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

Milagros Rojas, Mervin Chávez-Castillo, Jordan Bautista, Ángel Ortega, Manuel Nava, Juan Salazar, Edgar Díaz-Camargo, Oscar Medina, Joselyn Rojas-Quintero, Valmore Bermúdez

ORCID numbers: Milagros Rojas 0000-0003-2764-8846; Mervin Chávez-Castillo 0000-0001-8511-0230; Jordan Bautista 0000-0003-4059-7086; Ángel Ortega 0000-0002-7180-4765; Manuel Nava 0000-0001-9769-1693; Juan Salazar 0000-0003-4211-528X; Edgar Díaz-Camargo 0000-0002-7349-3059; Oscar Medina 0000-0002-2472-1238; Joselyn Rojas-Quintero 0000-0003-4994-075X; Valmore Bermúdez 0000-0003-1880-8887.

Author contributions: Rojas M, Chávez-Castillo M and Bautista J conceived of the idea of the study and determined its general focus; Rojas M, Chávez-Castillo M, Bautista J, Ortega Á and Nava M contributed to the literature and wrote and revised the manuscript; Rojas M, Chávez-Castillo M, Salazar J, Bermúdez V, Díaz-Camargo E, Medina O and Rojas-Quintero J contributed to the review study and corrected the manuscript; all authors reviewed and approved the final version of the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external

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.
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; 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

---

WJD | https://www.wjgnet.com

June 15, 2021 | Volume 12 | Issue 6
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[15]. 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 neurodegenerative 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
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 (αβγ). 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 fibrillary 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 conditions[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-e4 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.

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 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 pathophysiology 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].
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-GlcNAcylation), 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\cite{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 carboxylation\cite{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\cite{86}.

The increase in ROS inhibits the cellular production of energy and decreases insulin secretion and sensitivity\cite{87}. Similarly, oxidative damage affects a variety of signaling pathways related to the unfolded protein response and protein degradation, which could lead to IR\cite{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\cite{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\cite{92}. Different studies have reported that autophagy is a crucial deleterious process in AD and T2DM\cite{93-95}. Furthermore, evidence suggests autophagic dysfunction in β-pancreatic cells and other peripheral tissues could contribute to IR\cite{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\cite{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\cite{100-102}. This association has been supported by animal and human studies related to AD, reporting alterations in genes and proteins associated with autophagy\cite{95}. Transgenic mice studies have focused on the role of defective lysosomal degradation in the pathogenesis of this condition\cite{103,104}. Studies in patients with AD have reported that mutations in PSEN1 contribute to the defective proteolysis of autophagy substrates\cite{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\cite{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\cite{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\cite{108,109}. Alterations at the beginning of autophagy, deficient clearance of autophagy substrates, and dysfunction in mitophagy constitute the physiopathological processes important in AD\cite{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 Eε4, or brain infarctions, which could explain the progressive emergence of cognitive deterioration and clinical diagnosis of AD in patients with T2DM\cite{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\cite{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 |
|------|-------------|---------|
| Gadala 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 |
| Prefenno 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: 1.20-9.03) 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] |
| Feila 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 1299 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/Aβ42, 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
Preclinical study in mice in which a group received liraglutide for 8 weeks and their cognitive performance was evaluated using a Morris water labyrinth. 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.

Different parameters were used to determine the level of oxidative stress, including paraoxonase-1, total antioxidative status, and malondialdehyde. Malondialdehyde, Akt, phosphorylated Akt, phosphorylated tau, and acetylcholinesterase levels were determined.

Treatment with 20 UI of insulin improved delayed memory (P ≤ 0.05). According to caretakers, a functional improvement was observed in the groups receiving 20 and 40 UI of insulin, respectively (P ≤ 0.01).

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 ≤ 0.05).

The amylin levels in AD patients, patients with mild cognitive deficits, 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.

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.

**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 ≤ 0.05). According to caretakers, a functional improvement was observed in the groups receiving 20 and 40 UI of insulin, respectively (P ≤ 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 ≤ 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 |
| NCT01840751[196] | Liraglutide | Multicenter, randomized, double-blind, placebo-controlled Phase IIb study in patients with mild AD | - |
| NCT03980730[208] | Azeiragon | Multicenter, randomized, double-blind, placebo-controlled, Phase II/III studies to evaluate the safety and efficacy of azeiragon 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 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.
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 I 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 antiabetics 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 insulinojective 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 lixivtaglutide 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 microcirculation [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-alanyl-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, Wiium-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].

Aziliragon, a novel drug, has been reported to decrease amyloid deposition and brain inflammation by antagonizing the AG receptor[206,207]. Based on the preliminary results from a phase III 18-month clinical trial in AD patients, the use of aziliragon 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.

REFERENCES

1 World Health Organization. Dementia. [cited 21 October 2020]. In: World Health Organization [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/dementia

2 American Diabetes Association. 12. Older Adults: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020; 43: S152-S162 [PMID: 31862755 DOI: 10.2337/dc20-S012]

3 International Diabetes Federation. Worldwide toll of diabetes. [cited 21 October 2020]. In: International Diabetes Federation [Internet]. Available from: https://diabetesatlas.org/en/sections/worldwide-toll-of-diabetes.html

4 Bermudez V, Salazar J. Prevalence and Risk Factors associated with Impaired Fasting Glucose in Adults from Maracaibo City, Venezuela. J Diabetes Metab 2016; 7 [DOI: 10.4172/2155-6156.1000683]

5 De La Cruz Vargas JA, Dos Santos F, Dyzinger W, Herzog S. Medicina del Estilo de Vida: trabajando juntos para revertir la epidemia de las enfermedades crónicas en Latinoamérica. Cienc E Innov En Salud 2017; 4: 1-7 [DOI: 10.17081/innosa.4.2.2870]

6 Alicie BZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol 2017; 12: 2032-2045 [PMID: 28522654 DOI: 10.2215/CJN.11491116]

7 Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BE, Klein R, Krisniah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang J, Wang N, West S, Xu L, Yauatsa M, Zhang X, Mitchell P, Wong TY; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012; 35: 556-564 [PMID: 22301125 DOI: 10.2337/dc11-1999]

8 Mirhoseini M, Saleh N, Momeni A, Deris F, Asadi-Samani M. A study on the association of diabetic dermopathy with nephropathy and retinopathy in patients with type 2 diabetes mellitus. J Nephropathol 2016; 5: 139-143 [PMID: 27921026 DOI: 10.15171/jnp.2016.26]

9 Thiruvoorpaati T, Kielhorn CE, Armstrong EJ. Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. World J Diabetes 2015; 6: 961-969 [PMID: 26185603 DOI: 10.4239/wjd.v6.i7.961]

10 Xue M, Xu W, Ou YN, Cao XP, Tan MS, Tan L, Yu JT. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies. Ageing Res Rev 2019; 55: 100944 [DOI: 10.1016/j.arr.2019.100944]

11 Dá Mesquita S, Ferreira AC, Sousa JC, Correia-Neves M, Sousa N, Marques F. Insights on the pathophysiology of Alzheimer's disease: The crosstalk between amyloid pathology, neuroinflammation and the peripheral immune system. Neurosci Biobehav Rev 2016; 68: 547-562 [PMID: 27328788 DOI: 10.1016/j.neubiorev.2016.06.014]

12 Sandhir R, Gupta S. Molecular and biochemical trajectories from diabetes to Alzheimer's disease: A critical appraisal. World J Diabates 2015; 6: 1223-1242 [PMID: 26464760 DOI: 10.4239/wjd.v6.i12.1223]

