The Interaction between Insulin Resistance and Alzheimer's Disease: A Review Article

Nezar Y Albar[1], Hamdi Hassaballa[2], Hamza Shikh[3], Yassin Albar[4], Abdullatif Sheikh Ibrahim[5], Ahmed Hafez Mousa[6,7], Asim Muhammed Alshanberi[8,9], Ahmed Elgebaly[10], Eshak I. Bahbah[11]

[1]Internal Medicine Department, Dr. Samir Abbas Hospital, Jeddah, Saudi Arabia

[2] Assistant Professor Critical Care Medicine, Cairo University, Cairo, Egypt

[3]Ibn Sina National College for Medical Studies, Jeddah, Saudi Arabia

[4]Fakeeh College of Medical Sciences, Jeddah, Saudi Arabia

[5]Batterjee Medical College, Jeddah, Saudi Arabia

[6]Department of Neurosurgery, Postgraduate Medical Education, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates.

[7]Department of Neurosurgery, Rashid Hospital, Dubai Academic Health Cooperation, Dubai, United Arab Emirates

[8]Department of Community Medicine and Pilgrims Health Care, Umm Alqura University, Makkah, Saudi Arabia

[9]Medicine Program, Batterjee Medical College, Jeddah, Saudi Arabia

[10]Smart Health Academic Unit, University of East London, London, E16 2RD, UK.

[11] Faculty of Medicine, Al-Azhar University, Damietta, Egypt

ORCID:

Nezar Albar: 0000-0003-3271-8976

Hamdi Hassaballa: 0009-0007-4792-7101

Hamza Shikh: 0009-0004-3810-9658

Yassin Albar: 0009-0003-8432-4327

Abdullatif Sheikh Ibrahim: 0000-0003-4862-312X

Ahmed Hafez Mousa: 0000-0001-7064-8281

Asim Muhammed Alshanberi: 0000-0002-5215-0049

Ahmed Elgebaly: 0000-0002-8324-0960

Eshak I. Bahbah: 0000-0002-6168-9134

Correspondence:

Eshak I. Bahbah, MD

Faculty of Medicine, Al-Azhar University, Damietta, Egypt

Isaacbahbah@gmail.com; +201094919098

Abstract

Insulin serves multiple functions as a growth-promoting hormone in peripheral tissues. It manages glucose metabolism by promoting glucose uptake into cells and curbing the production of glucose in the liver. Beyond this, insulin fosters cell growth, drives differentiation, aids protein synthesis, and deters degradative processes like glycolysis, lipolysis, and proteolysis. Receptors for insulin and insulin-like growth factor-1 are widely expressed in the central nervous system. Their widespread presence in the brain underscores the varied and critical functions of insulin signaling there. Insulin aids in bolstering cognition, promoting neuron extension, adjusting the release and absorption of catecholamines, and controlling the expression and positioning of gamma-aminobutyric acid (GABA). Importantly, insulin can effortlessly traverse the blood-brain barrier. Furthermore, insulin resistance (IR)-induced alterations in insulin signaling might hasten brain aging, impacting its plasticity and potentially leading to neurodegeneration. Two primary pathways are responsible for insulin signal transmission: the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway, which oversees metabolic responses, and the mitogen-activated protein kinase (MAPK) pathway, which guides cell growth, survival, and gene transcription. This review aimed to explore the potential shared metabolic traits between Alzheimer's disease (AD) and IR disorders. It delves into the relationship between AD and IR disorders, their overlapping genetic markers, and shared metabolic indicators. Additionally, it addresses existing therapeutic interventions targeting these intersecting pathways.

Keywords: Alzheimer's disease, Type 2 Diabetes, Insulin resistance, insulin, Insulin-like growth factor

1. Introduction

Alzheimer's disease (AD) is a degenerative neurological condition that profoundly impacts individuals' mental, emotional, physical, and social well-being. In 2020, AD was responsible for 134,242 deaths in the United States (US), as per the Centers for Disease Control and Prevention (CDC) data [1]. The World Health Organization (WHO) has highlighted that of the 50 million people worldwide living with dementia, AD accounts for 60-70% of these cases [2]. As noted by the Alzheimer's Association, AD ranks as the fifth primary cause of death for Americans aged above 65 and holds sixth place for all age groups [3]. Unfortunately, there's still no definitive cure for AD [2,3]. Nonetheless, by identifying specific biomarkers, it may be possible to pinpoint at-risk individuals and better understand the disease's progression.

One of the underlying mechanisms of AD is the accumulation of Amyloid beta peptide (Aβ) outside neurons and the accumulation and clumping of tau proteins within neurons [4–6]. Other significant markers of AD can include brain shrinkage, especially in the hippocampus and neocortex [7], and extensive white matter hyperintensities (WMH) [8]. The disease has also been linked to diminished neurotransmitter levels like acetylcholine, norepinephrine, and dopamine [9,10]. AD is a complex disease influenced by genetics and various environmental or non-genetic contributors [11–13]. Some of these factors encompass aging, cardiovascular conditions, type 2 diabetes (T2DM), metabolic syndrome (MS), obesity, depression, post-menopausal stage in women, cognitive stagnancy, poor lipid levels, smoking, drug misuse, and unhealthy diets [2,11,14–16]. These elements can instigate disease-causing pathways such as oxidative stress, mitochondrial issues, chronic inflammation, inefficient glucose use, and brain insulin resistance (IR) [17–19]. The precise mechanism of this connection remains elusive. It might relate to shared genetic factors or other underlying elements that lead to the manifestation of the disease [20,21].

One promising approach to uncovering these mechanisms is metabolomics, which identifies disease-associated metabolic characteristics [22–24]. This method is beneficial as it mirrors broader biological processes like genomics and proteomics [23]. By integrating metabolomics data with genomics and proteomics data, researchers can gain a more complete understanding of the complex interplay between genes, proteins, and metabolites. For example, changes in metabolite levels can be linked to specific genetic variants or protein expression patterns, providing insights into the functional consequences of these changes. In recent research, the author reviewed common metabolomics markers related to cardiometabolic diseases, finding that around 40 markers were shared across these conditions [25].

This review aimed to explore the potential shared metabolic traits between AD and IR disorders. It delves into the relationship between AD and IR disorders, their overlapping genetic markers, and shared metabolic indicators. Additionally, it addresses existing therapeutic interventions targeting these intersecting pathways.

2. Molecular Pathophysiology of AD

AD, the leading cause of dementia globally, is more common in western and developed nations [26]. It can be classified into two primary types based on etiology: familial AD (fAD) and sporadic AD (sAD). fAD, representing a small minority (approximately 2%) of cases, is characterized by autosomal-dominant inheritance patterns linked to mutations in specific genes, notably those encoding apolipoprotein E (apoE-ε4), presenilin-1 (PSEN1), presenilin-2 (PSEN2), and amyloid precursor protein (APP) [27]. In contrast, sAD, the predominant form of AD encompassing roughly 98% of cases, arises from a complex interplay of genetic predispositions, epigenetic modifications, and environmental exposures. Most individuals with sAD are older with multiple health conditions, including obesity and cardiovascular issues like stroke and T2DM, which may

further exacerbate their AD [28]. Delving deeper into the intertwined molecular pathways of AD and T2DM could enhance diagnostic methods for diabetic patients and reveal potential treatments targeting both neuronal and pancreatic β-cell deterioration.

2.1.The Role of Aβ and Tau

Neuroinflammation, tau neurofibrillary tangles (NFT), and Aβ neuronal plaques are the primary pathological factors of AD [29]. Aβ plaques, the defining characteristic of AD, are derived from the APP, a protein predominantly located within the central nervous system (CNS) [30]. APP can be processed through two pathways: the secretory and the amyloidogenic. The secretory pathway involves cleavages by α-secretase, linked to ADAM-7 and ADAM-10, and then by γ-secretase [31]. In contrast, the amyloidogenic pathway begins with β-secretase (BACE1) cleavage, followed by γ-secretase cleavage, producing Aβ peptides. These peptides aggregate quickly, with Aβ42 being the most neurotoxic due to its high aggregation propensity [32]. While Aβ plaques and fibrils were initially thought to be the primary toxic agents in AD, recent findings suggest Aβ oligomers play a more crucial role in neurotoxicity [33].

Tau NFT, the second primary hallmark of AD, consist of aggregated hyperphosphorylated tau proteins. Tau, critical for axonal activity maintenance in neurons, needs phosphorylation to function correctly. In AD, tau is over-phosphorylated, with its levels being about three times higher than in healthy brains. This precise balance of phosphorylation is maintained by a combination of kinases and phosphatases. Key kinases, such as glycogen synthase kinase-3 beta (GSK3β) and cyclin-dependent kinase 5 (CDK5), contribute significantly to AD-related tau phosphorylation, with evidence pointing towards cooperative actions of various kinases [34]. On the other end, phosphatases like phosphoprotein phosphatase 2A (PP2A) target tau to counteract its hyperphosphorylation. Hyperphosphorylated tau disrupts microtubule-dependent functions,

including the trafficking of neurotrophins, leading to neuronal complications. While some studies suggest hyperphosphorylated tau might protect neurons from apoptosis, the resultant functional loss makes neurons more vulnerable to other AD-related damages [34].

3. Insulin

Human insulin, a peptide hormone with 51 amino acids divided into two chains, is produced in the β-cells located in the islets of Langerhans. This hormone prevents prolonged high blood sugar levels, or hyperglycemia, by being released into the bloodstream when there's a spike in glucose, whether internally sourced or externally [35]. In body tissues, insulin plays multiple roles. It aids in glucose use, limits the liver's glucose generation, and enhances glucose entry into cells. This is achieved by shifting glucose transporters like glucose transporter type 4 (GLUT 4) from inside the cell to the cell surface [36]. Moreover, insulin is involved in cellular growth, maturation, and protein creation. As a constructive hormone, insulin supports the absorption of fatty and amino acids and facilitates energy storage. Still, it also hinders activities such as glycolysis, fat breakdown, and protein breakdown [37].

While insulin's presence is noticeably lower in the cerebrospinal fluid (CSF) than in blood plasma, the two are somewhat correlated. This association indicates that the brain's insulin primarily originates from the insulin circulating in the blood [38]. Insulin can travel from the blood to the brain, passing through the blood-brain barrier (BBB) capillary cells, following a specific and capacity-limited process that's receptor-dependent [39]. Once in the brain, insulin connects with the insulin receptor, forming a complex. This complex then moves through the brain to the endothelial cells via transcytosis. The efficiency of this transport can be affected by factors like diet, obesity, inflammation, diabetes, and blood triglyceride levels [40,41]. Moreover, animal research has discovered that fasting decreases CSF insulin levels, which rise post-meal [42,43].

3.1.The Role of Insulin in the Brain

Insulin receptors are present in all brain cell types, with varying expression in specific brain regions, as demonstrated in animal studies pinpointing regions like the hippocampus, cerebral cortex, and cerebellum [44–46]. While human brains also exhibit these receptors [47,48], alterations in insulin signaling within the CNS might hasten brain aging, impact plasticity, and contribute to neurodegeneration [49].

3.1.1. Insulin Signaling in the Brain

Insulin and insulin-like growth factor 1 (IGF-1) interact with their receptors, notably the insulin receptor and the IGF-1 receptor (IGF-1R), which have a broad presence in the brain [50]. Research on animals reveals the significant expression of insulin receptors in regions like the olfactory bulb, hippocampus, and hypothalamus, among others. Conversely, in mouse brains, IGF-1R displays prominent expression in the hippocampus, neocortex, and thalamus [51,52]. These receptors can combine in the brain to enhance their signaling processes [53]. Further classification of insulin receptors reveals two primary isoforms: IR-A, prevalent in the adult nervous system, and IR-B, which predominantly exists in tissues such as adipose, liver, and muscles [54]. Notably, both IGF-1 and IGF-2 can be associated with the insulin receptor [55], and these insulin receptors are found in neurons and glial cells alike.

The intricate process of insulin signaling is initiated when insulin binds to its tyrosine kinase receptor, a complex composed of two alpha and beta subunits [56]. The binding action prompts several cellular responses, one of which is activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway, which is pivotal for metabolism, protein synthesis, and cell survival [55,57]. This pathway plays diverse roles, from DNA replication and protein synthesis to

maintaining mitochondrial health [58,59]. Another critical signaling mechanism is the mitogen-activated protein kinase (MAPK) pathway, which is triggered by the binding of the growth factor receptor-bound protein-2 (Grb-2) [60]. This pathway manages the functions of several transcription factors and proteins, influencing processes like glucose metabolism and cell division [60].

3.1.2. Insulin and Brain Glucose Metabolism

In the brain, neurons primarily utilize glucose through GLUT 3, but they also express other insulin-regulated glucose transporters like GLUT 4 and GLUT 8, found specifically in areas including the hippocampus and hypothalamus [61]. Insulin promotes GLUT 4's translocation to the plasma membrane, enhancing glucose intake, which is crucial for cognitive functions like memory [62]. Moreover, during periods of intense metabolic needs, such as learning, the AKT pathway facilitates GLUT 4's translocation, highlighting the potential impact of disrupted insulin-mediated glucose transport on cognition [63,64]. Insulin's brain activity governs neuronal metabolism and modulates peripheral metabolic processes in organs like the liver and adipose tissue through hormonal actions in the hypothalamus, influencing pathways such as hepatic glucose production and lipolysis [65].

3.1.3. Insulin and Cognition

Insulin's presence in regions of the brain, such as the frontal cortex and the hippocampus, emphasizes its pivotal role in learning and memory. Studies have shown that spatial learning modifies insulin receptor expression in the hippocampus, and administering insulin can lead to observable improvements in memory. While these effects have been documented in both animal models and human subjects, the precise mechanisms by which insulin influences cognitive function remain to be fully elucidated [61]. Insulin appears to affect hippocampal synaptic

plasticity, promoting mechanisms like long-term potentiation (LTP) [66] and long-term depression (LTD) [67], both crucial for memory formation. Molecular mechanisms regulated by insulin, such as the expression of the N-methyl-D-aspartate (NMDA) receptor, which is controlled by insulin-stimulated pathways like extracellular signal-regulated kinase 1/2 (ERK1/2) [68] or PI3-K [69], play roles in this process. Moreover, synaptic remodeling, integral to neuronal adaptability, is also influenced by insulin signaling [70,71].

Learning seems to modify the expression and function of insulin receptors in specific brain areas. Animal research points towards the upregulation of insulin receptor mRNA in the hippocampal CA1 region following spatial memory training, leading to heightened insulin receptor presence in the hippocampus [61,72]. Furthermore, insulin might significantly influence memory and learning, impacting the placement of IRs within the hippocampus. Beyond cognition, insulin's signaling might also regulate emotional states. For instance, rats with diminished hypothalamic insulin receptors showcased symptoms resembling depression and anxiety [72]. Conversely, insulin administration in mice bolstered object memory and displayed anxiety-reducing effects [73]. Such findings underline the significance of hippocampal insulin receptors in normal cognitive functions [74].

