau, and acetylcholinesterase levels were determined	The functionality of mice receiving scopolamine and a dose of metformin of 100 mg/kg per day was better than the group that was not administered with metformin. They also presented less inflammation and oxidative stress compared with the group receiving rivastigmine. An increase in phosphorylated Akt was observed
Qi *et al*[188]	Liraglutide	Forty mice were divided into four groups. The group with amyloid beta-induced AD was administered with liraglutide for 8 weeks and their cognitive performance was evaluated using a Morris water labyrinth	A protective effect in cognitive performance was observed in mice administered with liraglutide. Likewise, less structural changes in pyramidal neurons were observed, as well as a decrease in tau phosphorylation
Adler *et al* [209]	Amylin	The amylin levels in AD patients, patients with mild cognitive dysfunctions, and the control group were determined. Likewise, pramlintide, an amylin analog, was administered in AD mice in which oxidative stress and cognition were evaluated	Lower levels of amylin in patients with AD and mild cognitive dysfunction were observed compared with the control group. Mice administered with pramlintide showed improvement in cognition and synaptic markers as well as a decrease in oxidative stress in the hippocampus
NCT01843075 [190]	Liraglutide	Multicenter, randomized, double-blind, placebo-controlled Phase IIb study in patients with mild AD	-
NCT03980730 [208]	Azeliragon	Multicenter, randomized, double-blind, placebo-controlled, Phase II/III studies to evaluate the safety and efficacy of azeliragon as a treatment for subjects with mild AD	-
NCT02462161 [142]	Intranasal insulin aspart	Pilot phase I clinical trial that will examine the effects of intranasal insulin aspart on cognition, daily function, blood, and cerebral spinal fluid markers of AD	-
NCT02503501 [143]	Intranasal insulin glulisine	A phase II, single center, randomized, double-blind, placebo-controlled study that will evaluate the safety and effectiveness of intranasal glulisine in patients with probable AD	-

AD: Alzheimer's disease.

hypoglycemia caused by insulin therapy could be involved in the worsening of the cognitive deficit observed in certain patients with DM[133,134]. Therefore, this limits the use of insulin as treatment in patients with AD and other cognitive disorders[135]. Furthermore, pharmacological preparations for insulin injections do not entirely cross the BBB, limiting its distribution in the CNS[136]. Therefore, intranasal insulin administration emerges as a highly viable alternative[137-143].

Although only a few studies have evaluated its short-term effect on healthy individuals[138,139], the chronic administration of intranasal insulin in cognitively normal patients has been associated with higher memory performance. In this context, a study performed by Reger *et al*[140] showed that patients with cognitive defects who were administered with intranasal insulin (20 IU, 2×/d) displayed an improvement in both memory recall and their functional state based on the observations of their caretakers. Similar findings were reported by Benedict *et al*[139] who administered intranasal insulin (3×/d, 40 IU/doses) for 8 wk, which led to an improvement in late words recall. Likewise, a phase II/III clinical assay conducted by Craft *et al*[141] included patients with AD or mild cognitive deficits who were treated with intranasal insulin through a special device (Kurve Technology). Significant score improvements were found at months 15 and 18 (-5.70 and -5.78 points, nominal $P = 0.004$ and 0.018).

Alternatively, leptin and ghrelin are hormones with several functions in energetic balance and have a possible role in the pathophysiology and treatment of AD[144]. Indeed, late-life weight loss and midlife obesity — both of which involve dysfunctions

in leptin signaling — have been associated with a higher risk of developing AD[145]. Midlife obesity is linked to high levels of circulating leptin, which leads to the central resistance to these pathologically high levels. This has been described among obese individuals as a component in IR and T2DM. Meanwhile, late-life weight loss has been related to low circulating levels of leptin[145,146]. Low brain leptin signaling has been found to worsen hippocampus functionality and decrease the neuroprotection against various central processes in the pathogenesis of AD, such as the metabolism of amyloid beta and tau[145,147]. The administration of leptin may renew insulin sensitivity by interacting with the insulin receptor and its signaling pathway[148-150] and by decreasing the pro-inflammatory response[146]. Likewise, in mice with AD, leptin has shown a promising therapeutic effect, improving the formation of memory, synaptic plasticity, and performance in learning activities[151-153].