13 Lee SH, Zabolotny JM, Huang H, Lee H, Kim YB. Insulin in the nervous system and the mind: Functions in metabolism, memory, and mood. Mol Metab 2016; 5: 589-601 [PMID: 27656397 DOI: 10.1016/j.molmet.2016.06.011]

14 Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest 2016; 126: 12-22 [PMID: 26727229 DOI: 10.1172/JCI77812]

15 Craft S, Claxton A, Baker LD, Hanson AJ, Cholerton B, Tritesuhu EH, Dahl D, Caulder E, Neth B, Montine TJ, Jurg Y, Maldjian J, Whitlow C, Friedman S. Effects of Regular and Long-Acting Insulin on Cognition and Alzheimer's Disease Biomarkers: A Pilot Clinical Trial. J Alzheimers Dis 2017; 57: 1325-1334 [PMID: 28372335 DOI: 10.3233/JAD-161256]

16 Koepsell H. Glucose transporters in brain in health and disease. Pflugers Arch 2020; 472: 1299-
Rojas M et al. Alzheimer's disease and T2DM

1343 [PMID: 32789766 DOI: 10.1007/s00424-020-02441-x]

17 Mergenthaler P, Lindauer U, Dienel GA, Meisel A. Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci 2013; 36: 587-597 [PMID: 23968694 DOI: 10.1016/j.tins.2013.07.001]

18 McAllister MS, Krizanac-Benze L, Macchia F, Naftalin RJ, Pedley KC, Mayberg MR, Marroni M, Leeman S, Stamness KA, Janigro D. Mechanisms of glucose transport at the blood-brain barrier: an in vitro study. Brain Res 2001; 904: 20-30 [PMID: 11516408 DOI: 10.1016/s0006-8993(01)02418-0]

19 Bermudez V, Bermudez F, Arraz N, Leal E, Linares S, Menguél E, Valdelamar L, Seyfi H, Amell A, Carrillo M, Silva C. Biologia molecular de los transportadores de glucosa: clasificación, estructura y distribución. Arch Venec Farmacol Ter 2007; 26: 76-86

20 Juncarvicova J. Glucose transport in brain - effect of inflammation. Endocr Regul 2014; 48: 35-48 [PMID: 24523474 DOI: 10.1419/endo_2014_01_35]

21 Qtub AA, Hunt CA. Glucose transport to the brain: a systems model. Brain Res Brain Res Rev 2005; 49: 595-617 [PMID: 16269321 DOI: 10.1016/j.brainresrev.2005.03.002]

22 Bedse G, Di Domenico F, Serviddio G, Cassano T. Aberrant insulin signaling in Alzheimer's disease: current knowledge. Front Neurosci 2015; 9: 204 [PMID: 26136647 DOI: 10.3389/fnnns.2015.00204]

23 Blázquez E, Velázquez E, Hurtado-Carneiro V, Ruiz-Albusac JM. Insulin in the brain: its pathophysiological implications for States related with central insulin resistance, type 2 diabetes and Alzheimer's disease. Front Endocrinol (Lausanne) 2014; 5: 161 [PMID: 25346723 DOI: 10.3389/fendo.2014.00161]

24 Rojas J, Bermúdez V, Leal E, Cano R, Luti Y, Acosta L, Finol F, AparicioD, Arraz N, Linares S, Rojas E, Canelon R, Desirze S. Insulinorresistencia e hiperinsulinemia como factores de riesgo para enfermedad cardiovascular. Arch Venec Farmacol Ter 2008; 27: 30-40

25 Baranowska-Bik A, Bik W. Insulin and brain aging. Prz Menopauzalny 2017; 16: 44-46 [PMID: 28721128 DOI: 10.5114/pm.2017.68590]

26 Tascone LDS, Bottino CMC. Neurobiología of neuropsychiatric symptoms in Alzheimer's disease: A critical review with a focus on neuroimaging. Dement Neuropsychol 2013; 7: 236-243 [PMID: 29213845 DOI: 10.1590/s1980-57642013dennp703000002]

27 Narvaez E, Pelaez J, Almeida K, Alvarez C, Mendoza C, Morales A, Godos D, Del Salto Ocaña T, Catota M. Implication of apolipoprotein e polymorphisms in the atherosclerosis and Alzheimer’s disease physiopathology. Rev Latinoam Hipertens 2018; 13: 97-102

28 Vanegas H. Buscando las bases moleculares de la enfermedad de Alzheimer. Gac Méd Caracas 2017; 125: 4-11

29 Gilbert BJ. The role of amyloid β in the pathogenesis of Alzheimer's disease. J Clin Pathol 2013; 66: 362-366 [PMID: 23526599 DOI: 10.1136/jclinpath-2013-201515]

30 Yu JT, Tan L, Hardy J. Apolipoprotein E in Alzheimer's disease: an update. Ann Rev Neurosci 2014; 37: 79-100 [PMID: 24821312 DOI: 10.1146/annurev-neuro-071013-014300]

31 Sadigh-Eteghad S, Sabernarouf B, Majdi A, Talebi M, Farhoudi M, Mahmoudi J. Amyloid-beta: a crucial factor in Alzheimer's disease. Med Princ Pract 2015; 24: 1-10 [PMID: 25471398 DOI: 10.1155/2015/3069101]

32 Varma VR, Varma S, An Y, Hofman TJ, Seddighi S, Casanova R, Beri A, Dammer EB, Seyfried NT, Pletnikova O, Moghekar A, Wilson MR, Lah JJ, O'Brien RJ, Levey AL, Troncoso JC, Albert MS, Thambisetty M. Alpha-2 macroglobulin in Alzheimer's disease: a marker of neuronal injury through the RCAN1 pathway. Mol Psychiatry 2017; 22: 13-23 [PMID: 27872486 DOI: 10.1038/mp.2016.206]

33 Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacoal Rep 2015; 67: 195-203 [PMID: 25712639 DOI: 10.1016/j.pharesp.2014.09.004]

34 Hasegawa M. Molecular Mechanisms in the Pathogenesis of Alzheimer's disease and Tauopathies-Prion-Like Seeded Aggregation and Phosphorylation. Biomolecules 2016; 6: 27136595 DOI: 10.3390/biom60200023

35 Barbier P, Zajneli O, Martinho M, Lasorsa A, Belle V, Smet-Nocco C, Tsvetkov PO, Devred F, Landrieu I. Role of Tau as a Microtubule-Associated Protein: Structural and Functional Aspects. Front Aging Neurosci 2019; 11: 204 [PMID: 31447664 DOI: 10.3389/fnagi.2019.00204]

36 Chesser AS, Pritchard SM, Johnson GV. Tau clearance mechanisms and their possible role in the pathogenesis of Alzheimer disease. Front Neurol 2013; 4: 122 [PMID: 24027553 DOI: 10.3389/fneur.2013.00122]

37 Šimić G, Babic Leko M, Wray S, Harrington C, Delalle I, Jovanov-Milošević N, Bažadona D, Buée L, de Silva R, Di Giovanni G, Wischik C, Hof PR. Tau Protein Hyperphosphorylation and Aggregation in Alzheimer's Disease and Other Tauopathies, and Possible Neuroprotective Strategies. Biomolecules 2016; 6: 6 [PMID: 26751493 DOI: 10.3390/biom6010006]

38 Tsartsalis S, Kekardaki A, Höf PR, Kövari E, Bouras C. Early Alzheimer-type lesions in cognitively normal subjects. Neurobiol Aging 2018; 62: 34-44 [PMID: 29107845 DOI: 10.1016/j.neurobiolaging.2017.10.002]