3.1.4. The Effects of Insulin on Neurons

Insulin receptors are notably present in both postsynaptic and presynaptic regions of synapses, emphasizing their key role in neural communication. The hormone acts on neurons through the MAPK and AKT signaling pathways, contributing to neuron outgrowth, modulating catecholamine release and uptake, and influencing the expression and localization of γ-aminobutyric acid (GABA) [75,76]. GABA is central to various functions like sleep, learning, memory, reproductive system activity, food intake regulation, body weight, and even neural

activities in the frontal cortex [77,78]. Additionally, insulin modulates the expression of both NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors [79] and has a hand in activity-driven synaptic plasticity, guiding processes such as long-term potentiation and depression via interactions with NMDA receptor signaling and the AKT pathway [67].

Moreover, insulin has a pivotal role in shaping excitatory synapses' development and sustainability, fostering dendritic spine formation [80,81]. The hormone's ability to regulate AKT and GSK3β is crucial for maintaining the equilibrium between long-term potentiation and depression [82]. Insulin further supports neuronal health by counteracting apoptosis through the activation of the AKT pathway [83] and impacts the phosphorylation of the forkhead box O (FOXO) transcription factor, which manages the expression of cell death-promoting agents. Studies using intrahippocampal microinjections of insulin in animals showed that cognitive performance varies with the dosage: high insulin concentrations considerably improve spatial learning and memory, while low concentrations hinder cognitive abilities [84].

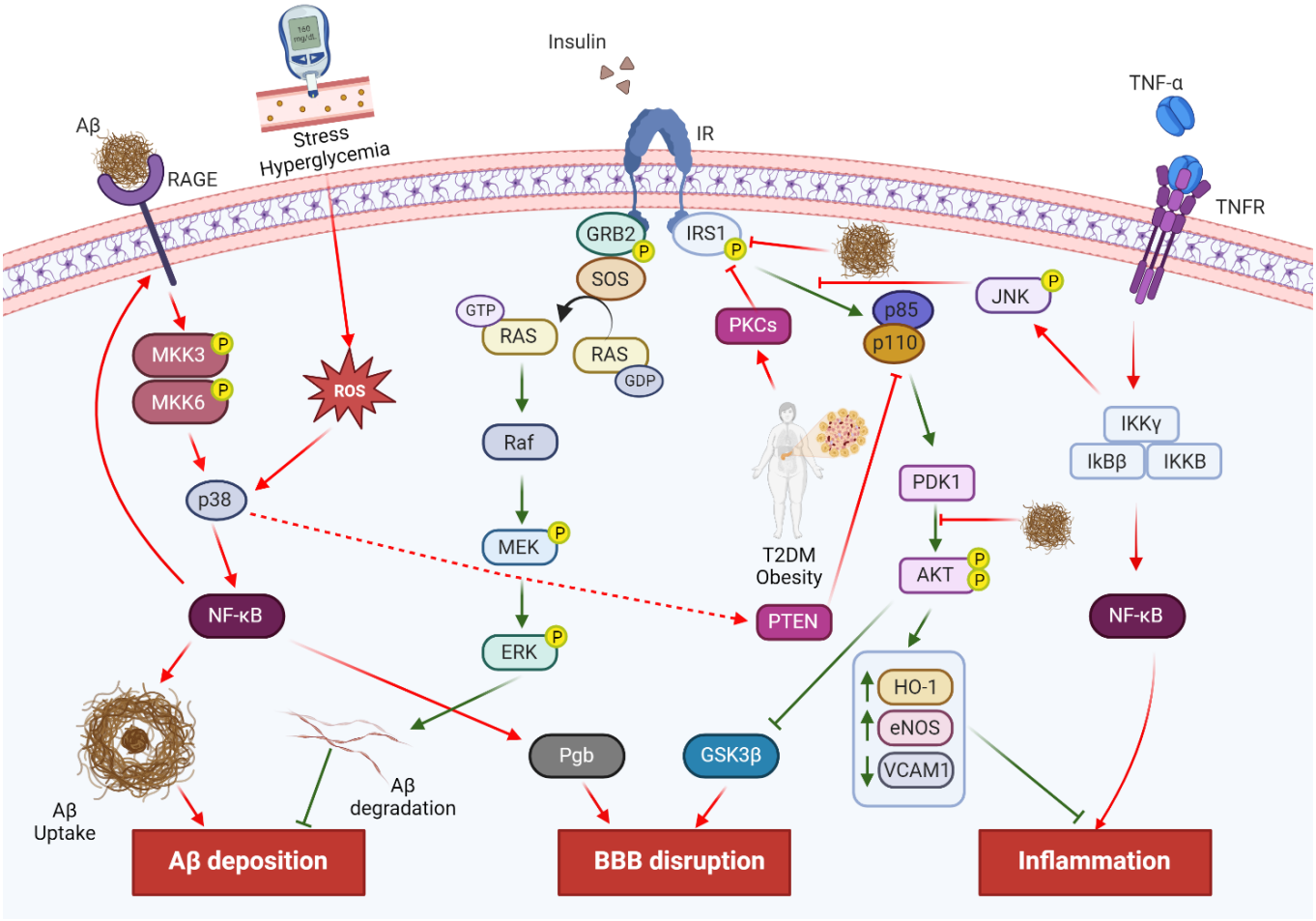

Figure 1: **Insulin signaling pathway and AD;** Inflammation: The activation of eNOS, mediated by the PI3K/Akt pathway, has been identified as a potential inhibitor of VCAM-1 expression in endothelial cells. This process is integral in reducing inflammatory responses. BBB Disruption: Research indicates that GSK3β inhibition can enhance the stability of tight junctions in the blood-brain barrier (BBB). Furthermore, insulin has been shown to bolster BBB integrity through the PI3K/Akt/GSK3β pathway. Aβ Accumulation: It's been observed that insulin exposure can promote the degradation of Aβ. This occurs through an increase in insulin-degrading enzyme (IDE) expression in astrocytes, triggered by the activation of the ERK-mediated pathway. In contrast, in neurons, Aβ exposure has been linked to the induction of IR. This resistance is characterized by the inhibition of IRS1, PDK-dependent Akt activation, and the activation of the p38 pathway. Our preliminary laboratory data suggests that Aβ might exert similar effects on these pathways in BBB endothelial cells. Aβ: Amyloid beta, RAGE: Receptor for Advanced Glycation Endproducts, ROS: Reactive Oxygen Species, MKK3: Mitogen-Activated Protein Kinase Kinase 3, MKK6: Mitogen-Activated Protein Kinase Kinase 6, NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells, IR: Insulin Receptor, IRS1: Insulin Receptor Substrate 1, PKCs: Protein Kinase C , PI3K (p85, p110): Phosphoinositide 3-Kinases (regulatory subunit p85, catalytic subunit p110), PTEN: Phosphatase and Tensin Homolog, PDK1: 3-Phosphoinositide Dependent Protein Kinase-1, Akt: Protein Kinase B, GSK3β: Glycogen Synthase Kinase 3 beta, HO-1: Heme Oxygenase 1, eNOS: Endothelial Nitric Oxide Synthase, VCAM-1: Vascular Cell Adhesion Molecule 1, TNF-α: Tumor Necrosis Factor alpha, TNFR: Tumor Necrosis Factor Receptor, JNK: c-Jun N-terminal kinase, IKKγ: IκB kinase gamma, IκBβ: Inhibitor of kappa B beta, IκB: Inhibitor of kappa B, ERK: Extracellular signal-Regulated Kinases, MEK: Mitogen-Activated Protein Kinase Kinase, Raf: RAF proto-oncogene serine/threonine-protein kinase, GRB2: Growth Factor Receptor-Bound Protein 2

3.1.5. Effects of Insulin on Glial Cells and Hippocampal Adult Neurogenesis

Astrocytes, the primary homeostatic cells in the human brain's grey matter, utilize GLUT 1 for glucose transport and can also supply neurons with lactate as an energy source during hypoglycemic events, a mechanism termed the astrocyte-neuron lactate shuttle [85,86]. These cells

display the presence of insulin receptors and other downstream signaling molecules like AKT and MAPK, which are activated by insulin and IGF-1. Extended exposure to high insulin levels can lead to decreased insulin receptor expression in glial cells, though neuronal insulin receptor expression remains consistent. Furthermore, insulin plays a pivotal role in astrocytes by adjusting the release of inflammatory cytokines in response to inflammation triggers [87]. Insulin also impacts oligodendrocytes through AKT signaling, influencing their proliferation, differentiation, and myelination, with IGF activation of the AKT pathway promoting axonal coverage [88]. Microglial inflammatory reactions are intricately regulated by insulin, which can both enhance and inhibit various inflammatory cytokine secretions [87].

Neurogenesis is an ongoing process in mammals, particularly evident in the sub-granular zone of the hippocampus, where neural stem cells (NSCs) multiply and evolve to form new neurons [89,90]. This hippocampal neurogenesis is integral for learning and memory functions, and disruptions in this process in neurodegenerative diseases have been linked to cognitive impairments [91]. The activation of the insulin/IGF-1 pathway helps regulate neuroblast activity [92,93], and both insulin and IGF-1 foster neurogenesis by guiding NSC proliferation, differentiation, and survival [94]. Nevertheless, sustained overactivation of the insulin/IGF-1 pathways can lead to early depletion of the NSC pool [95]. The effects of insulin on the neural stem niche can vary, being either beneficial or harmful, depending on the timing and duration of its activation [96].

4. Brain IR

4.1.Definition and assessment

IR refers to the decreased efficacy of tissues in responding to insulin, often evaluated using the Homoeostatic Model Assessment for IR (HOMA-IR) method, though the hyperinsulinemic-

euglycaemic (HI-EG) clamp is considered the gold standard [97–99]. In this technique, insulin and dextrose are infused to assess insulin sensitivity, with any change in insulin concentrations in the CNS being noted. The HI-EG clamp, combined with MRI or similar tools, helps understand insulin's brain effects and its peripheral sensitivity [100]. Some limitations, like potentially reduced insulin reaching the CNS, are noted [101]. As an alternative, intranasal insulin delivers insulin directly to the CNS [102]. Using intranasal insulin with controlled stimuli (e.g., food images), studies have revealed a link between peripheral IR and decreased CNS responsiveness [103]. Various factors, including diet and peripheral metabolism treatments, can influence CNS insulin sensitivity, underlining a tight link between insulin function in the body and brain [103].

At a molecular scale, IR might result from factors like diminished insulin receptors or interruptions in the insulin signaling process. Insulin operates predominantly through the Ras-MAPK and PI3K-Akt pathways [104]. Activation of an insulin receptor can lead to the activation or inhibition of the PI3K-Akt pathway, depending on the phosphorylation site. The balance between phosphorylated substrates can serve as an IR marker, a technique that's shown promise in AD research [105,106]. Another promising technique for gauging brain IR involves analyzing neuronal-enriched extracellular vesicles in plasma to identify changes in insulin signaling [107]. This method has shown increased markers of IR in patients with T2DM and AD [108].

4.2.Systemic and brain IR

A connection between T2DM and brain dysfunction has long been recognized. Early observations from the 1920s identified memory, processing speed, and arithmetic deficiencies in T2DM patients [109]. By the 1980s, formal studies began linking more severe cognitive deficits, such as memory problems, with higher haemoglobin A1c levels in the bloodstream [110]. These findings were bolstered by later research that highlighted challenges in complex attention, information

processing, and executive function in T2DM patients [111–115]. These cognitive impairments seemed more pronounced in older individuals with extended diabetes duration, poor glycaemic control, diabetic complications, and accompanying conditions like hypertension and depression. Interestingly, emerging evidence also points to cognitive and structural brain changes in young T2DM patients, suggesting both age-related neurodegeneration and early disease processes play roles in the observed deficits [116–119].

Advanced neuroimaging tools have uncovered significant differences in brain structures and functions in those with T2DM compared to non-diabetic individuals [120]. People with longstanding T2DM exhibit increased instances of both large-vessel atherosclerosis and stroke, and small-vessel ischaemic diseases. Additionally, cerebral atrophy, especially in areas related to cognition, is more prevalent among the elderly with IR and T2DM than those without these conditions [121]. When using FDG-PET scans, middle-aged and older individuals with IR (either having T2DM or on the cusp of developing it) and still possessing standard cognition display regional cortical hypometabolism in critical cognitive regions often associated with AD [122].

The specific mechanisms driving the observed cognitive impairments and neuroimaging differences in T2DM remain uncertain. While some suggest these changes may result from brain IR, others point to co-existing conditions often found in T2DM, such as inflammation, dyslipidaemia, or hypertension, which may affect brain function independently of insulin signalling. The BBB function also appears to be compromised in T2DM. There's evidence to suggest that systemic IR can impact BBB function, which might reduce brain insulin levels and impact neural activity [123]. Additionally, T2DM can also lead to BBB damage, increasing its permeability to various substances [124,125]. Animal studies further suggest a link between systemic and brain IR. However, human studies yield inconclusive results, with some highlighting

potential brain IR in obesity [126] and others pointing to BBB transport issues rather than genuine brain IR as the cause. Intriguingly, certain interventions, like intranasal insulin administration, have shown promise in normalizing brain function and improving cognitive performance in T2DM patients, hinting at possible therapeutic avenues [127].

5. IR and AD

Brain IR at a cellular level might manifest as compromised neuroplasticity and neurotransmitter release, leading to both metabolic dysregulation and cognitive or mood disturbances [97]. Remarkably, the metabolic anomalies seen in T2DM mirror those in AD brains, prompting some researchers to propose that AD is essentially a cerebral variant of diabetes, termed "type 3 diabetes" [128,129].

5.1.IR and Tau Phosphorylation

The Tau protein may be implicated in the irregularities of insulin signaling and consequent brain pathologies [130]. Recognized as the primary constituent of NFT in AD patients [131], the human brain contains six distinct Tau isoforms due to alternative splicing [132]. Classified as a microtubule-associated protein (MAP) [133], Tau aids in microtubule assembly and stability, crucial for various cellular functions including cell morphogenesis and intracellular trafficking [134]. Despite its release into extracellular spaces, the function of extracellular Tau remains enigmatic [135].

Tau's activity is predominantly regulated by phosphorylation, and it holds over 85 sites potentially subject to this process [136]. Intriguingly, both Tau gene expression and the Tau protein's phosphorylation respond to insulin and IGF stimulations [137]. AD-afflicted brains notably exhibit

Tau hyperphosphorylation, with over 40 identified phosphorylation sites, of which 28 are exclusively phosphorylated. This hyperphosphorylation might be attributed to imbalances between various kinases and phosphatases. Specifically, GSK3-β, which phosphorylates Tau at more than 30 sites, is central to the emergence of AD and neurofibrillary tangle (NFT) [138]. Furthermore, defective insulin or IGF-1 signaling might augment Tau phosphorylation, with additional connections to pathways like Wnt signaling and oxidative stress, both intertwined with IR [139].