On the other hand, many researchers have recently focused on evaluating the influence of the ghrelin-insulin system in glucose homeostasis. Ghrelin is unable to improve insulin sensitivity as it is activated with low levels of blood glucose and acts as a counterregulatory hormone[154]. However, it activates a vast number of signaling pathways for growth factors that compensate the loss of insulin signaling[155]. Although a large long-term impact in glycogenic metabolism has not been observed, the administration of ghrelin in AD patients has emerged as a possible therapeutic target by improving the pathological markers of the disease. This could be due to an interaction with the growth hormone secretagogue receptor 1α (GHSR1α). Ghrelin/GHSR1α signaling plays an important role in the synaptic physiology of the hippocampus and memory maintenance through the regulation of the D1 dopamine receptor (DRD1)[155,156]. Current emergent evidence suggests that the disruption of GHSR1α function induces hippocampal stress and memory deficits[157]. Furthermore, animal model studies have reported that the administration of ghrelin or analogs, such as MK0677 and LY444711, can inhibit the accumulation of amyloid beta and the hyperphosphorylation of tau protein by phosphorylating GSK-3β *via* the AMPK and PI3K/Akt pathways[158-160]. This may also reduce oxidative stress, excitotoxicity, and neuroinflammation and improve cognition and memory[158,161,162].

Clinical evidence has shown that the use of certain oral hypoglycemic drugs is associated with a lower risk of dementia[163]. Sulfonylureas have been observed to modulate diabetes-induced oxidative stress[70]. In this context, Alp *et al*[164] reported that the administration of gliclazide can potentiate antioxidant mechanisms and decrease the oxidative index in the brain of diabetic rats. These findings are consistent with that of Baraka and ElGhotny[165] and Abdallah *et al*[166], in which the administration of glibenclamide in mice reduced the hyperphosphorylation of tau and modulation of oxidative stress. However, further research is required to demonstrate the efficacy of sulfonylureas as a possible treatment for AD. In addition, it has been demonstrated that just as insulin therapy, sulfonylureas also have severe hypoglycemic effects[167,168], and repeated hypoglycemia episodes could lead to cognitive alterations or a worsening of cognitive deficits.

Evidence regarding the use of metformin in the treatment of AD has been particularly controversial recently. In theory, it could decrease tau phosphorylation[169] and the interleukin-1β-mediated activation of phosphokinases Akt and MAPK[170]. Moreover, it can inhibit complex 1 of the mitochondrial respiratory chain, inducing an increase in cyclic adenosine monophosphate (cAMP) and activating PKA and AMPK [171,172]. Likewise, a study evaluated the ability of metformin treatment for a year in mice models of AD, reporting a gender-dependent effect, wherein AMPK activation in female mice improved memory and learning, while in male mice memory and cognitive behavior worsened, possibly due to hormonal issues[173]. Furthermore, Mostafa *et al*[174] reported that only low doses of metformin (100 mg/kg) in rats were associated with a delay in memory loss, possibly due to the suppression of Akt. Despite this, a study assessing the risk of AD in patients treated with antidiabetics found that those with long-term metformin treatment were associated with worse cognitive performance[175]. Long-term studies, with a greater number of patients and a standardized methodology, are needed to understand the true role of metformin in AD treatment, as current evidence appears contradictory.

The use of TZD has also been a subject of study for the treatment of AD, as they cause an overexpression of PPARγ in the temporal cortex, which has been associated with a decrease in amyloid beta plaque formation, a decrease in β-secretase levels, and the expression of PPA. Likewise, it modulates calcium homeostasis in the hippocampus, in association with an improvement in cognition[176-178]. Cheng *et al* [179] reported that pioglitazone can improve memory and cognition in the early stages of AD. Similarly, in a pilot study performed in individuals with AD and T2DM, Sato *et al*[180] have found that patients treated with pioglitazone for 6 mo showed cognitive

improvement compared with the placebo group. However, another study in which AD patients without diabetes were treated with TZD for 18 mo did not find any significant cognitive improvement[181]. Currently, an active clinical assay (NCT1931566) with a more extensive sample intends to determine the efficacy of pioglitazone treatment for a longer period in patients with mild cognitive impairment [182].