39 Sonne DP, Hemmingsen B. Comment on American Diabetes Association. Standards of Medical Care in Diabetes-2017. Diabetes Care 2017;40(Suppl. 1):S1-S135. Diabetes Care 2017; 40: e92-e93 [PMID: 28637892 DOI: 10.2337/dc17-0299]
Jayaraman A, Pike CJ. Alzheimer's disease and type 2 diabetes: multiple mechanisms contribute to interactions. Curr Diab Rep 2014; 14: 476 [PMID: 24526623 DOI: 10.1007/s11892-014-0476-2]

Claxton A, Baker LD, Hanson A, Trittschuh EH, Cholerton B, Morgan A, Callaghan M, Arbuckle M, Behl C, Craft S. Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. J Alzheimers Dis 2015; 44: 897-906 [PMID: 25374101 DOI: 10.3233/JAD-141791]

Fröhlich L, Blum-Degen D, Bernstein HG, Engelsberger S, Humrich J, Lauter F, Muschner D, Thalheimser A, Türk A, Hoyer S, Zöchling R, Boisal KW, Jellinger K, Riedler P. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neurotransm (Vienna) 1998; 105: 423-438 [PMID: 9720972 DOI: 10.1007/s007020050068]

Craft S, Peskind E, Schwartz MW, Shellenberg GD, Raskind M, Porte D Jr. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype. Neurology 1998; 50: 164-168 [PMID: 9443474 DOI: 10.1212/wnl.50.1.164]

Craft S, Asthana S, Shellenberg G, Baker L, Cherrier M, Boyt AA, Martins RN, Raskind M, Peskind E, Plymate S. Insulin effects on glucose metabolism, memory, and plasma amyloid precursor protein in Alzheimer's disease differ according to apolipoprotein-E genotype. Ann N Y Acad Sci 2000; 903: 222-228 [PMID: 10818510 DOI: 10.1111/j.1749-6632.2000.tb06371.x]

Craft S, Asthana S, Cook DG, Baker LD, Cherrier M, Purganan K, Wai C, Petrova A, Latendresse S, Watson GS, Newcomer JW, Shellenberg GD, Krohn AJ. Insulin dose-response effects on memory and plasma amyloid precursor protein in Alzheimer's disease: interactions with apolipoprotein E genotype. Psychoneuroendocrinology 2003; 28: 809-822 [PMID: 12812866 DOI: 10.1016/S0306-4530(02)00087-2]

Baker LD, Cross DJ, Minoshima S, Belonga D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol 2011; 68: 51-57 [PMID: 20837822 DOI: 10.1001/archneurol.2010.225]

Femmennilla GD, Livingston NR, Raza S, van der Doef T, Frangou E, Love S, Busza G, Calsolaro V, Carver S, Holmes C, Ritchie CW, Lawrence RM, McFarlane B, Tadros G, Ridha BH, Bannister C, Walker Z, Archer H, Coulthard E, Underwood B, Prasanna K, Kandimalla R, Femalec FG, Thirumala V, Reddy PH. Is Alzheimer's disease a Type 3 Diabetes? J Alzheimers Dis 2013; 31: 107-113 [PMID: 23853088 DOI: 10.1007/s10528-012-1599-4]

Watson KT, Wroolie TE, Tong G, Foland-Ross LC, Frangou S, Singh M, McIntyre RS, Roat-Shumway S, Myoraku A, Reiss AL, Rascalov S. Neural correlates of irisin effects in persons at risk for Alzheimer's disease. Behav Brain Res 2019; 356: 271-278 [PMID: 30009030 DOI: 10.1016/j.bbr.2018.08.006]

Koenig AM, Mechanic-Hamilton D, Xie SX, Combs MF, Cappola AR, Xie L, Detre JA, Wolfs AS. Effects of the Insulin Sensitizer Metformin in Alzheimer Disease: Pilot Data From a Randomized Placebo-controlled Crossover Study. Alzheimer Dis Assoc Disord 2017; 31: 107-113 [PMID: 28538088 DOI: 10.1097/WAD.0000000000000202]

Kandimalla R, Thirumala V, Reddy PH. Is Alzheimer's disease a Type 3 Diabetes? Biochim Biophys Acta Mol Basis Dis 2017; 1863: 1078-1089 [PMID: 27567931 DOI: 10.1016/j.bbadis.2016.08.018]

De Felice FG, Lorenzo MV, Ferreira ST. How does brain insulin resistance develop in Alzheimer's disease? Alzheimers Dement 2014; 10: S26-S32 [PMID: 24529521 DOI: 10.1016/j.jalz.2013.12.004]

Ahmad W. Overlapped metabolic and therapeutic links between Alzheimer and diabetes. Mol Neurobiol 2013; 47: 399-424 [PMID: 23018180 DOI: 10.1007/s12035-012-8532-z]

De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes 2014; 63: 2262-2272 [PMID: 24931033 DOI: 10.2337/db13-1945]

Ansari SA, Emerald BS. The Role of Insulin Resistance and Protein O-GlcNAcylation in Neurodegeneration. Front Neuroschr 2019; 13: 473 [PMID: 31143098 DOI: 10.3389/fnins.2019.00473]

Mravec B, Horvathova L, Padova A. Brain Under Stress and Alzheimer's Disease. Cell Mol Neurobiol 2018; 38: 73-84 [PMID: 28699112 DOI: 10.1007/s10571-017-0521-1]

Simó R, Ciudin A, Simó-Servat O, Hernández C. Cognitive impairment and dementia: a new emerging complication of type 2 diabetes—The diabetologists perspective. Acta Diabetol 2017; 54: 417-424 [PMID: 28210868 DOI: 10.1007/s00592-017-0970-5]

Shah K, Desilva S, Abruuscato T. The role of glucose transporters in brain disease: diabetes and Alzheimer's Disease. Int J Mol Sci 2012; 13: 12629-12655 [PMID: 23202918 DOI: 10.3390/ijms131012629]
Lustbader JW, Cirilli M, Lin C, Xu HW, Takuma K, Wang N, Nason C, Chen X, Pollak S, Moaibo D, Wang X, Perry G, Smith MA. Mitochondrial abnormalities in Alzheimer’s disease: functional alterations in Alzheimer’s disease: decreased glucose transporter 3 immunoreactivity in the periventricular terminal zone. J Neurophysiol 1995; 54: 38-41 [PMID: 8715078]

Kam A, Kovacs R. Mitochondria and neuronal activity. Am J Physiol Cell Physiol 2007; 292: C641-C657 [PMID: 17092996 DOI: 10.1152/ajpcell.00222.2006]

Nonomura A, Honda K, Takeda A, Hirai K, Zhu X, Smith MA, Perry G. Oxidative damage to RNA in neurodegenerative diseases. J Biomed Biotechnol 2006; 2006: 82523 [PMID: 17047315 DOI: 10.1155/JBB/2006/82523]

Correia SC, Santos RX, Carvalho C, Cardoso S, Candeias E, Santos MS, Oliveira CR, Moreira P. Insulin signaling, glucose metabolism and mitochondria: major players in Alzheimer’s disease and diabetes interrelation. Brain Res 2012; 1441: 64-78 [PMID: 22990178 DOI: 10.1016/j.brainres.2011.12.063]

Butterfield DA, Di Domenico F, Barone E. Elevated risk of type 2 diabetes for development of Alzheimer’s disease: a key role for oxidative stress in brain. Biochim Biophys Acta 2014; 1842: 1693-1706 [PMID: 24949886 DOI: 10.1016/j.bbadis.2014.06.010]

Sorbi S, Bird ED, Blass JP. Decreased pyruvate dehydrogenase complex activity in Huntington and Alzheimer brain. Ann Neurol 1983; 13: 72-78 [PMID: 6219611 DOI: 10.1002/ana.410130116]