Such hyperphosphorylation alters Tau's conformation, undermining its microtubule-binding capacity and leading to its aggregation within neurons. These aggregates are the foundational elements of diseases termed tauopathies. This accumulation is not benign; hyperphosphorylated Tau obstructs the normal protein's interactions with microtubules, disrupting cell morphology and organelle transport [140]. Exacerbating the scenario, animal studies hint at Tau's role in regulating brain insulin signaling, suggesting that Tau dysfunction could culminate in brain IR, significantly impacting cognitive and metabolic functions in AD patients [141]. As AD advances, Tau pathologies are discernible, initially in the brainstem and entorhinal cortex, eventually spreading to the hippocampus [142,143]. Interestingly, a complete absence of Tau is also detrimental, correlating with increased brain iron accumulation and potentially contributing to disorders like Parkinson’s disease [144].

5.2.IR and Aβ Pathology

APP is a multifunctional membrane protein present in various tissues, especially within the synapses of neurons in the CNS. It serves several roles including synapse formation, neuron adaptability, antimicrobial activity, and iron transportation. The processing of APP follows two distinct pathways: the majority (90%) undergoes the non-amyloidogenic process, while the remainder goes through the amyloidogenic route. Notably, insulin facilitates the non-

amyloidogenic processing by modulating APP's phosphorylation. Thus, disruptions in insulin signaling can amplify the buildup of the problematic Aβ protein [145]. Furthermore, both insulin and Aβ are broken down by the insulin-degrading enzyme (IDE), and diminished insulin signaling can lead to decreased Aβ degradation due to the reduced levels of IDE [146].

In the non-amyloidogenic route, APP is cleaved by α-secretase, yielding specific fragments (sAPPα and CTFα). In contrast, the amyloidogenic pathway, more prevalent in acidic endosomes, sees APP being acted upon by β-secretase, creating distinct N-terminal and C-terminal fragments. The latter undergoes another cleavage, releasing Aβ fragments into the extracellular space. Once outside the cell, these Aβ fragments are prone to forming various aggregates, culminating in β-amyloid plaques [147]. The Aβ peptide chains come in various lengths: Aβ38, Aβ40, and Aβ42. Familial or early-onset AD is linked to mutations in the PS1/PS2 genes and APP, coupled with inheriting the ApoE-ε4 allele. These genetic factors amplify the production of Aβ42, thereby elevating Aβ peptide deposition in the brain. However, the mechanisms leading to Aβ accumulation in sporadic AD cases remain under rigorous scrutiny [148,149].

Functionally, the native APP aids memory and learning processes via its synaptic actions and dendritic spine formation [150]. Under normal conditions, Aβ is released outside neurons during their activity and is regulated by surrounding proteases [151]. But aberrations in the cleavage position can elevate the neurotoxic Aβ42 variant. As a downstream effect, these Aβ peptides can cluster, forming fibrils and amyloid plaques that hinder cell communication and induce cell death. Studies indicate that an overabundance of neurotoxic Aβ mirrors memory lapses seen in AD patients, largely because of the disruption of neural adaptability from intraneuronal Aβ accumulation [152]. This detrimental influence on neurons might be due to the activation of

immune-inflammatory responses in glial cells, leading to the engulfment of neuronal structures [153]. Hence, the internal buildup of Aβ is pivotal in various synaptopathies.

Insulin plays a pivotal role in the metabolism of the APP, which subsequently affects the balance between the production and breakdown of Aβ. A deficiency or inactivity of insulin can lead to the formation of NFT and induce oxidative stress on cells [154]. Additionally, diminished insulin levels correlate with elevated Aβ concentrations, leading to the formation of amyloid plaques in the brain. The IDE is responsible for breaking down several molecules, including insulin and Aβ [155]. Disturbances in IDE function, marked by increased immunoreactivity around senile plaques and decreased IDE expression in the AD patient's hippocampus, can contribute to AD progression [156]. This enzyme's role in regulating insulin and Aβ levels in the brain is significant, with animal models revealing that an overexpression of IDE can lead to conditions like hyperinsulinemia and heightened Aβ brain levels, ultimately impacting insulin signaling and resistance [157].

The effects of Aβ oligomers on brain function have been extensively studied in animal models. Specifically, Aβ42 peptides have been found to induce liver IR in certain transgenic mice, highlighting the potential of inhibiting Aβ42 synthesis as a treatment strategy [158]. When Aβ oligomers were introduced directly to rodent neurons, synaptic loss and neuronal dysfunctions were observed, which might be a precursor to memory impairments [159]. Moreover, introducing these oligomers into primates' brains resulted in behavioral alterations and AD-like pathologies [160]. Such introductions also caused inflammatory responses and metabolic disruptions, as observed in models where Aβ oligomers were injected intracerebrally [161]. Interestingly, research on a monkey model of T1DM revealed increased Aβ levels, particularly in the hippocampus, coupled with decreased concentrations of the Aβ-degrading enzyme, neprilysin [162]. Additionally, diet-induced IR in the brain seems to be intertwined with Aβ pathology in AD

mouse models. While factors leading to IR, such as metabolic stress or inflammation due to unhealthy diets, might directly accelerate Aβ accumulation, the role of insulin signaling in this context appears less direct [163].

Insulin's interaction with Aβ metabolism extends to influencing Aβ peptide trafficking and promoting its secretion, while also hindering its degradation by IDE. The relationship between insulin and APP metabolism may be mediated through signaling pathways like MAPK [164]. Paradoxically, Aβ can disrupt insulin signaling, either by competing for insulin receptor binding sites or diminishing its binding efficacy [165]. Such accumulation of Aβ can further amplify Tau hyperphosphorylation, instigating tauopathies. The neurotoxic activities of Aβ underscore its detrimental effects on the nervous system. For instance, intracellular Aβ can disrupt signaling pathways, enhancing tau hyperphosphorylation and, in turn, fostering APP processing and Aβ buildup [166].

5.3.IR and Inflammation

Inflammation is intrinsically linked to the onset and progression of AD. Central to the neuroinflammation theory of AD is the accumulation of Aβ, which triggers the release of inflammatory molecules by persistently activated glial cells [167]. In the cerebrospinal fluid of those with AD, inflammatory proteins like IL-1, IL-6, TNF-α, and TGF-β are often present in elevated amounts [168]. The term "neuroinflammation" refers to the activation of brain cells, notably microglia and astrocytes, leading to the release of inflammatory and harmful agents [169]. As the main immune players in the brain, microglial cells, when activated, are indicative of central inflammation, which could foretell brain diseases [170]. The importance of neuroinflammation is seen across various neurodegenerative disorders, with evidence suggesting it significantly

advances the neurodegeneration seen in AD, leading to neuronal damage, oxidative stress, and impaired synaptic function [171].

Further complicating the situation is the role of IR in perpetuating neuroinflammation. Peripheral IR might influence AD pathology by acting on neurodegeneration [172]. This resistance boosts the expression of IDE and encourages the buildup of advanced glycation end products (AGEs), which are modified proteins and fats formed through a reaction with glucose [173]. Notably, individuals with IR have increased AGE levels [174]. AGEs are harmful and have been discovered in AD hallmark structures like amyloid plaques and NFT. Furthermore, AGEs can cause vascular issues in the brain and act on the receptor for AGEs (RAGE) [175]. RAGE's expression, which is higher in those with AD and T2DM, interacts with AGEs and Aβ to amplify inflammatory reactions, impairing the brain's vascular system and exacerbating neurodegenerative processes [176]. Macrophages, vital components of the neuroinflammatory landscape, release inflammatory agents that disrupt insulin signaling, further linking inflammation and IR [177]. While insulin can counteract some inflammatory actions and even promote the synthesis of particular neuronal proteins, multiple factors, including apoE-ε4, affect insulin signaling in the brain, contributing to AD's progression [178].

5.4.IR and Oxidative Stress

IR can drive oxidative stress through multiple mechanisms, including imbalances in carbohydrate and lipid metabolism, enhanced activation of GSK-3β, and disruptions in cellular survival, energy equilibrium, and mitochondrial function [179]. Furthermore, brain IR diminishes the expression of vital molecules like choline acetyltransferase and neurotrophin, correlating with elevated levels of modified Tau and Aβ42 [180]. Factors such as hypoxia and ischemia can further induce oxidative stress, which in turn amplifies the production of reactive species like ROS and RNS.

These reactive species can inflict harm on crucial cellular components, including lipids, proteins, and DNA, leading to neurotoxic consequences [181,182]. Notably, the onset of neurodegeneration is characterized by oxidative damage, which is linked to mitochondrial dysfunction seen in AD [183,184]. Oxidative stress typically manifests when the cellular generation of reactive species surpasses the antioxidant defenses, or when the body can't efficiently clear the excessive ROS and RNS [185].

Mitochondria, essential for processes like energy metabolism and free radical production, play a pivotal role in aging and neurodegenerative disease prevention. However, dysfunctional mitochondria are less efficient in ATP production but produce heightened ROS levels, which could be central to the oxidative imbalance in AD [17]. The enzymes involved in metabolic processes including the respiratory chain, glycolysis, and Krebs cycle deteriorate in AD brains. The resulting diminished activity impairs glucose metabolism, culminating in reduced ATP synthesis, neuronal dysfunction, synaptic loss, and neurodegeneration [17,186]. Interestingly, the early AD phase is marked by heightened mitochondrial enzyme activity and oxidative stress, even before the evident accumulation of amyloid plaques in animal AD models [187]. Despite these findings, the exact relationship between Aβ oligomers, mitochondrial activity, and ROS production remains ambiguous due to inconsistent results from past studies [188], necessitating further research to ascertain the initiating factors.

5.5.IR and Cognitive Impairment

IR and brain insulin deficiency have been implicated in cognitive dysfunction. In individuals with AD, insulin levels in the brain and CSF are reduced, while plasma levels are elevated, possibly due to compromised signal transduction [189,190]. Insulin's role in long-term neural protection makes its deficiency detrimental, potentially leading to neurodegeneration. Though IR is believed

to be an early factor in cognitive impairment, the exact mechanism remains elusive. Some postulated contributors include changes in APP metabolism, increased Tau protein, brain inflammation, the involvement of the ApoE ε4 allele, and IR-induced disruptions in hippocampal plasticity [191]. Brain IR might independently heighten the risk of cognitive issues [192]. Notably, insulin plays a crucial role in synaptic neurotransmission, influencing learning and memory, especially via GABA receptors [192]. In AD animal models, disrupted insulin signaling has been linked to memory deficits [193], and in prediabetic patients, cognitive decline, particularly in memory, appears more tied to IR than elevated blood sugar levels [194]. The interplay between brain IR and AD pathology, specifically through IRS-1 dysfunction potentially induced by Aβ oligomers, warrants further exploration [195].

Brain plasticity, the ability to adapt structurally and functionally to environmental cues, may be influenced by various factors, including insulin signaling. Altered insulin signaling can impact brain plasticity and further IR [96]. For example, in middle-aged people who are cognitively asymptomatic but have euglycemic hyperinsulinemia, IR is linked to increased brain glucose absorption [196] as well as reduced cortical perfusion and blood flow [197]. Such resistance correlates with diminished cerebral glucose metabolism, which might be predictive of memory performance decline [198]. Cognitive alterations and brain functions are also influenced by age [199]. Insulin plays a crucial function in stimulating the uptake of glucose into neurons by causing GLUT 4 to translocate to the membrane of the neuron. This activity is critical for improving spatial memory and is necessary in conditions requiring a high metabolic demand, such as learning [200]. Disruptions in this insulin-regulated glucose transport mechanism could lead to cognitive deficits [200]. The full spectrum of IR's impact on cognition remains to be fully elucidated, necessitating more research.

5.6. IR and Cholinergic Deregulation

Acetylcholine, a crucial neurotransmitter, plays a significant role in several central nervous system functions, including attention, memory, motivation, and arousal. The cholinergic projections originating from the nucleus basalis of Meynert (NBM) to the cerebral cortex are implicated in cognitive function and the regulation of blood flow. Direct electrical stimulation of the NBM has been shown to trigger a widespread increase in cortical blood flow (CBF), as evidenced by multiple studies [201,202]. Furthermore, peripheral sensory input can activate the NBM, thereby increasing CBF, a process mediated by acetylcholine and its muscarinic and nicotinic receptors [203].

In AD, cholinergic dysfunction of these projections is observed, along with neuronal loss in the NBM [203]. Pharmacological inhibition of the enzyme that degrades acetylcholine, leading to an increase in its presynaptic levels, has been found to have positive effects on cognition and behavior in AD patients. Interestingly, a decrease in the expression of cholinergic receptors has been noted in the hippocampus of autopsied brains of individuals with T2DM and in corresponding mouse models [204]. Consequently, it has been hypothesized that cholinergic alterations may be involved in the modified pathology of AD patients who also have T2DM [205].

Recent studies have suggested that IR could induce AD via cholinergic dysfunction. In a study using APP-KI and APP/IR-dKI mice, IR was found to exacerbate cognitive dysfunction and alter cerebral blood flow (CBF) regulation, which was associated with downregulation of nicotinic acetylcholine receptor alpha7 (nAChRα7) expression and function [202,206,207]. Reduced expression of nAChRα7 has been reported to impair cognitive functions, including long-term memory [208]. Furthermore, gene expression analyses revealed that the expression of neuronal activity markers (Egr1 and Nptx2) and Chrna7 was reduced in APP/IR-dKI mice compared with APP-KI mice. Insulin signaling in the brain affects neuronal activity [209], and reduced expression

of EGR1 has been reported in the frontal cortex of AD patients [210]. Considering that EGR1 is involved in cholinergic function [210], reduced expression of Egr1 in APP/IR-dKI could reflect cholinergic malfunction in these mice. Therefore, IR could induce AD via cholinergic dysfunction, and targeting the insulin/IR pathway-specific cascade may be an effective strategy for the treatment of AD.

5.7.Hyperglycemia and Its Consequences on AD Pathologic Development

Hyperglycemia, often seen in T2DM patients, can have significant implications for AD pathogenesis. Repeated episodes of transient hyperglycemia can disturb neuronal balance by affecting KATP channels and elevating Aβ levels [211]. Aging and imbalances in glucose metabolism can lead to the formation of advanced glycation end-products (AGEs), which are notably higher in AD patients with diabetes [212]. These AGEs, especially the prevalent glyceraldehyde-AGEs, are toxic to neurons [213] and interact with receptors RAGEs found in various brain cells. These interactions can mediate inflammatory effects, influence Aβ transport across the blood-brain barrier, and boost Aβ formation [214,215]. Additionally, AGEs can stimulate tau hyperphosphorylation via the RAGEs-GSK3β signaling pathway [216]. Studies have shown that direct injection of AGEs into mice brains led to AD-like symptoms, including memory decline and increased tau phosphorylation [217,218].