Since the activation of glucagon-like peptide 1 (GLP-1) receptors and glucose-dependent insulinotropic polypeptides (GIP) in the CNS has been associated with neuroprotective effects[183], the use of GLP-1 and GIP analogs in AD has emerged as a promising therapeutic option. In preclinical studies, the administration of liraglutide in mice has demonstrated to decrease tau hyperphosphorylation and the deposition of amyloid plaque. Likewise, it prevents neuronal loss and the deterioration of synaptic plasticity and promotes beneficial effects on neurogenesis and brain microcir-culation [184-188]. A pilot study that evaluated the administration of liraglutide for 6 mo in AD patients did not find any significant cognitive improvement. However, it was shown that patients treated with GLP-1 agonists had less deterioration of glucose metabolism compared with those treated with placebo[189]. Moreover, a clinical trial assessing the efficacy of liraglutide in a larger group of patients with AD is ongoing[190].

With regard to GIP, different analogs have been able to show improvement in neurodegenerative diseases. Gault and Hölscher[191] reported that the use of D-ala2-GIP and N-glyc-GIP analogs reversed the synaptic plasticity alterations that had been induced by amyloid. D-Ala2-GIP has also been reported to decrease the amyloid plaque load, chronic inflammation, and oxidative stress, improving memory formation and synaptic plasticity as well as normalizing neurogenesis in AD animal models[192, 193]. Based on these findings, the therapeutic effect of novel dual GLP-1/GIP agonists has been evaluated, as well as more recent triple GLP-1/GIP/glucagon agonists[194]. Clear neuroprotective effects have also been observed, reducing inflammation, oxidative stress, and apoptotic signaling and protecting memory formation and synaptic activity[194-196]. On the other hand, the administration of DPP4 inhibitors, such as saxagliptin and vildagliptin, have also been associated with a decrease in amyloid beta deposition, tau phosphorylation, and improvement in memory retention [197,198]. However, these findings are limited to preclinical studies in mice.

Similarly, sodium-glucose transport protein 2 inhibitors (SGLT2i) have been proven to have neuroprotective effects in animal models[199]. This has been reported in obese and diabetic mice, in which positive results on metabolic and brain function parameters have been observed. In addition, the attenuation of physiopathological processes like mitochondrial dysfunction, IR, inflammation, oxidative stress, and apoptosis as well as improvement in cognition, neurogenesis, synaptic density, and synaptic plasticity of the hippocampus has been reported[200-202].

These findings have been recently observed in AD-T2M mice in a study performed by Hierro-Bujalance *et al*[203], in which it was reported that empagliflozin can reduce the density of the senile plaque and the levels of amyloid beta in the brain cortex and hippocampus.

There is a scarce number of studies providing clinical evidence on the use of SGLT2i in AD. In this sense, Wium-Andersen *et al*[204] performed a nested case-control study in which they established that the use of SGLT2i reduces the risk of dementia in diabetic patients (odds ratio of 0.58; 95% confidence interval: 0.42-0.81; $P < 0.05$). Currently, a double-blind, randomized, placebo-controlled, parallel group, 12-wk study is underway. Its goal is to investigate the effect of dapagliflozin in patients who possibly have AD[205].

Azeliragon, a novel drug, has been reported to decrease amyloid deposition and brain inflammation by antagonizing the AGE receptor[206,207]. Based on the preliminary results from a phase III 18-month clinical trial in AD patients, the use of azeliragon decreased pro-inflammatory markers, hippocampus atrophy, and cognitive deterioration. More clinical trials are needed to confirm these findings[208]. Finally, amylin, which can cross the BBB and has effects at the CNS level, has been suggested to have a role in mood disorders as well as neurodegenerative disorders[136]. In AD patients, amylin plasma levels are considerably low, and the administration of analogs, such as pramlintide, has been associated with a decrease in neuroinflammation, oxidative stress, and memory improvement in AD mice[209]. Therefore, its potential use in clinical studies in the upcoming years could be promising.

CONCLUSION

Different studies have demonstrated the existence of a marked association between T2DM and the development of AD. Significant advances in the field of neuroendocrinology have investigated the underlying molecular mechanisms involved in the link between both disorders. Although various confounding factors may intervene in this relationship, studies have found that these diseases may share pathophysiological phenomena, including several abnormalities in insulin signaling in the PI3K and MAPK pathways in the brain tissues as well as the disruption of mitochondrial function, autophagy, GLUTs 1 and 3, and oxidative stress. This overlap leads to new common therapeutic perspectives, and various antidiabetic treatments have been implemented in multiple large-scale clinical and epidemiological studies. However, future clinical trials on the efficacy of these novel therapeutic interventions are needed to better characterize the true scope of this prospect.

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