Butterworth RF, Besnard AM. Thiamine-dependent enzyme changes in temporal cortex of patients with Alzheimer’s disease. Metab Brain Dis 1990; 5: 179-184 [PMID: 2087217 DOI: 10.1007/BF00997071]

Yao J, Irwin RW, Zhao L, Nilsen J, Hamilton RT, Brinton RD. Mitochondrial bioenergetic deficit precedes Alzheimer’s pathology in female mouse model of Alzheimer’s disease. Proc Natl Acad Sci USA 2009; 106: 14670-14675 [PMID: 19667196 DOI: 10.1073/pnas.0903563106]

Hirai K, Aiyel G, Nonomura A, Fujioka H, Russell RL, Atwood CS, Johnson AB, Kress Y, Vinters HV, Tabaton M, Shimohama S, Cash AD, Siedlak SL, Harris PL, Jones PK, Petersen RB, Perry G, Smith MA. Mitochondrial abnormalities in Alzheimer’s disease. J Neurosci 2001; 21: 3017-3023 [PMID: 11312286 DOI: 10.1523/JNEUROSCI.21-09-03017.2001]

Parker WD Jr, Parks JK. Cytochrome c oxidase in Alzheimer’s disease: brain. Biochim Biophys Acta 2003; 1607: 17-22 [PMID: 14217973 DOI: 10.1016/S0005-2728(03)00406-3]

Bonda DJ, Wang X, Perry G, Smith MA, Zhu X. Mitochondrial dynamics in Alzheimer’s disease: opportunities for future treatment strategies. Drugs Aging 2010; 27: 181-192 [PMID: 20210366 DOI: 10.2165/11532410-000000000-00000]

Lloret A, Badia MC, Mora NJ, Ortega A, Pallarido V, Alonso MD, Atamna H, Viña J. Gender and age-dependent differences in the mitochondrial apoptotic pathway in Alzheimer’s disease. Free Radic Biol Med 2008; 44: 2019-2025 [PMID: 18387371 DOI: 10.1016/j.freeradbiomed.2008.02.017]

Devi L, Prabhu BM, Galati DF, Avadhani NG, Anandatheerthavarada HK. Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer’s disease brain is associated with mitochondrial dysfunction. J Neurosci 2006; 26: 9057-9068 [PMID: 16943564 DOI: 10.1523/JNEUROSCI.1469-06.2006]

Cardoso SM, Santos S, Swardlow RH, Oliveira CR. Functional mitochondria are required for amyloid beta-mediated neurotoxicity. FASEB J 2001; 15: 1439-1441 [PMID: 11387250 DOI: 10.1096/fj.00-0561fje]

Du H, Guo L, Fang F, Chen D, Sosunov AA, McKhann GM, Yan Y, Wang C, Zhang H, Molkentin JD, Gunn-Moore FJ, Vonsattel JP, Arancio O, Chen JX, Yan SD. Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer’s disease. Nat Med 2008; 14: 1097-1105 [PMID: 18806802 DOI: 10.1038/nm.1868]
Neuronal autophagy: a housekeeper or a fighter in neuronal cell survival? [PMID: 15087549]

Moriond F, Corsi M, Carboni L. Cross-disease analysis of Alzheimer's disease and type-2 Diabetes: oxidative stress: a driving factor in Alzheimer’s disease? [PMID: 26729350]

Autophagy induction and treatment leads to less cognitive impairment in Alzheimer's disease patients. [PMID: 22658669]

Lee JA, Yu WH, Kumar A, Lee S, Mohan PS, Peterhoff CM, Wolfe DM, Martinez-Vicente M, Massey AC, Sovak G, Uchiyama Y, Westaway D, Cuervo AM, Nixon RA. Lysosomal proteolysis dysfunction: a driving factor in Alzheimer’s disease? [PMID: 28974774]

Whyte LS, Lauderback CM. Lipid peroxidation and protein oxidation in Alzheimer's disease brain: potential causes and consequences involving amyloid beta-peptide-associated free radical oxidative stress. [PMID: 12031889]

Chaney M, Trinchese F, Liu S, Gunn-Moore F, Lee LF, Walker DG, Kuppusamy P, Zewier ZL, Arancio O, Stern D, Yan SS, Wu H. ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. Science 2004; 304: 448-452 [PMID: 15087549 DOI: 10.1126/science.1091230]

Moreira PI, Santos MS, Seica R, Oliveira CR. Brain mitochondrial dysfunction as a link between Alzheimer's disease and diabetes. J Neurol Sci 2007; 257: 206-214 [PMID: 17316694 DOI: 10.1016/j.jns.2007.01.017]
107 Pickford F, Masliyah J, Britschgi M, Linc I, Narasimhan R, Jaeger PA, Small S, Spencer B, Rockenstein E, Levine B, Wyss-Coray T. The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid beta accumulation in mice. *J Clin Invest* 2008; 118: 2190-2199 [PMID: 18497889 DOI: 10.1172/JCI33585]

108 Correia SC, Perry G, Moreira PI. Mitochondrial traffic jams in Alzheimer's disease - pinpointing the roadblocks. *Biochim Biophys Acta* 2016; 1862: 1909-1917 [PMID: 27460705 DOI: 10.1016/j.bbadis.2016.07.010]

109 Kerr JS, Adriaanse BA, Groig NH, Mattson MP, Cader MZ, Bohr VA, Fang EF. Mitophagy and Alzheimer's Disease: Cellular and Molecular Mechanisms. *Trends Neurosci* 2017; 40: 151-166 [PMID: 28190529 DOI: 10.1016/j.tins.2017.01.002]

110 Nixson RA, Yang DS. Autophagy failure in Alzheimer's disease--locating the primary defect. *Neurobiol Dis* 2011; 43: 38-45 [PMID: 21296668 DOI: 10.1016/j.nbd.2011.01.021]

111 Vagelatos NT, Eslick GD. Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. *Epidemiol Rev* 2013; 35: 152-160 [PMID: 23314404 DOI: 10.1093/epirev/mxs012]

112 Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. *J Diabetes Investig* 2013; 4: 640-650 [PMID: 24843720 DOI: 10.1111/jdi.12087]

113 Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biol Psychiatry* 2010; 67: 505-512 [PMID: 19358976 DOI: 10.1016/j.biopsych.2009.02.013]

114 Ohara T, Doi Y, Ninomiya T, Hirakawa Y, Hata J, Iwaki T, Kanba S, Kiyohara Y. Glucose tolerance status and risk of dementia in the community: the Hisayama study. *Neurology* 2011; 77: 1126-1134 [PMID: 21931106 DOI: 10.1212/WNL.0b013e31822f0435]

115 Xu WL, von Strauss E, Qiu CX, Winblad B, Fratiglioni L. Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. *Diabetologia* 2009; 52: 1031-1039 [PMID: 19280172 DOI: 10.1007/s00125-009-1323-x]

116 Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L. Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology* 2004; 63: 1181-1186 [PMID: 15477535 DOI: 10.1212/01.wnl.0000140291.86406.d1]

117 Peila R, Rodriguez BL, Launer LJ; Honolulu-Asia Aging Study. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes Care* 2002; 51: 1256-1262 [PMID: 11916953 DOI: 10.2337/diabetes.51.4.1256]

118 McIntosh EC, Nation DA; Alzheimer's Disease Neuroimaging Initiative. Importance of Treatment Status in Links Between Type 2 Diabetes and Alzheimer's Disease. *Diabetes Care* 2019; 42: 972-979 [PMID: 30833734 DOI: 10.2337/dc18-1399]