6. Genetics variabilities shared between AD and IR disorders

Several studies have highlighted the genetic intersections between AD and IR disorders. Research has shown a genetic link involving the fat mass and obesity-associated (FTO) gene, particularly with single-nucleotide polymorphisms (SNPs) like rs3751812, which has associations with obesity-related brain volume deficits [20] and other IR disorders, such as MS and T2DM [219,220].

The FTO gene has a potential role in AD pathogenesis through its influence on hormones like ghrelin and leptin, impacting hunger signals and weight gain, which subsequently can lead to IR, MS, and T2DM [221,222]. Increased levels of the ghrelin hormone have also been linked to reduced cognitive function, suggesting its potential involvement in AD pathogenesis [223,224].

Additional research has identified other genetic variants associated with both T2DM and AD. Wang et al. discovered eight novel pleiotropic SNPs that correlate with both conditions, highlighting their role in pathways related to oxidative stress, mitochondrial dysfunction, and phosphoinositide-3-kinase (PI3K) regulation [225]. Other SNPs, such as rs6859 and rs2075650, have associations with obesity, dyslipidemia, ischemic stroke (IS), and coronary artery disease (CAD) [226–230], both of which are AD risk factors and are metabolically linked to IR disorders. Similarly, the IDE gene and its rs1887922 SNP have associations with AD and T2DM, possibly due to its impact on Aβ accumulation and hepatic insulin degradation [231–233]. Another gene of interest is the ApoE gene, which interacts with multiple risk factors and has a significant correlation with AD, particularly in individuals with T2DM, hypertension, and other conditions [234–237]. The rs11136000 SNP in the APOJ/CLU gene, which encodes for clusterin, is another point of interest due to its role as an AD biomarker, especially in patients with IR disorders [238]. The intricate genetic interplay between AD and IR disorders underscores the need for a more in-depth understanding of their shared pathways and mechanisms.

7. Therapy

7.1. Pharmacological treatment

Research indicates that insulin plays a pivotal role in maintaining brain health, and imbalances in insulin regulation, both peripherally and within the brain, may be implicated in the onset of AD and associated cerebrovascular conditions. This understanding opens up a new avenue for

therapeutic exploration, focusing on elevating insulin availability in the CNS or enhancing its sensitivity, aiming to thwart or postpone AD and related ailments. This discussion will initially delve into intranasal insulin, which offers a direct intervention for the brain, and will subsequently transition into other strategies that bolster insulin sensitivity both centrally and systemically (Table 1).

7.1.1. Intranasal insulin

Administering insulin peripherally, as done in diabetes treatments, can pose risks of hypoglycemia in non-diabetic individuals and may not effectively reach the brain due to the BBB. Hence, researchers have been examining the use of intranasal insulin delivery. This method allows insulin to bypass the BBB, traveling to the brain through olfactory and trigeminal perivascular channels. In studies with healthy adults, intranasal insulin demonstrated effects on various CNS measures, such as EEG and functional MRI [103]. Moreover, rodent AD models revealed that intranasal insulin could mitigate disease pathology and conserve both short-term and long-term memory [239]. Preliminary human trials have shown improvements in episodic memory in both cognitively healthy participants and those with mild cognitive impairment or AD, although results varied with the APOE genotype and the duration of treatment [240–243].

A particular study involving 104 participants administered either two doses of intranasal insulin or a placebo for 120 days. Both insulin doses enhanced performance on the "AD Assessment Scale-Cognitive subscale (ADAS-Cog12)", which gauges overall cognition. Additionally, both doses maintained functional capabilities and improved cerebral glucose uptake as detected by FDG-PET. Intriguingly, post-hoc analyses indicated that intranasal insulin's effects might be influenced by factors such as the APOE genotype and gender, with males possibly benefiting more from higher

doses [244,245]. However, the underlying mechanisms for these variable responses, especially those related to APOE, haven't been thoroughly investigated in human trials [246,247].

An ambitious multi-site trial was conducted with 289 participants with mild cognitive impairment or AD, assessing the safety and efficacy of intranasal insulin over a year, followed by an open-label extension of six months [248]. This study faced challenges with its delivery devices. The initial device, which had been used in prior AD research [245,249], was replaced due to malfunctions by a newer device [250]. Outcomes showed contrasting results between the two devices. The newer device's cohort did not display significant benefits with insulin treatment, whereas the initial device's group showed improved cognitive performance. These conflicting outcomes underscore the need to prove direct access of insulin to the CNS, suggesting that the choice of delivery device is crucial in therapeutic intranasal applications. The study also highlighted the potential therapeutic promise of intranasal insulin in AD, as evidenced by notable differences in ADAS-Cog12 scores and CSF biomarkers, emphasizing the importance of further research in this area [251,252].

7.1.2. Insulin sensitisers

Rather than boosting insulin levels, another approach focuses on enhancing tissue responsiveness to existing insulin levels. Metformin, a widely-used drug for T2DM, has shown potential in mouse AD models by improving memory and reducing markers of the disease, along with enhanced brain insulin signaling [253,254]. In a 12-month trial with non-diabetic individuals with mild cognitive impairment, metformin showed some promise in memory outcomes, but not in other key measures [255], leading to a further ongoing trial (NCT04098666). PPAR agonists, another class of insulin sensitizers, have yielded inconsistent results. While a pilot study saw memory improvements with rosiglitazone [256], subsequent trials revealed selective benefits based on genetic factors or no

significant cognitive effects [257,258]. Moreover, a large-scale trial involving pioglitazone was halted due to ineffectiveness (NCT01931566), although detailed results remain unpublished. In essence, while insulin sensitizers show some potential, robust evidence of their efficacy in AD remains limited.

7.1.3. GLP-1 receptor agonists

Hormones that stimulate insulin secretion, such as GLP-1 receptor agonists, play a crucial role in maintaining blood sugar balance. In the brain, GLP-1 receptor agonists are present and are responsible for promoting cell growth and proliferation, while also offering protection from excitotoxic cell death and programmed cell death [259,260]. These agonists, used in enhancing peripheral insulin sensitivity, serve as treatments for T2DM [261]. One such agonist, Liraglutide, has been put forward as a potential therapeutic avenue for AD [262]. Studies in mice revealed that liraglutide administration led to enhanced memory retention and increased neuronal density in the hippocampus [263]. Further, a primate study indicated that liraglutide offered protection against the loss of insulin receptors, countered synaptic dysfunction, and mitigated the presence of hyperphosphorylated tau [264]. However, in a clinical setting involving 18 AD patients, 26 weeks of daily subcutaneous liraglutide injections preserved brain glucose metabolism in contrast to a placebo but showed no notable changes in cognitive function or Aβ accumulation [265]. Currently, a phase 2 clinical trial spanning 12 months is underway to evaluate the impacts of daily liraglutide treatments on AD patients, with the primary objective being FDG-PET outcomes and secondary focuses on cognitive scores and various imaging markers (NCT01843075).

Table 1: Clinical trials of pharmacological therapy

Class	Study ID	Design	Groups	Population	Findings
PPAR-γ agonist	Watson et al., 2005 [256]	Double-blind RCT	Placebo (n=10) Rosiglitazone (n=20)	Mild AD or aMCI	Subjects receiving rosiglitazone exhibited better-delayed recall (at Months 4 and 6) and selective attention (Month 6)
	Risner et al., 2006 [257]	Parallel, multicentre RCT	Placebo (n=122) Rosiglitazone (n=389)	Mild to moderate AD	APOE epsilon4 non-carriers exhibited cognitive and functional improvement in response to RSG
	Gold et al., 2010 [266]	Parallel, multicentre RCT	Placebo (n=159) Rosiglitazone (n=394)	Mild to moderate AD	No significant treatment difference was detected in ADAS-Cog; however, a significant difference was detected in the CIBIC+
	Tzimopoulou et al., 2010 [267]	Parallel, multicentre RCT	Placebo (n=38) Rosiglitazone (n=38)	Mild to moderate AD	Rosiglitazone was linked to an initial rise in brain glucose metabolism but did not show any significant biological or clinical signs of slowing AD progression over one year.
	Harrington et al., 2011 (REFLECT-2 and -3) [258]	Parallel RCT	Placebo (n=940) Rosiglitazone (n=1882)	Mild to moderate AD	Rosiglitazone did not show significant efficacy in cognitive or global function as an adjunct to AChEIs, and its safety profile was as expected, with edema being the most common adverse event.
	Hanyu et al., 2009 [268]	Parallel RCT	Placebo (n=17) Pioglitazone (n=15)	AD and aMCI with DM	ADAS-Jcog scores decreased significantly in the pioglitazone group, and WMS-R logical memory-I scores increased significantly compared to the control group.
	Hanyu et al., 2010 [269]	Parallel RCT	Placebo (n=17) Pioglitazone (n=17)	Mild AD with DM	The pioglitazone group showed a notable reduction in ADAS-Jcog scores and TNF-α levels over six months.
	Geldmacher et al., 2011 [270]	Parallel RCT	Placebo (n=13) Pioglitazone (n=12)	AD without DM	Peripheral edema was more common in patients treated with pioglitazone compared to placebo, and no significant differences in laboratory measures or clinical efficacy were found.
	Sato et al., 2011 [271]	Parallel RCT	Placebo (n=10) Pioglitazone	Mild AD with DM	Pioglitazone led to cognitive and parietal lobe blood flow improvements, stabilized disease progression, and enhanced insulin sensitivity.
Intranasal insulin	Reger et al., 2008 [241]	Parallel RCT	Placebo (n=12) Insulin (n=13)	Mild AD or MCI	Insulin led to improved verbal memory, attention, and functional status, while increasing fasting plasma concentrations of beta-

					amyloid peptide Aβ40, thus altering the Aβ40/42 ratio, without affecting fasting glucose and insulin levels
	Craft et al., 2012 [245]	Parallel RCT	Placebo (n=30) Insulin (n=74)	Mild AD or aMCI	Insulin improved delayed memory and maintained functional abilities in AD patients, with younger participants also seeing preservation in general cognition, without significant changes in cerebrospinal fluid biomarkers, and no severe adverse events.
	Kellar et al., 2021 [272]	Parallel RCT	Placebo (n=20) Insulin (n=20)	Mild AD or MCI	Insulin significantly slowed the progression of white matter hyperintensity volume in deep and frontal brain regions over 12 months.
	Rosenbloom et al., 2021 [273]	Parallel RCT	Placebo (n=16) Insulin (n=19)	Mild AD or aMCI	There was no significant difference in cognitive and functional measures between the glulisine and saline treatment groups over 6 months; however, the glulisine group experienced higher rates of nasal irritation and respiratory symptoms, with no differences in blood sugar control or hypoglycemia rates.
	Kellar et al., 2022 [274]	Parallel RCT	Placebo (n=20) Insulin (n=18)	Mild AD or MCI	Insulin increased interferon-γ and eotaxin levels, and decreased interleukin-6 compared to placebo.
	Craft et al., 2017 [249]	Parallel RCT	Placebo (n=12) Insulin detemir (n=12) Regular Insulin (n=12)	Mild AD or MCI	Regular insulin improved memory at two and four months compared to placebo, preserved brain volume on MRI, and reduced the tau-P181/Aβ42 ratio, while detemir showed no significant effects, and neither treatment impacted daily functioning.
GLP-1	Mullins et al., 2019 [275]	Parallel RCT	Placebo (n=9) Exenatide (n=9)	Patients with high probability AD based on CSF	Exenatide increased nausea and decreased appetite compared to placebo, and it reduced glucose and GLP-1 during tests but showed no significant differences in clinical and cognitive measures, MRI results, or most biomarkers, except for a reduction in Aβ42 in extracellular vesicles.
	Watson et al., 2018 [276]	Parallel RCT	Placebo (n=16) Liraglutide (n=25)	Normal late middle-aged individuals with subjective cognitive complaints	Liraglutide treatment improved connectivity within the default mode network compared to placebo, with no cognitive differences detected between groups
	Gejl et al., 2017 [277]	Parallel RCT	Placebo (n=20) Liraglutide (n=18)	Mild AD	Baseline brain glucose transport and metabolism rates negatively correlated with disease duration and positively with cognitive function; GLP-1 analog treatment significantly increased these rates to levels seen in healthy individuals, supporting the hypothesis that it restores glucose transport at the blood-brain barrier.

ADAS-Jcog: Alzheimer's Disease Assessment Scale-Cognitive subscale, WMS-R: Wechsler Memory Scale-Revised logical memory-I, CIBIC+: Clinician's Interview-Based Impression of Change plus caregiver input, TNF-α: Tumor necrosis factor-alpha, AD: Alzheimer's disease, AChEIs: Acetylcholine esterase inhibitor, aMCI: amnestic mild cognitive impairment, CSF: Cerebrospinal fluid

7.2. Non-pharmacological approaches

Lifestyle modifications, encompassing diet and exercise, have emerged as pivotal players in managing peripheral IR. Since 2015, these interventions have been theorized to also provide preventive or therapeutic avenues for AD. Individuals with diets high in simple carbohydrates and saturated fats face a heightened risk for AD compared to those favoring lean proteins and poly-unsaturated fats [278]. A study showcased that a diet saturated with fats and simple sugars affected CSF insulin levels, reflecting patterns associated with AD. Conversely, diets low in fats and sugars normalized insulin levels in those with mild cognitive impairment to those seen in healthy participants [279]. Moreover, dietary shifts have been observed to influence CSF Aβ42 metrics [279]. In another investigative lens, dietary restrictions seemed to enhance the brain's response to food cues post-intranasal insulin administration [103]. It's worth noting that diet can modulate several risk factors tied to AD, such as brain and peripheral IR, inflammation, and vascular complications [280].

Recent systematic reviews have spotlighted dietary regimens that are rich in polyunsaturated fatty acids, nuts, and plant-centric foods while curtailing saturated fats, animal proteins, and refined sugars. Adherence to these dietary guidelines was linked with superior peripheral insulin sensitivity and diminished risk of age-induced cognitive decline and AD [278,281,282]. However, the direct influence of diet in augmenting brain insulin functionality remains a pivotal question for subsequent studies. In parallel, exercise, a potent modulator of peripheral IR, holds promise in curtailing AD risks [283]. Animal-centric studies have suggested that physical activity augments brain insulin sensitivity, alleviating several neural complications [284,285]. Yet, human-centric studies that corroborate these findings are limited, marking a significant realm for future exploration.

Conclusion

Research on insulin signaling in the brain has expanded rapidly, examining its role in both typical aging and conditions like T2DM and AD. IR, either at a cellular level or systemically, denotes a diminished physiological response to insulin, leading to cognitive, mood, and neurological disturbances in the brain. While both T2DM and AD exhibit links to brain IR, their direct correlation remains ambiguous. Amidst the escalating global crises of T2DM and AD, with profound human and economic impacts, there's an urgent call for a deeper understanding of their intertwined pathophysiology. Determining if T2DM and AD are distinct outcomes of shared IR origins or interconnected in a detrimental cycle is pivotal. A multidisciplinary approach to uncovering the complexities of IR across the body and brain will enhance our grasp and treatment strategies for both conditions.