119 Ahtiluoto S, Polvikoski T, Peltonen M, Salomaa V, Tuomilehto J, Winblad B, Sulkava R, Kivipelto M. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. *Neurology* 2010; 75: 1195-1202 [PMID: 20739645 DOI: 10.1212/WNL.0b013e31818fdd78]

120 Matsuizaki T, Sasaki K, Taniizaki Y, Hata J, Fujimura K, Matsuy Y, Sekita A, Suzuki SO, Kanba S, Kiyohara Y, Iwaki T. Insulin resistance is associated with the pathology of Alzheimer disease: the Hisayama study. *Neurology* 2010; 75: 764-770 [PMID: 20739649 DOI: 10.1212/WNL.0b013e3181e2e257]

121 American Diabetes Association. 5. Lifestyle Management: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019; 42: S46-S60 [PMID: 30595231 DOI: 10.2337/dc19-S005]

122 Dunkley AJ, Bodicoat DH, Greaves CJ, Russell C, Yates T, Davies MJ, Khunti K. Diabetes prevention in the real world: effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations: a systematic review and meta-analysis. *Diabetes Care* 2014; 37: 922-933 [PMID: 24652723 DOI: 10.2337/dc13-2195]

123 Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013; 159: 543-551 [PMID: 24126648 DOI: 10.7326/0003-4819-159-9-201310150-00007]

124 Bhatti GK, Reddy AP, Reddy PH, Bhatti JS. Lifestyle Modifications and Nutritional Interventions in Aging-Associated Cognitive Decline and Alzheimer's Disease. *Front Aging Neurosci* 2019; 11: 369 [PMID: 31998117 DOI: 10.3389/fnagi.2019.00369]

125 Bayer-Carter JI, Green PS, Montine TJ, VanFossen B, Baker LD, Watson GS, Bonner LM, Callaghan M, Lenerverz JB, Walter BS, Tsai E, Plymate SR, Postupna N, Wilkinson CW, Zhang J, Lampe J, Kahn SE, Craft S. Diet intervention and cerebrospinal fluid biomarkers in amnestic mild cognitive impairment. *Arch Neurol* 2011; 68: 743-752 [PMID: 21670398 DOI: 10.1001/archneur.2011.125]

126 Dhana K, Evans DA, Rajan KB, Bennett DA, Morris MC. Healthy lifestyle and the risk of Alzheimer dementia: Findings from 2 Longitudinal studies. *Neurology* 2020; 95: e374-e383 [PMID: 32554763 DOI: 10.1212/WNL.0000000000009816]

127 Kern W, Peters A, Fruehwald-Schultes B, Deininger E, Born J, Fehm HL. Improving influence of insulin on cognitive functions in humans. *Neuroendocrinology* 2001; 74: 270-280 [PMID: 11598383 DOI: 10.1159/000054694]

128 Craft S, Asthana S, Newcomer JW, Wilkinson CW, Matos IT, Baker LD, Cherrier M, Lofgren C, Latendresse S, Petrova A, Plymate S, Raskind M, Grimwood K, Veith RC. Enhancement of memory in Alzheimer disease with insulin and somatostatin, but not glucose. *Arch Gen Psychiatry* 1999; 56: 203-210 [PMID: 10570670]
1135-1140 [PMID: 10591291] DOI: 10.1001/archpsyc.56.12.1135

129 **Craft S**, Newcomer J, Kanne S, Dagogo-Jack S, Cryer P, Sheline Y, Luby J, Dagogo-Jack A, Alderson A. Memory improvement following induced hyperinsulinemia in Alzheimer's disease. *Neurobiol Aging* 1996; 17: 123-130 [PMID: 8786794] DOI: 10.1016/0197-4580(95)02002-0

130 **McCall AL**. Insulin therapy and hypoglycemia. *Endocrinol Metab Clin North Am* 2012; 41: 57-87 [PMID: 22575407] DOI: 10.1016/j.cem.2012.03.001

131 **Herman ME**, O'Keeffe JH, Bell DSH, Schwartz SS. Insulin Therapy Increases Cardiovascular Risk in Type 2 Diabetes. *Prog Cardiovasc Dis* 2017; 60: 422-434 [PMID: 28955751] DOI: 10.1016/j.pcmd.2017.09.001

132 **Margolis DJ**, Hoffstad O, Strom BL. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. *Pharmacoepidemiol Drug Saf* 2008; 17: 753-759 [PMID: 18613215] DOI: 10.1002/pds.1630

133 **Graveling AJ**, Deary IJ, Frier BM. Acute hypoglycemia impairs executive cognitive function in adults with and without type 1 diabetes. *Diabetes Care* 2013; 36: 3209-3246 [PMID: 23780950] DOI: 10.2337/dc13-0194

134 **Lacy ME**, Gilsanz P, Eng C, Beeri MS, Karter AJ, Whitmer RA. Severe Hypoglycemia and Cognitive Function in Older Adults With Type 1 Diabetes: The Study of Longevity in Diabetes (SOLID). *Diabetes Care* 2020; 43: 541-548 [PMID: 31882410] DOI: 10.2337/dci19-0906

135 **Weinstein G**, Davis-Plourde KL, Conner S, Himali JJ, Beiser AS, Lee A, Rawlings AM, Sedaghat S, Ding J, Mosher E, van Duijn CM, Beeri MS, Selvin E, Ikrum MA, Launer LJ, Haan MN, Seshadrin S. Association of metformin, sulfonylureas and insulin use with brain structure and function and risk of dementia and Alzheimer's disease: Pooled analysis from 5 cohorts. *PLoS One* 2019; 14: e0212293 [PMID: 30766825] DOI: 10.1371/journal.pone.0212293

136 **Verdile G**, Fuller SJ, Martins RN. The role of type 2 diabetes in neurodegeneration. *Neurobiol Dis* 2015; 84: 22-38 [PMID: 25926349] DOI: 10.1016/j.nbd.2015.04.008

137 **Craft S**, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, Arbuckle M, Callaghan M, Tsai E, Plymate SR, Green PS, Leverenz J, Cross D, Gerton B. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. *Arch Neurol* 2012; 69: 29-38 [PMID: 21911655] DOI: 10.1001/archneur.2011.233

138 **Renger MA**, Watson GS, Grey WH 2nd, Baker LD, Cholerton B, Keeling ML, Belongia DA, Fishel MA, Plymate SR, Schellenberg GD, Cherrier MM, Craft S. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. *Neurobiol Aging* 2006; 27: 451-458 [PMID: 15964100] DOI: 10.1016/j.neurobiolaging.2005.03.016

139 **Benedict C**, Hallschmid M, Schmitz K, Schultes B, Ratter F, Fehm HL, Born J, Kern W. Intranasal insulin improves memory in humans: superiority of insulin aspart. *Neuropsychopharmacology* 2007; 32: 239-243 [PMID: 16936707] DOI: 10.1038/sj.npp.1301193

140 **Renger MA**, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton B, Fishel MA, Plymate SR, Breitner JC, DeGroot W, Mehta P, Craft S. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. *Neurology* 2008; 70: 440-448 [PMID: 17942819] DOI: 10.1212/01.wnl.0000265401.62434.36

141 **Craft S**, Ramar R, Chow TW, Rafii MS, Rissman RA, Brewer JB, Donohue MC, Sun C-K, Harless K, Gessert D, Aisen PS. DT-02-03: Open label extension results from a phase ii/iii trial of intranasal insulin modulates beta-amyloid in early AD. *Neurology* 2010; 75: 2257-2265 [PMID: 20712115] DOI: 10.1212/01.wnl.0000391929.66868.00