Declaration of funding:

None.

Declaration of financial/other relationships:

The authors report there are no competing interests to declare.

Acknowledgments:

Medical writing and editorial support in preparing this paper were provided by Advocacy for Pharmaceutical Consultancy, Egypt.

Author contributions:

All authors contributed to the conceptualization, writing, and review & editing of the present review. All authors have approved the manuscript before submission.

References

[1] CDC WONDER National Vital Statistics System. Underlying Cause of Death, 1999-2020 Results via CDC WONDER [Internet]. U.S.D.o.H.a.H. Serv. Centers Dis. Control Prev. Natl. Cent. Heal. Stat. 2020. Available from: https://wonder.cdc.gov/ucd-icd10.html.

[2] World Health Organization. Fact Sheets: Dementia, 2020. [Internet]. 2020. Available from: https://www.who.int/%0Anews-room/fact-sheets/detail/dementia#:~:text=Worldwide%252C%2520around%25%0A2050%2520million%2520people,dependency%2520among%2520older%2520people%25%0A20worldwide.

[3] 2021 Alzheimer's disease facts and figures. Alzheimers Dement. 2021;17:327–406.

[4] Stoyanova II. Ghrelin: a link between ageing, metabolism and neurodegenerative disorders. Neurobiol Dis. 2014;72 Pt A:72–83.

[5] d'Errico P, Meyer-Luehmann M. Mechanisms of Pathogenic Tau and Aβ Protein Spreading in Alzheimer's Disease. Front Aging Neurosci. 2020;12:265.

[6] Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacol Rep. 2015;67:195–203.

[7] Pini L, Pievani M, Bocchetta M, et al. Brain atrophy in Alzheimer's Disease and aging. Ageing Res Rev. 2016;30:25–48.

[8] Garnier-Crussard A, Bougacha S, Wirth M, et al. White matter hyperintensity topography in Alzheimer's disease and links to cognition. Alzheimers Dement. 2022;18:422–433.

[9] Rivera EJ, Goldin A, Fulmer N, et al. Insulin and insulin-like growth factor expression

and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimers Dis. 2005;8:247–268.

[10] Pan X, Kaminga AC, Jia P, et al. Catecholamines in Alzheimer's Disease: A Systematic Review and Meta-Analysis. Front. Aging Neurosci. Switzerland; 2020. p. 184.

[11] Neu SC, Pa J, Kukull W, et al. Apolipoprotein E Genotype and Sex Risk Factors for Alzheimer Disease: A Meta-analysis. JAMA Neurol. 2017;74:1178–1189.

[12] Yassine HN, Anderson A, Brinton R, et al. Do menopausal status and APOE4 genotype alter the long-term effects of intensive lifestyle intervention on cognitive function in women with type 2 diabetes mellitus? Neurobiol Aging. 2020;92:61–72.

[13] Kulminski AM, Loika Y, Culminskaya I, et al. Independent associations of TOMM40 and APOE variants with body mass index. Aging Cell. 2019;18:e12869.

[14] Tao Q, Ang TFA, DeCarli C, et al. Association of Chronic Low-grade Inflammation With Risk of Alzheimer Disease in ApoE4 Carriers. JAMA Netw open. 2018;1:e183597.

[15] Ogama N, Sakurai T, Kawashima S, et al. Postprandial Hyperglycemia Is Associated With White Matter Hyperintensity and Brain Atrophy in Older Patients With Type 2 Diabetes Mellitus. Front Aging Neurosci. 2018;10:273.

[16] Malek-Ahmadi M, Beach T, Obradov A, et al. Increased Alzheimer's disease neuropathology is associated with type 2 diabetes and ApoE ε.4 carrier status. Curr Alzheimer Res. 2013;10:654–659.

[17] Chen Z, Zhong C. Decoding Alzheimer's disease from perturbed cerebral glucose metabolism: implications for diagnostic and therapeutic strategies. Prog Neurobiol.

2013;108:21–43.

[18] Rojas-Gutierrez E, Muñoz-Arenas G, Treviño S, et al. Alzheimer's disease and metabolic syndrome: A link from oxidative stress and inflammation to neurodegeneration. Synapse. 2017;71:e21990.

[19] Bosco D, Fava A, Plastino M, et al. Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. J Cell Mol Med. 2011;15:1807–1821.

[20] Ho AJ, Stein JL, Hua X, et al. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. Proc Natl Acad Sci U S A. 2010;107:8404–8409.

[21] Wang X-F, Lin X, Li D-Y, et al. Linking Alzheimer's disease and type 2 diabetes: Novel shared susceptibility genes detected by cFDR approach. J Neurol Sci. 2017;380:262–272.

[22] Rangel-Huerta OD, Gil A. Nutrimetabolomics: An Update on Analytical Approaches to Investigate the Role of Plant-Based Foods and Their Bioactive Compounds in Non-Communicable Chronic Diseases. Int J Mol Sci. 2016;17.

[23] Amin AM. Metabolomics applications in coronary artery disease personalized medicine. Adv Clin Chem. 2021;102:233–270.

[24] Ivanisevic J, Thomas A. Metabolomics as a Tool to Understand Pathophysiological Processes. Methods Mol Biol. 2018;1730:3–28.

[25] Amin AM. The metabolic signatures of cardiometabolic diseases: Does the shared metabotype offer new therapeutic targets? Lifestyle Med [Internet]. 2021;2:e25. Available from: https://doi.org/10.1002/lim2.25.

[26] Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. Biomed Res Int. 2014;2014:908915.

[27] Querfurth HW, LaFerla FM. Alzheimer's Disease. N Engl J Med. 2010;362:329–344.

[28] Aubert L, Pichierri S, Hommet C, et al. Association between comorbidity burden and rapid cognitive decline in individuals with mild to moderate Alzheimer's disease. J Am Geriatr Soc. 2015;63:543–547.

[29] Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020;25.

[30] Recuero M, Serrano E, Bullido MJ, et al. Abeta production as consequence of cellular death of a human neuroblastoma overexpressing APP. FEBS Lett. 2004;570:114–118.

[31] Lammich S, Kojro E, Postina R, et al. Constitutive and regulated alpha-secretase cleavage of Alzheimer's amyloid precursor protein by a disintegrin metalloprotease. Proc Natl Acad Sci U S A. 1999;96:3922–3927.

[32] Multhaup G, Huber O, Buée L, et al. Amyloid Precursor Protein (APP) Metabolites APP Intracellular Fragment (AICD), Aβ42, and Tau in Nuclear Roles. J Biol Chem. 2015;290:23515–23522.

[33] Walsh DM, Selkoe DJ. A beta oligomers - a decade of discovery. J Neurochem. 2007;101:1172–1184.

[34] Wang J-Z, Xia Y-Y, Grundke-Iqbal I, et al. Abnormal hyperphosphorylation of tau: sites, regulation, and molecular mechanism of neurofibrillary degeneration. J Alzheimers Dis. 2013;33 Suppl 1:S123-39.

[35] Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005;26:19–39.

[36] Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. Physiol Rev. 2018;98:2133–2223.

[37] Dimitriadis G, Mitrou P, Lambadiari V, et al. Insulin effects in muscle and adipose tissue. Diabetes Res Clin Pract. 2011;93 Suppl 1:S52-9.

[38] Bromander S, Anckarsäter R, Ahrén B, et al. Cerebrospinal fluid insulin during non-neurological surgery. J Neural Transm. 2010;117:1167–1170.

[39] Banks WA. The source of cerebral insulin. Eur J Pharmacol. 2004;490:5–12.

[40] Banks WA, Owen JB, Erickson MA. Insulin in the brain: there and back again. Pharmacol Ther. 2012;136:82–93.

[41] Gray SM, Aylor KW, Barrett EJ. Unravelling the regulation of insulin transport across the brain endothelial cell. Diabetologia. 2017;60:1512–1521.

[42] Strubbe JH, Porte DJ, Woods SC. Insulin responses and glucose levels in plasma and cerebrospinal fluid during fasting and refeeding in the rat. Physiol Behav. 1988;44:205–208.

[43] Yang YJ, Hope ID, Ader M, et al. Insulin transport across capillaries is rate limiting for insulin action in dogs. J Clin Invest. 1989;84:1620–1628.

[44] Adamo M, Raizada MK, LeRoith D. Insulin and insulin-like growth factor receptors in the nervous system. Mol Neurobiol [Internet]. 1989;3:71–100. Available from: https://doi.org/10.1007/BF02935589.

[45] MARKS JL, PORTE JR. D, STAHL WL, et al. Localization of insulin receptor mRNA in

rat brain by in situ hybridization. Endocrinology [Internet]. 1990;127:3234–3236. Available from: https://doi.org/10.1210/endo-127-6-3234.

[46] WERTHER GA, HOGG A, OLDFIELD BJ, et al. Localization and Characterization of Insulin Receptors in Rat Brain and Pituitary Gland Using in Vitro Autoradiography and Computerized Densitometry*. Endocrinology [Internet]. 1987;121:1562–1570. Available from: https://doi.org/10.1210/endo-121-4-1562.

[47] Roth RA, Morgan DO, Beaudoin J, et al. Purification and characterization of the human brain insulin receptor. J Biol Chem. 1986;261:3753–3757.

[48] Kotzke G, Schütt M, Missler U, et al. Binding of human, porcine and bovine insulin to insulin receptors from human brain, muscle and adipocytes and to expressed recombinant alternatively spliced insulin receptor isoforms. Diabetologia. 1995;38:757–763.

[49] Kullmann S, Heni M, Hallschmid M, et al. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiol Rev [Internet]. 2016;96:1169–1209. Available from: https://doi.org/10.1152/physrev.00032.2015.

[50] Belfiore A, Frasca F, Pandini G, et al. Insulin Receptor Isoforms and Insulin Receptor/Insulin-Like Growth Factor Receptor Hybrids in Physiology and Disease. Endocr Rev [Internet]. 2009;30:586–623. Available from: https://doi.org/10.1210/er.2008-0047.

[51] Fernandez AM, Torres-Alemán I. The many faces of insulin-like peptide signalling in the brain. Nat Rev Neurosci. 2012;13:225–239.

[52] Brüning JC, Gautam D, Burks DJ, et al. Role of Brain Insulin Receptor in Control of Body

Weight and Reproduction. Science (80-) [Internet]. 2000;289:2122–2125. Available from: https://doi.org/10.1126/science.289.5487.2122.

[53] Bailyes EM, Navé BT, Soos MA, et al. Insulin receptor/IGF-I receptor hybrids are widely distributed in mammalian tissues: quantification of individual receptor species by selective immunoprecipitation and immunoblotting. Biochem J. 1997;327 (Pt 1:209–215.

[54] Ghasemi R, Haeri A, Dargahi L, et al. Insulin in the Brain: Sources, Localization and Functions. Mol Neurobiol [Internet]. 2013;47:145–171. Available from: https://doi.org/10.1007/s12035-012-8339-9.

[55] Kleinridders A, Ferris HA, Cai W, et al. Insulin Action in Brain Regulates Systemic Metabolism and Brain Function. Diabetes [Internet]. 2014;63:2232–2243. Available from: https://doi.org/10.2337/db14-0568.

[56] Dyer AH, Vahdatpour C, Sanfeliu A, et al. The role of Insulin-Like Growth Factor 1 (IGF-1) in brain development, maturation and neuroplasticity. Neuroscience [Internet]. 2016;325:89–99. Available from: https://doi.org/10.1016/j.neuroscience.2016.03.056.

[57] 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.

[58] Grillo CA, Piroli GG, Hendry RM, et al. Insulin-stimulated translocation of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent. Brain Res. 2009;1296:35–45.

[59] Condorelli F, Salomoni P, Cotteret S, et al. Caspase Cleavage Enhances the Apoptosis-

Inducing Effects of BAD. Mol Cell Biol [Internet]. 2001;21:3025–3036. Available from: https://doi.org/10.1128/MCB.21.9.3025-3036.2001.

[60] Le Roith D, Zick Y. Recent Advances in Our Understanding of Insulin Action and Insulin Resistance. Diabetes Care [Internet]. 2001;24:588–597. Available from: https://doi.org/10.2337/diacare.24.3.588.

[61] Neth BJ, Craft S. Insulin Resistance and Alzheimer's Disease: Bioenergetic Linkages. Front Aging Neurosci [Internet]. 2017;9. Available from: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00345/full.

[62] de la Monte SM. Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. Curr Alzheimer Res. 2012;9:35–66.

[63] Surguchov A. Caveolin: A New Link Between Diabetes and AD. Cell Mol Neurobiol. 2020;40:1059–1066.

[64] McNay EC, Ong CT, McCrimmon RJ, et al. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. Neurobiol Learn Mem [Internet]. 2010;93:546–553. Available from: https://www.sciencedirect.com/science/article/pii/S1074742710000419.

[65] Kullmann S, Heni M, Hallschmid M, et al. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiol Rev [Internet]. 2016;96:1169–1209. Available from: https://www.physiology.org/doi/10.1152/physrev.00032.2015.

[66] Moult PR, Harvey J. Hormonal regulation of hippocampal dendritic morphology and synaptic plasticity. Cell Adh Migr [Internet]. 2008;2:269–275. Available from:

https://doi.org/10.4161/cam.2.4.6354.

[67] Van Der Heide LP, Kamal A, Artola A, et al. Insulin modulates hippocampal activity-dependent synaptic plasticity in a N-methyl-d-aspartate receptor and phosphatidyl-inositol-3-kinase-dependent manner. J Neurochem [Internet]. 2005;94:1158–1166. Available from: https://doi.org/10.1111/j.1471-4159.2005.03269.x.

[68] Wu S-P, Lu K-T, Chang W-C, et al. Involvement of mitogen-activated protein kinase in hippocampal long-term potentiation. J Biomed Sci [Internet]. 1999;6:409–417. Available from: https://doi.org/10.1007/BF02253672.

[69] Sanna PP, Cammalleri M, Berton F, et al. Phosphatidylinositol 3-Kinase Is Required for the Expression But Not for the Induction or the Maintenance of Long-Term Potentiation in the Hippocampal CA1 Region. J Neurosci [Internet]. 2002;22:3359–3365. Available from: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.22-09-03359.2002.

[70] Gratuze M, Joly-Amado A, Vieau D, et al. Mutual Relationship between Tau and Central Insulin Signalling: Consequences for AD and Tauopathies? Neuroendocrinology [Internet]. 2018;107:181–195. Available from: https://doi.org/10.1159/000487641.

[71] Skeberdis VA, Lan J, Zheng X, et al. Insulin promotes rapid delivery of N-methyl-D-aspartate receptors to the cell surface by exocytosis. Proc Natl Acad Sci U S A. 2001;98:3561–3566.

[72] Zhao W, Chen H, Xu H, et al. Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. J Biol Chem. 1999;274:34893–34902.

[73] Benedict C, Hallschmid M, Hatke A, et al. Intranasal insulin improves memory in humans. Psychoneuroendocrinology [Internet]. 2004;29:1326–1334. Available from: https://www.sciencedirect.com/science/article/pii/S0306453004000526.

[74] Folch J, Ettcheto M, Busquets O, et al. The Implication of the Brain Insulin Receptor in Late Onset Alzheimer's Disease Dementia. Pharmaceuticals. 2018.

[75] Nelson TJ, Sun M-K, Hongpaisan J, et al. Insulin, PKC signaling pathways and synaptic remodeling during memory storage and neuronal repair. Eur J Pharmacol. 2008;585:76–87.

[76] van der Heide LP, Ramakers GMJ, Smidt MP. Insulin signaling in the central nervous system: Learning to survive. Prog Neurobiol [Internet]. 2006;79:205–221. Available from: https://www.sciencedirect.com/science/article/pii/S030100820600058X.

[77] Kaur S, Singh S, Arora A, et al. Pharmacology of GABA and Its Receptors BT - Frontiers in Pharmacology of Neurotransmitters. In: Kumar P, Deb PK, editors. Singapore: Springer Singapore; 2020. p. 241–292. Available from: https://doi.org/10.1007/978-981-15-3556-7_8.

[78] Sandoval-Salazar C, Ramírez-Emiliano J, Trejo-Bahena A, et al. A high-fat diet decreases GABA concentration in the frontal cortex and hippocampus of rats. Biol Res [Internet]. 2016;49:15. Available from: https://doi.org/10.1186/s40659-016-0075-6.

[79] Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol [Internet]. 2018;14:168–181. Available from: https://doi.org/10.1038/nrneurol.2017.185.

[80] Lee C-C, Huang C-C, Hsu K-S. Insulin promotes dendritic spine and synapse formation by the PI3K/Akt/mTOR and Rac1 signaling pathways. Neuropharmacology [Internet]. 2011;61:867–879. Available from: https://www.sciencedirect.com/science/article/pii/S0028390811002395.

[81] Chiu S-L, Chen C-M, Cline HT. Insulin Receptor Signaling Regulates Synapse Number, Dendritic Plasticity, and Circuit Function In Vivo. Neuron [Internet]. 2008;58:708–719. Available from: https://doi.org/10.1016/j.neuron.2008.04.014.

[82] Kim S-J, Han Y. Insulin inhibits AMPA-induced neuronal damage via stimulation of protein kinase B (Akt). J Neural Transm. 2005;112:179–191.

[83] Peineau S, Taghibiglou C, Bradley C, et al. LTP Inhibits LTD in the Hippocampus via Regulation of GSK3β Neuron [Internet]. 2007;53:703–717. Available from: https://doi.org/10.1016/j.neuron.2007.01.029.

[84] Moosavi M, Naghdi N, Maghsoudi N, et al. The effect of intrahippocampal insulin microinjection on spatial learning and memory. Horm Behav [Internet]. 2006;50:748–752. Available from: https://www.sciencedirect.com/science/article/pii/S0018506X06001759.

[85] Wender R, Brown AM, Fern R, et al. Astrocytic glycogen influences axon function and survival during glucose deprivation in central white matter. J Neurosci Off J Soc Neurosci. 2000;20:6804–6810.

[86] Pellerin L, Pellegri G, Bittar PG, et al. Evidence Supporting the Existence of an Activity-Dependent Astrocyte-Neuron Lactate Shuttle. Dev Neurosci [Internet]. 1998;20:291–299. Available from: https://doi.org/10.1159/000017324.

[87] Spielman LJ, Bahniwal M, Little JP, et al. Insulin Modulates In Vitro Secretion of Cytokines and Cytotoxins by Human Glial Cells. Curr Alzheimer Res. 2015;12:684–693.

[88] Cui QL, Fragoso G, Miron VE, et al. Response of human oligodendrocyte progenitors to growth factors and axon signals. J Neuropathol Exp Neurol. 2010;69:930–944.

[89] Braun SMG, Jessberger S. Adult neurogenesis: mechanisms and functional significance. Development. 2014;141:1983–1986.

[90] Eriksson PS, Perfilieva E, Björk-Eriksson T, et al. Neurogenesis in the adult human hippocampus. Nat Med. 1998;4:1313–1317.

[91] Taylor CJ, Jhaveri DJ, Bartlett PF. The therapeutic potential of endogenous hippocampal stem cells for the treatment of neurological disorders. Front Cell Neurosci [Internet]. 2013;7. Available from: http://journal.frontiersin.org/article/10.3389/fncel.2013.00005/abstract.

[92] Chell JM, Brand AH. Nutrition-Responsive Glia Control Exit of Neural Stem Cells from Quiescence. Cell [Internet]. 2010;143:1161–1173. Available from: https://doi.org/10.1016/j.cell.2010.12.007.

[93] Sousa-Nunes R, Yee LL, Gould AP. Fat cells reactivate quiescent neuroblasts via TOR and glial insulin relays in Drosophila. Nature [Internet]. 2011;471:508–512. Available from: https://doi.org/10.1038/nature09867.

[94] Åberg MAI, Åberg ND, Palmer TD, et al. IGF-I has a direct proliferative effect in adult hippocampal progenitor cells. Mol Cell Neurosci [Internet]. 2003;24:23–40. Available from: https://www.sciencedirect.com/science/article/pii/S1044743103000824.

[95] Sun LY. Hippocampal IGF-1 expression, neurogenesis and slowed aging: clues to longevity from mutant mice. Age (Omaha) [Internet]. 2006;28:181–189. Available from: https://doi.org/10.1007/s11357-006-9009-5.

[96] Spinelli M, Fusco S, Grassi C. Brain Insulin Resistance and Hippocampal Plasticity: Mechanisms and Biomarkers of Cognitive Decline. Front Neurosci [Internet]. 2019;13. Available from: https://www.frontiersin.org/article/10.3389/fnins.2019.00788/full.

[97] Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol [Internet]. 2018;14:168–181. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29377010.

[98] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia [Internet]. 1985;28:412–419. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3899825.

[99] Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. Annu Rev Nutr [Internet]. 2005;25:391–406. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16011472.

[100] Fishel MA, Watson GS, Montine TJ, et al. Hyperinsulinemia provokes synchronous increases in central inflammation and beta-amyloid in normal adults. Arch Neurol [Internet]. 2005;62:1539–1544. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16216936.

[101] Rhea EM, Banks WA. Role of the Blood-Brain Barrier in Central Nervous System Insulin Resistance. Front Neurosci [Internet]. 2019;13:521. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/31213970.

[102] Heni M, Kullmann S, Preissl H, et al. Impaired insulin action in the human brain: causes and metabolic consequences. Nat Rev Endocrinol [Internet]. 2015;11:701–711. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26460339.

[103] Kullmann S, Heni M, Hallschmid M, et al. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiol Rev [Internet]. 2016;96:1169–1209. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27489306.

[104] Kim B, Feldman EL. Insulin resistance in the nervous system. Trends Endocrinol Metab [Internet]. 2012;23:133–141. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22245457.

[105] Talbot K, Wang H-Y, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest [Internet]. 2012;122:1316–1338. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22476197.

[106] Yarchoan M, Toledo JB, Lee EB, et al. Abnormal serine phosphorylation of insulin receptor substrate 1 is associated with tau pathology in Alzheimer's disease and tauopathies. Acta Neuropathol [Internet]. 2014;128:679–689. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25107476.

[107] Kapogiannis D, Boxer A, Schwartz JB, et al. Dysfunctionally phosphorylated type 1 insulin receptor substrate in neural-derived blood exosomes of preclinical Alzheimer's disease. FASEB J [Internet]. 2015;29:589–596. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25342129.

[108] Diehl T, Mullins R, Kapogiannis D. Insulin resistance in Alzheimer's disease. Transl Res [Internet]. 2017;183:26–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28034760.

[109] MILES WR. PSYCHOLOGIC TESTS APPLIED TO DIABETIC PATIENTS. Arch Intern Med [Internet]. 1922;30:767. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.1922.00110120086003.

[110] Perlmuter LC, Hakami MK, Hodgson-Harrington C, et al. Decreased cognitive function in aging non-insulin-dependent diabetic patients. Am J Med [Internet]. 1984;77:1043–1048. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6334441.

[111] Reaven GM, Thompson LW, Nahum D, et al. Relationship between hyperglycemia and cognitive function in older NIDDM patients. Diabetes Care [Internet]. 1990;13:16–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2298111.

[112] Grodstein F, Chen J, Wilson RS, et al. Type 2 diabetes and cognitive function in community-dwelling elderly women. Diabetes Care [Internet]. 2001;24:1060–1065. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11375371.

[113] Ruis C, Biessels GJ, Gorter KJ, et al. Cognition in the early stage of type 2 diabetes. Diabetes Care [Internet]. 2009;32:1261–1265. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19366968.

[114] Manschot SM, Brands AMA, van der Grond J, et al. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes [Internet]. 2006;55:1106–1113. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16567535.

[115] Ebady SA, Arami MA, Shafigh MH. Investigation on the relationship between diabetes mellitus type 2 and cognitive impairment. Diabetes Res Clin Pract [Internet]. 2008;82:305–309. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18848366.

[116] Weinstein G, Maillard P, Himali JJ, et al. Glucose indices are associated with cognitive and structural brain measures in young adults. Neurology [Internet]. 2015;84:2329–2337. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25948725.

[117] Rees DA, Udiawar M, Berlot R, et al. White Matter Microstructure and Cognitive Function in Young Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab [Internet]. 2016;101:314–323. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26574952.

[118] Yau PL, Castro MG, Tagani A, et al. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics [Internet]. 2012;130:e856-64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22945407.

[119] Yau PL, Javier DC, Ryan CM, et al. Preliminary evidence for brain complications in obese adolescents with type 2 diabetes mellitus. Diabetologia [Internet]. 2010;53:2298–2306. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20668831.

[120] Brundel M, Kappelle LJ, Biessels GJ. Brain imaging in type 2 diabetes. Eur Neuropsychopharmacol [Internet]. 2014;24:1967–1981. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24726582.

[121] Del Bene A, Ciolli L, Borgheresi L, et al. Is type 2 diabetes related to leukoaraiosis? an updated review. Acta Neurol Scand [Internet]. 2015;132:147–155. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25772411.

[122] Baker LD, Cross DJ, Minoshima S, et al. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol [Internet]. 2011;68:51–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20837822.

[123] Heni M, Schöpfer P, Peter A, et al. Evidence for altered transport of insulin across the blood-brain barrier in insulin-resistant humans. Acta Diabetol [Internet]. 2014;51:679–681. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24370925.

[124] Yoo DY, Yim HS, Jung HY, et al. Chronic type 2 diabetes reduces the integrity of the blood-brain barrier by reducing tight junction proteins in the hippocampus. J Vet Med Sci [Internet]. 2016;78:957–962. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26876499.

[125] Starr JM, Wardlaw J, Ferguson K, et al. Increased blood-brain barrier permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. J Neurol Neurosurg Psychiatry [Internet]. 2003;74:70–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12486269.

[126] Tschritter O, Preissl H, Yokoyama Y, et al. Variation in the FTO gene locus is associated with cerebrocortical insulin resistance in humans. Diabetologia [Internet]. 2007;50:2602–2603. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17917711.

[127] Zhang H, Hao Y, Manor B, et al. Intranasal insulin enhanced resting-state functional connectivity of hippocampal regions in type 2 diabetes. Diabetes [Internet]. 2015;64:1025–1034. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25249577.

[128] Hoyer S. The aging brain. Changes in the neuronal insulin/insulin receptor signal

transduction cascade trigger late-onset sporadic Alzheimer disease (SAD). A mini-review. J Neural Transm [Internet]. 2002;109:991–1002. Available from: https://doi.org/10.1007/s007020200082.

[129] de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. J Diabetes Sci Technol. 2008;2:1101–1113.

[130] Weingarten MD, Lockwood AH, Hwo SY, et al. A protein factor essential for microtubule assembly. Proc Natl Acad Sci U S A. 1975;72:1858–1862.

[131] Brion J-P. Immunological demonstration of tau protein in neurofibrillary tangles of Alzheimer's disease. J Alzheimer's Dis. 2006;9:177–185.

[132] Caillet-Boudin M-L, Buée L, Sergeant N, et al. Regulation of human MAPT gene expression. Mol Neurodegener. 2015;10:28.

[133] Cassimeris L, Spittle C. Regulation of microtubule-associated proteins. Int Rev Cytol. 2001;210:163–226.

[134] Arendt T, Stieler JT, Holzer M. Tau and tauopathies. Brain Res Bull. 2016;126:238–292.

[135] Pooler AM, Phillips EC, Lau DHW, et al. Physiological release of endogenous tau is stimulated by neuronal activity. EMBO Rep [Internet]. 2013;14:389–394. Available from: https://doi.org/10.1038/embor.2013.15.

[136] Sergeant N, Bretteville A, Hamdane M, et al. Biochemistry of Tau in Alzheimer's disease and related neurological disorders. Expert Rev Proteomics [Internet]. 2008;5:207–224. Available from: https://doi.org/10.1586/14789450.5.2.207.

[137] Schubert M, Brazil DP, Burks DJ, et al. Insulin Receptor Substrate-2 Deficiency Impairs

Brain Growth and Promotes Tau Phosphorylation. J Neurosci [Internet]. 2003;23:7084 LP-7092. Available from: http://www.jneurosci.org/content/23/18/7084.abstract.

[138] Avila J, León-Espinosa G, García E, et al. Tau Phosphorylation by GSK3 in Different Conditions. Rosenmann H, editor. Int J Alzheimer's Dis [Internet]. 2012;2012:578373. Available from: https://doi.org/10.1155/2012/578373.

[139] Doble BW, Woodgett JR. GSK-3: tricks of the trade for a multi-tasking kinase. J Cell Sci [Internet]. 2003;116:1175–1186. Available from: https://doi.org/10.1242/jcs.00384.

[140] Burillo J, Marqués P, Jiménez B, et al. Insulin Resistance and Diabetes Mellitus in Alzheimer's Disease. Cells. 2021.

[141] Marciniak E, Leboucher A, Caron E, et al. Tau deletion promotes brain insulin resistance. J Exp Med [Internet]. 2017;214:2257–2269. Available from: https://doi.org/10.1084/jem.20161731.

[142] Jucker M, Walker LC. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature [Internet]. 2013;501:45–51. Available from: https://doi.org/10.1038/nature12481.

[143] Rodriguez-Rodriguez P, Sandebring-Matton A, Merino-Serrais P, et al. Tau hyperphosphorylation induces oligomeric insulin accumulation and insulin resistance in neurons. Brain [Internet]. 2017;140:3269–3285. Available from: https://doi.org/10.1093/brain/awx256.

[144] Lei P, Ayton S, Finkelstein DI, et al. Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export. Nat Med [Internet]. 2012;18:291–295. Available

from: https://doi.org/10.1038/nm.2613.