142 **Craft S**. Study of Nasal Insulin to Fight Forgetfulness - Short-Acting Insulin Aspart (SNIFF-Quick). [accessed 2020 Dec 19]. In: ClinicalTrials.gov [Internet]. Winston-Salem (CA): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT02462161 ClinicalTrials.gov Identifier: NCT02462161

143 **Rosenbloom MH**. Intranasal Glulisine in Amnestic Mild Cognitive Impairment and Probable Mild Alzheimer's Disease. [accessed 2020 Dec 16]. In: ClinicalTrials.gov [Internet]. Saint Paul (MN): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT02503501 ClinicalTrials.gov Identifier: NCT02503501

144 **de Candia P**, Matarese G. Leptin and ghrelin: Sewing metabolism onto neurodegeneration. *Neuropharmacology* 2018; 136: 307-316 [PMID: 29248481] DOI: 10.1016/j.neuropharm.2017.12.025

145 **McGuire MJ**, Ishii M. Leptin Dysfunction and Alzheimer's Disease: Evidence from Cellular, Animal, and Human Studies. *Cell Mol Neurobiol* 2016; 36: 203-217 [PMID: 26993509] DOI: 10.1007/s10571-015-0282-7

146 **Salazar J**, Chávez-Castillo M, Rojas J, Ortega A, Nava M, Pérez J, Rojas M, Espinosa C, Chacín M, Herazo Y, Angarita L, Rojas DM, D'Marco L, Bermudez V J. "Leptin Resistance" Another Key ROI to Manage Type 2 Diabetes? *Curr Diabetes Rev* 2020; 16: 733-749 [PMID: 31886750] DOI: 10.2174/157399811666190123111838

147 **Tezapsidis N**, Johnston JM, Smith MA, Ashford JW, Casadesus G, Robakis NK, Wolozin B, Perry G, Zhu X, Greco SJ, Sarkar S. Leptin: a novel therapeutic strategy for Alzheimer's disease. *J Alzheimers Dis* 2009; 16: 731-740 [PMID: 19387109] DOI: 10.3233/JAD-2009-1021

148 **Frühbeck G**. Intracellular signalling pathways activated by leptin. *Biochem J* 2006; 393: 7-20 [PMID: 16336196] DOI: 10.1042/BJ20051578

149 **Paz-Filho G**, Mastronardi C, Wong ML, Licinio J. Leptin therapy, insulin sensitivity, and glucose homeostasis. *Indian J Endocrinol Metab* 2012; 16: S549-S555 [PMID: 23565489] DOI: 10.4103/2230-8210.105571
Rojas M et al. Alzheimer's disease and T2DM

150 Germain JP, Wisse BE, Thaler JP, Oh I S, Sarruf DA, Ogimoto K, Kiyayla KJ, Fischer JD, Matsen ME, Taborsky GJ Jr, Schwartz MW, Morton GJ. Leptin deficiency causes insulin resistance induced by uncontrolled diabetes. Diabets 2010; 59: 1626-1634 [PMID: 20424233 DOI: 10.2337/db09-1918]

151 Harvey J, Solovyova N, Irving A. Leptin and its role in hippocampal synaptic plasticity. Prog Lipid Res 2006; 45: 369-378 [PMID: 16673806 DOI: 10.1016/j.plipres.2006.03.001]

152 Greco SJ. Bryan KJ, Sarkar S, Zhu X, Smith MA, Ashfold JW, Johnston JM, Tzapsidis N, Casadesus G. Leptin reduces pathology and improves memory in a transgenic mouse model of Alzheimer's disease. J Alzhermers Dis 2010; 19: 1155-1167 [PMID: 20308782 DOI: 10.3233/JAD-100498]

153 Pérez-González R, Antequera D, Vargas T, Spuch C, Bolós M, Carro E. Leptin induces proliferation of neuronal progenitors and neuroprotection in a mouse model of Alzheimer's disease. J Alzhermers Dis 2011; 24 Suppl 2: 17-25 [PMID: 21335656 DOI: 10.3233/JAD-2011-102070]

154 Gómez Lago F, Gómez-Reino JJ, Gualillo O. Novel factors as therapeutic targets to treat diabetes. Focus on leptin and ghrelin. Expert Opin Ther Targets 2009; 13: 583-591 [PMID: 19397477 DOI: 10.1517/147282209029148834]

155 Seminara RS, Jeet C, Biswas S, Kanwal B, Ifhitkar W, Sakibuzzaman M, Rutkofsky IH. The Neurocognitive Effects of Ghrelin-induced Signaling on the Hippocampus: A Promising Approach to Alzheimer's Disease. Currnes 2018; 10: e3285 [PMID: 30443455 DOI: 10.7759/cureus.3285]

156 Kern A, Mavraki M, Ulrich C, Albarran-Zeckler R, Brantley AM, Smith RG. Hippocampal Dopamine/Drd1 Signaling Dependent on the Ghrelin Receptor. Cell 2015; 163: 1136-1149 [PMID: 26590421 DOI: 10.1016/j.cell.2015.03.062]

157 Tian J, Guo L, Sui S, Driskill C, Phensy A, Wang Q, Gauba E, Zigmam JM, Sverdlov RH, Kroener D, Su H. Disrupted hippocampal growth hormone secretagogue receptor 1a interaction with dopamine receptor D1 plays a role in Alzheimer's disease. Sci Transl Med 2019; 11 [PMID: 31413143 DOI: 10.1126/scitranslmed.aav6278]

158 Kunath N, van Groen T, Allison DB, Kumar A, Dozier-Sharpe M, Kadi sh I. Ghrelin agonist does not foster insulin resistance but improves cognition in an Alzheimer's disease mouse model. Diabetes 2015; 5: 11452 [PMID: 26090621 DOI: 10.1038/srep11452]

159 Chen Y, Cao CP, Li CR, Wang W, Zhang D, Han LL, Zhang XQ, Kim A, Kim S, Liu DD. Ghrelin modulates insulin sensitivity and tau phosphorylation in high glucose-induced hippocampal neurons. Biol Pharm Bull 2010; 33: 1165-1169 [PMID: 20606308 DOI: 10.1248/bpb.33.1165]

160 Dharurhandar EJ, Allison DB, van Groen T, Kadi sh I. Hunger in the absence of caloric restriction improves cognition and attenuates Alzheimer's disease pathology in a mouse model. PLoS One 2013; 8: e60437 [PMID: 23565247 DOI: 10.1371/journal.pone.0060437]

161 Eslami M, Sadeghi B, Goshadrou F. Chronic ghrelin administration restores hippocampal long-term potentiation and ameliorates memory impairment in rat model of Alzheimer's disease. Hippocampus 2018; 28: 724-734 [PMID: 30099391 DOI: 10.1002/hipo.23002]

162 Santos VV, Stark R, Rial D, Silva HB, Bayli ss JA, Lemus MB, Davies JS, Cunha RA, Prediger RD, Andrews ZB. Acyl ghrelin improves cognition, synaptic plasticity deficits and neuroinflammation following amyloid β (1-40) administration in mice. J Neuroendocrinol 2017; 29 [PMID: 28360673 DOI: 10.1111/jne.12476]

163 Hsu CC, Wahlqvist ML, Lee MS, Tsai HN. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. J Alzhermers Dis 2011; 24: 485-493 [PMID: 21297276 DOI: 10.3233/JAD-2011-101524]

164 Alp H, Varol S, Celik MM, Altun M, Evliyaoglu O, Tokgoz O, Tamverdi MH, Uzar E. Protective effects of beta glucan and gliclazide on brain tissue and sciatic nerve of diabetic rats induced by streptozozin. Exp Diabetes Res 2012; 2012: 230342 [PMID: 22291696 DOI: 10.1155/2012/230342]

165 Baraka A, ElGhotny S. Study of the effect of inhibiting galanin in Alzheimer's disease rats. Eur J Pharmacol 2010; 641: 123-127 [PMID: 20639139 DOI: 10.1016/j.ejphar.2010.05.030]

166 Abdullah DM, Nasser NN, Abdi El-Salam RM. Glibenclamide ameliorates ischemia-reperfusion injury via modulating oxidative stress and inflammatory mediators in the rat hippocampus. Brain Res 2011; 1385: 257-262 [PMID: 21316351 DOI: 10.1016/j.brainres.2011.02.007]

167 Schloot NC, Haupt A, Schütt M, Badenhoop K, Laimer M, Nicolay C, Reaney M, Fink K, Holl RW. Risk of severe hypoglycemia in sulfonylurea-treated patients from diabetes centers in Germany/Austria: How big is the problem? Diabetes Metab Res Rev 2016; 32: 316-324 [PMID: 26409039 DOI: 10.1002/dmr.2722]

168 Schopman JE, Simon AC, Hoefnagel SJ, Hoekstra JB, Scholten RJ, Holleman F. The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. Diabetes Metab Rev 2014; 30: 11-22 [PMID: 24039202 DOI: 10.1002/dmr.2470]

169 Kickstein E, Krauss S, Thornhill P, Rutschow D, Zeller R, Sharkey J, Williamson R, Fuchs M, Köhler A, Glossmann H, Schneider R, Sutherland C, Schweiger S, Biguanide metformin acts on brain phosphorylation via mTOR/protein phosphate 2A (PPP2A) signaling. Proc Natl Acad Sci USA 2010; 107: 21830-21835 [PMID: 21098287 DOI: 10.1073/pnas.0912793107]

170 Li SN, Wang X, Zeng QT, Feng YB, Cheng X, Mao X, Wang TH, Deng HP. Metformin inhibits nuclear factor kappaB activation and decreases serum high-sensitivity C-reactive protein level in experimental atherogenesis of rabbits. Heart Vessels 2009; 24: 446-453 [PMID: 20108078 DOI: 10.1007/s00380-008-1137-7]
Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights? Diabetologia 2013; 56: 1898-1906 [PMID: 23835523 DOI: 10.1007/s00125-013-2991-0]

Burcelin R. The antidiabetic gutsy role of metformin uncovered? Gut 2014; 63: 706-707 [PMID: 23840042 DOI: 10.1136/gutjnl-2013-305370]

Ibrahim OHM, Hassan MA. The Use of Anti-Diabetic Drugs in Alzheimer’s Disease, New Therapeutic Options and Future Perspective. Pharmacol Amp Pharm 2018; 9: 157-174 [DOI: 10.4236/pp.2018.96013]

Mostafa DK, Ismail CA, Ghareeb DA. Differential metformin dose-dependent effects on cognition in rats: role of Akt. Psychopharmacology (Berl) 2016; 233: 2513-2524 [PMID: 27113224 DOI: 10.1007/s00213-016-4301-2]

Infeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: a population-based case-control study. J Am Geriatr Soc 2012; 60: 916-921 [PMID: 22458300 DOI: 10.1111/j.1532-5415.2012.03916.x]

Wang L, Liu W, Fan Y, Liu T, Yu C. Effect of rosiglitazone on amyloid precursor protein processing and Aβ clearance in streptozotocin-induced rat model of Alzheimer's disease. Iran J Basic Med Sci 2017; 20: 474-480 [PMID: 28656081 DOI: 10.22038/IJMS.2017.8669]

Pancani T, Phelps JT, Seacry JL, Kilgore MW, Chen KC, Porter NM, Thibault O. Distinct modulation of voltage-gated and ligand-gated Ca2+ currents by PPAR-gamma agonists in cultured hippocampal neurons. J Neurochem 2009; 109: 1800-1811 [PMID: 19453298 DOI: 10.1111/j.1471-4159.2009.06107.x]

Femmimella GD, Bencivenega L, Petraglia L, Visaggi L, Gioia L, Greco FY, de Lucia C, Komici K, Corbei G, Edison P, Rengo G, Ferrara N. Antidiabetic Drugs in Alzheimer's Disease: Mechanisms of Action and Future Perspectives. J Diabetes Res 2017; 2017: 7420796 [DOI: 10.1155/2017/7420796]

Cheng H, Shang Y, Jiang L, Shi TL, Wang L. The peroxisome proliferators activated receptor-gamma agonists as therapeutics for the treatment of Alzheimer's disease and mild-to-moderate Alzheimer's disease: a meta-analysis. Int J Neurosci 2016; 126: 299-307 [PMID: 26001206 DOI: 10.3109/00216444.2015.1015722]

Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Efficacy of PPAR-γ agonist pioglitazone in mild Alzheimer disease. Neurobiol Aging 2011; 32: 1626-1633 [PMID: 19923083 DOI: 10.1016/j.neurobiolaging.2009.10.009]

Geldmacher DS, Fritsch T, McClendon MJ, Landreth G. A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease. Arch Neurol 2011; 68: 45-50 [PMID: 20837824 DOI: 10.1001/archneurol.2010.229]

Takeda. Biomarker Qualification for Risk of Mild Cognitive Impairment (MCI) Due to Alzheimer's Disease (AD) and Safety and Efficacy Evaluation of Pioglitazone in Delaying Its Onset (TOMMOROW). [accessed 2020 Dec 20]. In: ClinicalTrials.gov [Internet]. Zinfandel Pharmaceuticals Inc.: U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT01931566 ClinicalTrials.gov Identifier: NCT01931566

Hölscber C. Central effects of GLP-1: new opportunities for treatments of neurodegenerative diseases. J Endocrinol 2014; 221: T31-T41 [PMID: 23999914 DOI: 10.1530/JOE-13-0221]

McClean PL, Parthsarathy V, Faivre E, Hölscber C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J Neurosci 2011; 31: 6587-6594 [PMID: 21525299 DOI: 10.1523/JNEUROSCI.0529-11.2011]

Hän WN, Hölscber C, Yuan L, Yang W, Wang XH, Wu MN, Qi JS. Liraglutide protects against amyloid-β protein-induced impairment of spatial learning and memory in rats. Neurobiol Aging 2013; 34: 576-588 [PMID: 22592020 DOI: 10.1016/j.neurobiolaging.2012.04.009]

Parthsarathy V, Hölscber C. Chronic treatment with the GLP1 analogue liraglutide increases cell proliferation and differentiation into neurons in an AD mouse model. PLoS One 2013; 8: e58784 [PMID: 23536825 DOI: 10.1371/journal.pone.0058784]

Kelly P, McClean PL, Ackermann M, Konerding MA, Hölscber C, Mitchell CA. Restoration of cerebral and systemic microvascular architecture in APP/PS1 transgenic mice following treatment with Liraglutide™. Microcirculation 2015; 22: 133-145 [PMID: 25556713 DOI: 10.1111/micc.12186]

Qi L, Ke L, Liu X, Liao L, Ke S, Wang Y, Lin X, Zou Y, Wu L, Chen Z, Liu L. Subcutaneous administration of liraglutide ameliorates learning and memory impairment by modulating tau hyperphosphorylation via the glycogen synthase kinase-3β pathway in an amyloid β protein induced alzheimer disease mouse model. Eur J Pharmacol 2016; 783: 23-32 [PMID: 27138127 DOI: 10.1016/j.ejphar.2016.04.052]