[145] Pandini G, Pace V, Copani A, et al. Insulin has multiple antiamyloidogenic effects on human neuronal cells. Endocrinology. 2013;154:375–387.

[146] Zhao W-Q, Lacor PN, Chen H, et al. Insulin receptor dysfunction impairs cellular clearance of neurotoxic oligomeric a{beta}. J Biol Chem. 2009;284:18742–18753.

[147] Rad SK, Arya A, Karimian H, et al. Mechanism involved in insulin resistance via accumulation of β-amyloid and neurofibrillary tangles: link between type 2 diabetes and Alzheimer's disease. Drug Des Devel Ther. 2018;12:3999–4021.

[148] Walsh DM, Klyubin I, Fadeeva J V, et al. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature. 2002;416:535–539.

[149] de la Monte SM. Contributions of Brain Insulin Resistance and Deficiency in Amyloid-Related Neurodegeneration in Alzheimer's Disease. Drugs [Internet]. 2012;72:49–66. Available from: https://doi.org/10.2165/11597760-000000000-00000.

[150] Hoe H-S, Lee H-K, Pak DTS. The Upside of APP at Synapses. CNS Neurosci Ther [Internet]. 2012;18:47–56. Available from: https://doi.org/10.1111/j.1755-5949.2010.00221.x.

[151] Berlanga-Acosta J, Guillén-Nieto G, Rodríguez-Rodríguez N, et al. Insulin Resistance at the Crossroad of Alzheimer Disease Pathology: A Review. Front Endocrinol (Lausanne) [Internet]. 2020;11. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2020.560375/full.

[152] Klyubin I, Cullen WK, Hu N-W, et al. Alzheimer's disease Aβ assemblies mediating rapid disruption of synaptic plasticity and memory. Mol Brain [Internet]. 2012;5:25. Available from: https://doi.org/10.1186/1756-6606-5-25.

[153] Rajendran L, Paolicelli RC. Microglia-Mediated Synapse Loss in Alzheimer's Disease. J Neurosci [Internet]. 2018;38:2911–2919. Available from: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.1136-17.2017.

[154] Hamzé R, Delangre E, Tolu S, et al. Type 2 Diabetes Mellitus and Alzheimer's Disease: Shared Molecular Mechanisms and Potential Common Therapeutic Targets. Int J Mol Sci. 2022;23.

[155] Zhao L, Teter B, Morihara T, et al. Insulin-degrading enzyme as a downstream target of insulin receptor signaling cascade: implications for Alzheimer's disease intervention. J Neurosci Off J Soc Neurosci. 2004;24:11120–11126.

[156] Mullins RJ, Diehl TC, Chia CW, et al. Insulin Resistance as a Link between Amyloid-Beta and Tau Pathologies in Alzheimer's Disease. Front Aging Neurosci. 2017;9:118.

[157] de la Monte SM. Insulin resistance and Alzheimer's disease. BMB Rep. 2009;42:475–481.

[158] Zhang Y, Zhou B, Deng B, et al. Amyloid-β Induces Hepatic Insulin Resistance In Vivo via JAK2. Diabetes [Internet]. 2013;62:1159–1166. Available from: https://diabetesjournals.org/diabetes/article/62/4/1159/17795/Amyloid-Induces-Hepatic-Insulin-Resistance-In-Vivo.

[159] Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO

Mol Med [Internet]. 2016;8:595–608. Available from: https://www.embopress.org/doi/10.15252/emmm.201606210.

[160] Forny-Germano L, Lyra e Silva NM, Batista AF, et al. Alzheimer's disease-like pathology induced by amyloid-β oligomers in nonhuman primates. J Neurosci Off J Soc Neurosci. 2014;34:13629–13643.

[161] Clarke JR, Lyra e Silva NM, Figueiredo CP, et al. Alzheimer-associated Aβ oligomers impact the central nervous system to induce peripheral metabolic deregulation. EMBO Mol Med [Internet]. 2015;7:190–210. Available from: https://www.embopress.org/doi/10.15252/emmm.201404183.

[162] Morales-Corraliza J, Wong H, Mazzella MJ, et al. Brain-Wide Insulin Resistance, Tau Phosphorylation Changes, and Hippocampal Neprilysin and Amyloid-β Alterations in a Monkey Model of Type 1 Diabetes. J Neurosci Off J Soc Neurosci. 2016;36:4248–4258.

[163] Wakabayashi T, Yamaguchi K, Matsui K, et al. Differential effects of diet- and genetically-induced brain insulin resistance on amyloid pathology in a mouse model of Alzheimer's disease. Mol Neurodegener. 2019;14:15.

[164] Gasparini L, Netzer WJ, Greengard P, et al. Does insulin dysfunction play a role in Alzheimer's disease? Trends Pharmacol Sci [Internet]. 2002;23:288–293. Available from: https://doi.org/10.1016/S0165-6147(02)02037-0.

[165] Xie L, Helmerhorst E, Taddei K, et al. Alzheimer's beta-amyloid peptides compete for insulin binding to the insulin receptor. J Neurosci Off J Soc Neurosci. 2002;22:RC221.

[166] Doré S, Kar S, Quirion R. Insulin-like growth factor I protects and rescues hippocampal

neurons against beta-amyloid- and human amylin-induced toxicity. Proc Natl Acad Sci U S A. 1997;94:4772–4777.

[167] Gupta S, Nair A, Jhawat V, et al. Unwinding Complexities of Diabetic Alzheimer by Potent Novel Molecules. Am J Alzheimers Dis Other Demen. 2020;35:1533317520937542.

[168] Swardfager W, Lanctôt K, Rothenburg L, et al. A Meta-Analysis of Cytokines in Alzheimer's Disease. Biol Psychiatry [Internet]. 2010;68:930–941. Available from: https://doi.org/10.1016/j.biopsych.2010.06.012.

[169] de la Monte SM. Insulin Resistance and Neurodegeneration: Progress Towards the Development of New Therapeutics for Alzheimer's Disease. Drugs. 2017;77:47–65.

[170] Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science. 2005;308:1314–1318.

[171] Dandrea MR, Reiser PA, Gumula NA, et al. Application of triple immunohistochemistry to characterize amyloid plaque-associated inflammation in brains with Alzheimer's disease. Biotech Histochem Off Publ Biol Stain Comm. 2001;76:97–106.

[172] Femminella GD, Livingston NR, Raza S, et al. Does insulin resistance influence neurodegeneration in non-diabetic Alzheimer's subjects? Alzheimers Res Ther [Internet]. 2021;13:47. Available from: https://doi.org/10.1186/s13195-021-00784-w.

[173] Singh R, Barden A, Mori T, et al. Advanced glycation end-products: a review. Diabetologia [Internet]. 2001;44:129–146. Available from: https://doi.org/10.1007/s001250051591.

[174] Yamagishi S, Maeda S, Matsui T, et al. Role of advanced glycation end products (AGEs) and oxidative stress in vascular complications in diabetes. Biochim Biophys Acta. 2012;1820:663–671.

[175] Ramasamy R, Vannucci SJ, Yan SS Du, et al. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology. 2005;15:16R–28R.

[176] Verdile G, Keane KN, Cruzat VF, et al. Inflammation and Oxidative Stress: The Molecular Connectivity between Insulin Resistance, Obesity, and Alzheimer's Disease. Mediators Inflamm. 2015;2015:105828.

[177] De Felice FG, Lourenco M V, Ferreira ST. How does brain insulin resistance develop in Alzheimer's disease? Alzheimer's Dement [Internet]. 2014;10:S26–S32. Available from: https://doi.org/10.1016/j.jalz.2013.12.004.

[178] Robbins J, Busquets O, Tong M, et al. Dysregulation of Insulin-Linked Metabolic Pathways in Alzheimer's Disease: Co-Factor Role of Apolipoprotein E ε4. J Alzheimer's Dis reports. 2020;4:479–493.

[179] de la Monte SM, Tong M. Brain metabolic dysfunction at the core of Alzheimer's disease. Biochem Pharmacol [Internet]. 2014;88:548–559. Available from: https://www.sciencedirect.com/science/article/pii/S000629521300796X.

[180] de la Monte SM, Tong M, Bowling N, et al. si-RNA inhibition of brain insulin or insulin-like growth factor receptors causes developmental cerebellar abnormalities: relevance to fetal alcohol spectrum disorder. Mol Brain. 2011;4:13.

[181] Barone E, Di Domenico F, Mancuso C, et al. The Janus face of the heme oxygenase/biliverdin reductase system in Alzheimer disease: it's time for reconciliation. Neurobiol Dis. 2014;62:144–159.

[182] Nunomura A, Moreira PI, Castellani RJ, et al. Oxidative Damage to RNA in Aging and Neurodegenerative Disorders. Neurotox Res [Internet]. 2012;22:231–248. Available from: https://doi.org/10.1007/s12640-012-9331-x.

[183] Bonda DJ, Wang X, Lee H-G, et al. Neuronal failure in Alzheimer's disease: a view through the oxidative stress looking-glass. Neurosci Bull. 2014;30:243–252.

[184] de la Monte SM, Luong T, Neely TR, et al. Mitochondrial DNA Damage as a Mechanism of Cell Loss in Alzheimer's Disease. Lab Investig [Internet]. 2000;80:1323–1335. Available from: https://doi.org/10.1038/labinvest.3780140.

[185] Sun Y, Ma C, Sun H, et al. Metabolism: A Novel Shared Link between Diabetes Mellitus and Alzheimer's Disease. J Diabetes Res. 2020;2020:4981814.

[186] Butterfield DA, Di Domenico F, Barone E. Elevated risk of type 2 diabetes for development of Alzheimer disease: a key role for oxidative stress in brain. Biochim Biophys Acta. 2014;1842:1693–1706.

[187] Yao J, Irwin RW, Zhao L, et al. Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A. 2009;106:14670–14675.

[188] Reddy PH, Tripathi R, Troung Q, et al. Abnormal mitochondrial dynamics and synaptic degeneration as early events in Alzheimer's disease: Implications to mitochondria-

targeted antioxidant therapeutics. Biochim Biophys Acta - Mol Basis Dis [Internet]. 2012;1822:639–649. Available from: https://www.sciencedirect.com/science/article/pii/S0925443911002341.

[189] Ghasemi R, Dargahi L, Haeri A, et al. Brain Insulin Dysregulation: Implication for Neurological and Neuropsychiatric Disorders. Mol Neurobiol [Internet]. 2013;47:1045–1065. Available from: https://doi.org/10.1007/s12035-013-8404-z.

[190] Steen E, Terry BM, J. Rivera E, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes? J Alzheimer's Dis [Internet]. 2005;7:63–80. Available from: https://www.medra.org/servlet/aliasResolver?alias=iospress&doi=10.3233/JAD-2005-7107.

[191] Schrijvers EMC, Witteman JCM, Sijbrands EJG, et al. Insulin metabolism and the risk of Alzheimer disease. Neurology [Internet]. 2010;75:1982 LP-1987. Available from: http://n.neurology.org/content/75/22/1982.abstract.

[192] Ma L, Wang J, Li Y. Insulin resistance and cognitive dysfunction. Clin Chim Acta. 2015;444:18–23.

[193] Grillo CA, Piroli GG, Lawrence RC, et al. Hippocampal Insulin Resistance Impairs Spatial Learning and Synaptic Plasticity. Diabetes. 2015;64:3927–3936.

[194] Willmann C, Brockmann K, Wagner R, et al. Insulin sensitivity predicts cognitive decline in individuals with prediabetes. BMJ Open Diabetes Res & Care [Internet]. 2020;8:e001741. Available from: http://drc.bmj.com/content/8/2/e001741.abstract.

[195] Talbot K, Wang H-Y, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest [Internet]. 2012;122:1316–1338. Available from: http://www.jci.org/articles/view/59903.

[196] Rebelos E, Bucci M, Karjalainen T, et al. Insulin Resistance Is Associated With Enhanced Brain Glucose Uptake During Euglycemic Hyperinsulinemia: A Large-Scale PET Cohort. Diabetes Care [Internet]. 2021;44:788–794. Available from: https://doi.org/10.2337/dc20-1549.

[197] Hoscheidt SM, Kellawan JM, Berman SE, et al. Insulin resistance is associated with lower arterial blood flow and reduced cortical perfusion in cognitively asymptomatic middle-aged adults. J Cereb Blood Flow Metab [Internet]. 2016;37:2249–2261. Available from: https://doi.org/10.1177/0271678X16663214.

[198] Willette AA, Bendlin BB, Starks EJ, et al. Association of Insulin Resistance With Cerebral Glucose Uptake in Late Middle–Aged Adults at Risk for Alzheimer Disease. JAMA Neurol [Internet]. 2015;72:1013–1020. Available from: https://doi.org/10.1001/jamaneurol.2015.0613.

[199] Hohman TJ, Beason-Held LL, Lamar M, et al. Subjective cognitive complaints and longitudinal changes in memory and brain function. Neuropsychology [Internet]. 2011;25:125–130. Available from: http://doi.apa.org/getdoi.cfm?doi=10.1037/a0020859.

[200] Pearson-Leary J, McNay EC. Novel Roles for the Insulin-Regulated Glucose Transporter-4 in Hippocampally Dependent Memory. J Neurosci Off J Soc Neurosci. 2016;36:11851–11864.

[201] Biesold D, Inanami O, Sato A, et al. Stimulation of the nucleus basalis of Meynert increases cerebral cortical blood flow in rats. Neurosci Lett [Internet]. 1989;98:39–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/0304394089903704.

[202] Hotta H. Neurogenic control of parenchymal arterioles in the cerebral cortex. 2016. p. 3–39. Available from: https://linkinghub.elsevier.com/retrieve/pii/S007961231600039X.

[203] Akaishi T, Kimura A, Sato A, et al. Responses of neurons in the nucleus basalis of Meynert to various afferent stimuli in rats. Neuroreport [Internet]. 1990;1:37–40. Available from: http://journals.lww.com/00001756-199009000-00011.

[204] Xu Y, Cao K, Guo B, et al. Lowered levels of nicotinic acetylcholine receptors and elevated apoptosis in the hippocampus of brains from patients with type 2 diabetes mellitus and db/db mice. Aging (Albany NY) [Internet]. 2020;12:14205–14218. Available from: https://www.aging-us.com/lookup/doi/10.18632/aging.103435.

[205] Kandimalla R, Thirumala V, Reddy PH. Is Alzheimer's disease a Type 3 Diabetes? A critical appraisal. Biochim Biophys Acta - Mol Basis Dis [Internet]. 2017;1863:1078–1089. Available from: https://www.sciencedirect.com/science/article/pii/S0925443916302150.

[206] Duncan A, Heyer MP, Ishikawa M, et al. Habenular TCF7L2 links nicotine addiction to diabetes. Nature [Internet]. 2019;574:372–377. Available from: https://www.nature.com/articles/s41586-019-1653-x.