Gejl M, Gjedde A, Egefeldt L, Møller A, Hansen SB, Vang K, Rodell A, Brandgaard H, Gottrup H, Schacht A, Møller N, Brock B, Runghy J. In Alzheimer's Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial. Front Aging Neurosci 2016; 8: 108 [PMID: 27252647 DOI: 10.3389/fnagi.2016.00108]

Edison P. Evaluating Liraglutide in Alzheimer's Disease (ELAD). [accessed 2020 Dec 19]. In: ClinicalTrials.gov [Internet]. London: U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT01843075 ClinicalTrials.gov Identifier: NCT01843075

Gault VA, Hölscber C. Protease-resistant glucose-dependent insulinotropic polypeptide agonists facilitate hippocampal LTP and reverse the impairment of LTP induced by beta-amyloid. J...
Rojas M et al. Alzheimer's disease and T2DM

Neurophsiol 2008; 99: 1590-1595 [PMID: 18234983 DOI: 10.1152/jn.01161.2007]

Duffy AM, Hölscher C. The incretin analogue D-Ala2GIP reduces plaque load, astrogliosis and oxidative stress in an APP/PS1 mouse model of Alzheimer's disease. Neurosciience 2013; 228: 294-300 [PMID: 23103794 DOI: 10.1016/j.neuroscience.2012.10.043]

Faiivre E, Hölscher C. Neuroprotective effects of D-Ala(2)GIP on Alzheimer's disease biomarkers in an APP/PS1 mouse model. Alzheimers Res Ther 2013; 5: 20 [PMID: 23601582 DOI: 10.1186/alzchr174]

Hölscher C. Novel dual GLP-1/GIP receptor agonists show neuroprotective effects in Alzheimer's and Parkinson's disease models. Neuropharmacology 2018; 136: 251-259 [PMID: 29402504 DOI: 10.1016/j.neuropharm.2018.01.040]

Li T, Jiao JJ, Hölscher C, Wu MN, Zhang J, Tong JQ, Dong XF, Qu XS, Cao Y, Cai HY, Su Q, Qi JS. A novel GLP-1/GIP/Gcg triagonist reduces cognitive deficits and pathology in the 3xTg model of Alzheimer's disease. Hippocampus 2018; 28: 358-372 [PMID: 29473979 DOI: 10.1002/hipo.22837]

Camins A, Etcheto M, Busquets O, Manzine PR, Castro-Torres RD, Beas-Zarate C, Verdaguer E, Sureda FX, Bulló M, Olloquequi J, Auladell C, Folch J. Triple GLP-1/GIP/glucagon receptor agonists, a potential novel treatment strategy in Alzheimer's disease. Expert Opin Investig Drugs 2019; 28: 93-97 [PMID: 30480461 DOI: 10.1080/13543784.2019.1552677]

Kosaraju J, Gali CC, Kathwal RB, Dubula A, Chinni S, Holsinger RM, Madhunapantula VS, Muthureddy Nataraj SK, Basavan D. Saxagliptin: a dipeptidyl peptidase-4 inhibitor ameliorates streptozotocin induced Alzheimer's disease. Neuropharmacology 2013; 72: 291-300 [PMID: 23563201 DOI: 10.1016/j.neuropharm.2013.04.008]

Kosaraju J, Murthy V, Kathwal RB, Dubula A, Chinni S, Muthureddy Nataraj SK, Basavan D. Vildagliptin: an anti-diabetes agent ameliorates cognitive deficits and pathology observed in streptozotocin-induced Alzheimer's disease. J Pharm Pharmacol 2013; 65: 1773-1784 [PMID: 24117480 DOI: 10.1111/jphp.12148]

Wieczynski M, Wodziewicz E, Górski K, Walczak M, Malinowski B. Perspective of SGLT2 Inhibition in Treatment of Conditions Connected to Neuronal Loss: Focus on Alzheimer's Disease and Ischemia-Related Brain Injury. Pharmaceuticals (Basel) 2020; 13 [PMID: 33187206 DOI: 10.3390/ph13101379]

Sa-Nguanmoo P, Tanajak P, Kerdphoo S, Jaiwongkam T, Pratchayasakul W, Chattipakorn N, Chattipakorn SC. SGLT2-inhibitor and DPP-4 inhibitor improve brain function via attenuating mitochondrial dysfunction, insulin resistance, inflammation, and apoptosis in HFD-induced obese rats. Toxicol Appl Pharmacol 2017; 333: 43-50 [PMID: 28807765 DOI: 10.1016/j.taap.2017.08.005]

Millar P, Pathak N, Parthsarathy V, Bjourson AJ, O'Kane M, Pathak V, Moffett RC, Flatt PR, Gault VA. Metabolic and neuroprotective effects of dapagliflozin and iraglutide in diabetic mice. J Endocrinol 2017; 234: 255-267 [PMID: 28611221 DOI: 10.1530/JEO-17-0263]

Lin B, Koibuchi N, Hasegawa Y, Sueta D, Toyama K, Uekawa K, Ma M, Nakagawa T, Kusaka H, Kim-Mitsuyama S. Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. Cardiovasc Diabetol 2014; 13: 148 [PMID: 25344694 DOI: 10.1186/s12933-014-0148-1]

Hierro-Bujalance C, Infante-Garcia C, Del Marco A, Herrera M, Carranza-Naval MJ, Suarez J, Alves-Martinez P, Lubian-Lopez S, Garcia-Alloza M. Empagliflozin reduces vascular damage and cognitive impairment in a mixed murine model of Alzheimer's disease and type 2 diabetes. Alzheimers Res Ther 2020; 12: 40 [PMID: 32264944 DOI: 10.1186/s13195-020-00607-4]

Wium-Andersen IK, Oster M, Jørgensen MB, Rungby J, Wium-Andersen MK. Antidiabetic medication and risk of dementia in type 2 diabetes: a nested case-control study. Eur J Endocrinol 2019; 181: 499-507 [PMID: 31437816 DOI: 10.1530/EJE-19-0259]

Burns J. Dapagliflozin In Alzheimer's Disease. [accessed 2021 Mar 14]. In: ClinicalTrials.gov [Internet]. Kansas City (KS): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03801642 ClinicalTrials.gov Identifier: NCT03801642

Dhananjayan K, Forbes J, Münch G. Advanced Glycation, Diabetes, and Dementia. In: Srikanth V, Arvanitakis Z. Type 2 Diabetes and Dementia. Elsevier; 2018: 169-193

Burstein AH, Sabbagh M, Andrews R, Valcarce C, Dunn I, Alstel L. Development of Azeliragon, an Oral Small Molecule Antagonist of the Receptor for Advanced Glycation Endproducts, for the Potential Slowing of Loss of Cognition in Mild Alzheimer's Disease. J Prev Alzheimers Dis 2018; 5: 149-154 [PMID: 29616769 DOI: 10.14283/jpad.2018.18]

vTv Therapeutics. Study of Azeliragon in Patients With Mild Alzheimer's Disease and Impaired Glucose Tolerance (Elevage). [accessed 2020 Dec 19]. In: ClinicalTrials.gov [Internet]. Tucson (AZ): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03980730 ClinicalTrials.gov Identifier: NCT03980730

Adler BL, Yarchooan M, Hwang HM, Louneva N, Blair JA, Palm R, Smith MA, Lee HG, Arnold SE, Casadesus G. Neuroprotective effects of the amylin analogue pramlintide on Alzheimer's disease pathogenesis and cognition. Neurobiol Aging 2014; 35: 793-801 [PMID: 24239383 DOI: 10.1016/j.neurobiolaging.2013.10.076]