[207] Izuo N, Watanabe N, Noda Y, et al. Insulin resistance induces earlier initiation of cognitive dysfunction mediated by cholinergic deregulation in a mouse model of Alzheimer's disease. Aging Cell. 2023;22:e13994.

[208] Fernandes C, Hoyle E, Dempster E, et al. Performance deficit of α7 nicotinic receptor knockout mice in a delayed matching-to-place task suggests a mild impairment of working/episodic-like memory. Genes, Brain Behav [Internet]. 2006;5:433–440. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1601-183X.2005.00176.x.

[209] Suzuki R, Lee K, Jing E, et al. Diabetes and Insulin in Regulation of Brain Cholesterol Metabolism. Cell Metab [Internet]. 2010;12:567–579. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1550413110003980.

[210] Jin B, Cheng X, Fei G, et al. Identification of diagnostic biomarkers in Alzheimer's disease by integrated bioinformatic analysis and machine learning strategies. Front Aging Neurosci [Internet]. 2023;15. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1169620/full.

[211] Macauley SL, Stanley M, Caesar EE, et al. Hyperglycemia modulates extracellular amyloid-β concentrations and neuronal activity in vivo. J Clin Invest [Internet]. 2015;125:2463–2467. Available from: https://doi.org/10.1172/JCI79742.

[212] Valente T, Gella A, Fernàndez-Busquets X, et al. Immunohistochemical analysis of human brain suggests pathological synergism of Alzheimer's disease and diabetes mellitus. Neurobiol Dis [Internet]. 2010;37:67–76. Available from: https://www.sciencedirect.com/science/article/pii/S0969996109002496.

[213] Arab L, Sadeghi R, G. Walker D, et al. Consequences of Aberrant Insulin Regulation in the Brain: Can Treating Diabetes be Effective for Alzheimers Disease. Curr Neuropharmacol [Internet]. 2011;9:693–705. Available from: http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1570-

159X&volume=9&issue=4&spage=693.

[214] Chuah YK, Basir R, Talib H, et al. Receptor for Advanced Glycation End Products and Its Involvement in Inflammatory Diseases. Bhatia M, editor. Int J Inflam [Internet]. 2013;2013:403460. Available from: https://doi.org/10.1155/2013/403460.

[215] Deane R, Bell R, Sagare A, et al. Clearance of Amyloid-β Peptide Across the Blood-Brain Barrier: Implication for Therapies in Alzheimers Disease. CNS Neurol Disord - Drug Targets [Internet]. 2009;8:16–30. Available from: http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1871-5273&volume=8&issue=1&spage=16.

[216] Li X-H, Lv B-L, Xie J-Z, et al. AGEs induce Alzheimer-like tau pathology and memory deficit via RAGE-mediated GSK-3 activation. Neurobiol Aging [Internet]. 2012;33:1400–1410. Available from: https://www.sciencedirect.com/science/article/pii/S0197458011000169.

[217] Kong Y, Wang F, Wang J, et al. Pathological Mechanisms Linking Diabetes Mellitus and Alzheimer's Disease: the Receptor for Advanced Glycation End Products (RAGE). Front Aging Neurosci. 2020;12:217.

[218] Batkulwar K, Godbole R, Banarjee R, et al. Advanced Glycation End Products Modulate Amyloidogenic APP Processing and Tau Phosphorylation: A Mechanistic Link between Glycation and the Development of Alzheimer's Disease. ACS Chem Neurosci. 2018;9:988–1000.

[219] Wang H, Dong S, Xu H, et al. Genetic variants in FTO associated with metabolic syndrome: a meta- and gene-based analysis. Mol Biol Rep [Internet]. 2012;39:5691–5698.

Available from: https://doi.org/10.1007/s11033-011-1377-y.

[220] Younus LA, Algenabi AHA, Abdul-Zhara MS, et al. FTO gene polymorphisms (rs9939609 and rs17817449) as predictors of Type 2 Diabetes Mellitus in obese Iraqi population. Gene [Internet]. 2017;627:79–84. Available from: https://www.sciencedirect.com/science/article/pii/S0378111917304559.

[221] Bertram L, Heekeren H. Obesity and the brain: a possible genetic link. Alzheimers Res Ther [Internet]. 2010;2:27. Available from: https://doi.org/10.1186/alzrt51.

[222] Benedict C, Axelsson T, Söderberg S, et al. Fat mass and obesity-associated gene (FTO) is linked to higher plasma levels of the hunger hormone ghrelin and lower serum levels of the satiety hormone leptin in older adults. Diabetes. 2014;63:3955–3959.

[223] Cao H, Feng F, Xun M, et al. Effect of carbonized apple wood on nitrogen-transforming microorganisms and nitrogen oxides in soil of apple tree root zone. Eur J Soil Sci [Internet]. 2018;69:545–554. Available from: https://doi.org/10.1111/ejss.12532.

[224] Shi L, Du X, Jiang H, et al. Ghrelin and Neurodegenerative Disorders—a Review. Mol Neurobiol [Internet]. 2017;54:1144–1155. Available from: https://doi.org/10.1007/s12035-016-9729-1.

[225] Caputo V, Termine A, Strafella C, et al. Shared (epi)genomic background connecting neurodegenerative diseases and type 2 diabetes. World J Diabetes [Internet]. 2020;11:155–164. Available from: https://www.wjgnet.com/1948-9358/full/v11/i5/155.htm.

[226] Webb TR, Erdmann J, Stirrups KE, et al. Systematic Evaluation of Pleiotropy Identifies 6

Further Loci Associated With Coronary Artery Disease. J Am Coll Cardiol [Internet]. 2017;69:823–836. Available from: https://www.sciencedirect.com/science/article/pii/S0735109716373417.

[227] Schunkert H, König IR, Kathiresan S, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet [Internet]. 2011;43:333–338. Available from: https://doi.org/10.1038/ng.784.

[228] Miao L, Yin R-X, Pan S-L, et al. BCL3-PVRL 2-TOMM40 SNPs, gene-gene and gene-environment interactions on dyslipidemia. Sci Rep. 2018;8:6189.

[229] Ronald J, Rajagopalan R, Ranchalis JE, et al. Analysis of recently identified dyslipidemia alleles reveals two loci that contribute to risk for carotid artery disease. Lipids Health Dis. 2009;8:1–12.

[230] Yamase Y, Horibe H, Ueyama C, et al. Association of TOMM40 and SLC22A4 polymorphisms with ischemic stroke. Biomed Rep [Internet]. 2015;3:491–498. Available from: https://doi.org/10.3892/br.2015.457.

[231] Rudovich N, Pivovarova O, Fisher E, et al. Polymorphisms within insulin-degrading enzyme (IDE) gene determine insulin metabolism and risk of type 2 diabetes. J Mol Med [Internet]. 2009;87:1145–1151. Available from: https://doi.org/10.1007/s00109-009-0540-6.

[232] Karamohamed S, Demissie S, Volcjak J, et al. Polymorphisms in the Insulin-Degrading Enzyme Gene Are Associated With Type 2 Diabetes in Men From the NHLBI Framingham Heart Study . Diabetes [Internet]. 2003;52:1562–1567. Available from: https://doi.org/10.2337/diabetes.52.6.1562.

[233] Cui P-J, Cao L, Wang Y, et al. The association between two single nucleotide polymorphisms within the insulin-degrading enzyme gene and Alzheimer's disease in a Chinese Han population. J Clin Neurosci [Internet]. 2012;19:745–749. Available from: https://www.sciencedirect.com/science/article/pii/S0967586811006424.

[234] Cai R, Han J, Sun J, et al. Plasma clusterin and the CLU gene rs11136000 variant are associated with mild cognitive impairment in type 2 diabetic patients. Front Aging Neurosci. 2016;8:179.

[235] Ciftci-Yilmaz S, Oznur M, Ayturk Z, et al. Association of Clusterin (CLU) Gene Polymorphism, Rs11136000, with Alzheimer's Disease and Diabetes in the Turkish Population. Clin Investig Med. 2015;38:E200.

[236] Sun Y, Wei R, Yan D, et al. Association between APOE polymorphism and metabolic syndrome in Uyghur ethnic men. BMJ Open [Internet]. 2016;6:e010049. Available from: http://bmjopen.bmj.com/content/6/1/e010049.abstract.

[237] Cheng Y, Li Y, Liang X, et al. Genetic Effects of NDUFAF6 rs6982393 and APOE on Alzheimer's Disease in Chinese Rural Elderly: A Cross-Sectional Population-Based Study. Clin Interv Aging [Internet]. 2022;Volume 17:185–194. Available from: https://www.dovepress.com/genetic-effects-of-ndufaf6-rs6982393-and-apoe-on-alzheimers-disease-in-peer-reviewed-fulltext-article-CIA.

[238] Seo JA, Kang M-C, Yang W-M, et al. Apolipoprotein J is a hepatokine regulating muscle glucose metabolism and insulin sensitivity. Nat Commun. 2020;11:2024.

[239] Barone E, Tramutola A, Triani F, et al. Biliverdin Reductase-A Mediates the Beneficial Effects of Intranasal Insulin in Alzheimer Disease. Mol Neurobiol [Internet].

2019;56:2922–2943. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30073505.

[240] Claxton A, Baker LD, Hanson A, et al. Long Acting Intranasal Insulin Detemir Improves Cognition for Adults with Mild Cognitive Impairment or Early-Stage Alzheimer's Disease Dementia. J Alzheimers Dis [Internet]. 2015;45:1269–1270. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25869922.

[241] Reger MA, Watson GS, Green PS, et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology [Internet]. 2008;70:440–448. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17942819.

[242] Benedict C, Hallschmid M, Schmitz K, et al. Intranasal insulin improves memory in humans: superiority of insulin aspart. Neuropsychopharmacology [Internet]. 2007;32:239–243. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16936707.

[243] Benedict C, Hallschmid M, Hatke A, et al. Intranasal insulin improves memory in humans. Psychoneuroendocrinology [Internet]. 2004;29:1326–1334. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15288712.

[244] Claxton A, Baker LD, Wilkinson CW, et al. Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or Alzheimer's disease. J Alzheimers Dis [Internet]. 2013;35:789–797. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23507773.

[245] Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol [Internet]. 2012;69:29–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21911655.

[246] Zhao N, Liu C-C, Van Ingelgom AJ, et al. Apolipoprotein E4 Impairs Neuronal Insulin Signaling by Trapping Insulin Receptor in the Endosomes. Neuron [Internet]. 2017;96:115–129.e5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28957663.

[247] Rhea EM, Raber J, Banks WA. ApoE and cerebral insulin: Trafficking, receptors, and resistance. Neurobiol Dis [Internet]. 2020;137:104755. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31978603.

[248] Craft S, Raman R, Chow TW, et al. Safety, Efficacy, and Feasibility of Intranasal Insulin for the Treatment of Mild Cognitive Impairment and Alzheimer Disease Dementia. JAMA Neurol [Internet]. 2020;77:1099. Available from: https://jamanetwork.com/journals/jamaneurology/fullarticle/2767376.

[249] Craft S, Claxton A, Baker LD, et al. Effects of Regular and Long-Acting Insulin on Cognition and Alzheimer's Disease Biomarkers: A Pilot Clinical Trial. J Alzheimers Dis [Internet]. 2017;57:1325–1334. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28372335.

[250] Erdő F, Bors LA, Farkas D, et al. Evaluation of intranasal delivery route of drug administration for brain targeting. Brain Res Bull [Internet]. 2018;143:155–170. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30449731.

[251] Janelidze S, Zetterberg H, Mattsson N, et al. CSF Aβ42/Aβ40 and Aβ42/Aβ38 ratios: better diagnostic markers of Alzheimer disease. Ann Clin Transl Neurol [Internet]. 2016;3:154–165. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27042676.

[252] Dumurgier J, Hanseeuw BJ, Hatling FB, et al. Alzheimer's Disease Biomarkers and Future Decline in Cognitive Normal Older Adults. J Alzheimers Dis [Internet].

2017;60:1451–1459. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29036824.

[253] Farr SA, Roesler E, Niehoff ML, et al. Metformin Improves Learning and Memory in the SAMP8 Mouse Model of Alzheimer's Disease. J Alzheimers Dis [Internet]. 2019;68:1699–1710. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30958364.

[254] Ou Z, Kong X, Sun X, et al. Metformin treatment prevents amyloid plaque deposition and memory impairment in APP/PS1 mice. Brain Behav Immun [Internet]. 2018;69:351–363. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29253574.

[255] Luchsinger JA, Perez T, Chang H, et al. Metformin in Amnestic Mild Cognitive Impairment: Results of a Pilot Randomized Placebo Controlled Clinical Trial. J Alzheimers Dis [Internet]. 2016;51:501–514. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26890736.

[256] Watson GS, Cholerton BA, Reger MA, et al. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. Am J Geriatr Psychiatry [Internet]. 2005;13:950–958. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16286438.

[257] Risner ME, Saunders AM, Altman JFB, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J [Internet]. 2006;6:246–254. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16446752.

[258] Harrington C, Sawchak S, Chiang C, et al. Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies. Curr Alzheimer Res [Internet]. 2011;8:592–606.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/21592048.

[259] Perfetti R, Zhou J, Doyle ME, et al. Glucagon-like peptide-1 induces cell proliferation and pancreatic-duodenum homeobox-1 expression and increases endocrine cell mass in the pancreas of old, glucose-intolerant rats. Endocrinology [Internet]. 2000;141:4600–4605. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11108273.

[260] Hamilton A, Hölscher C. Receptors for the incretin glucagon-like peptide-1 are expressed on neurons in the central nervous system. Neuroreport [Internet]. 2009;20:1161–1166. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19617854.

[261] Anderson J. The Pharmacokinetic Properties of Glucagon-like Peptide-1 Receptor Agonists and Their Mode and Mechanism of Action in Patients with Type 2 Diabetes. J Fam Pract [Internet]. 2018;67:S8–S13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29912996.

[262] Freiherr J, Hallschmid M, Frey WH, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. CNS Drugs [Internet]. 2013;27:505–514. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23719722.

[263] Hansen HH, Fabricius K, Barkholt P, et al. The GLP-1 Receptor Agonist Liraglutide Improves Memory Function and Increases Hippocampal CA1 Neuronal Numbers in a Senescence-Accelerated Mouse Model of Alzheimer's Disease. J Alzheimers Dis [Internet]. 2015;46:877–888. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25869785.

[264] Batista AF, Forny-Germano L, Clarke JR, et al. The diabetes drug liraglutide reverses

cognitive impairment in mice and attenuates insulin receptor and synaptic pathology in a non-human primate model of Alzheimer's disease. J Pathol [Internet]. 2018;245:85–100. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29435980.

[265] Gejl M, Gjedde A, Egefjord L, et al. 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 [Internet]. 2016;8:108. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27252647.

[266] Gold M, Alderton C, Zvartau-Hind M, et al. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dement Geriatr Cogn Disord. 2010;30:131–146.

[267] Tzimopoulou S, Cunningham VJ, Nichols TE, et al. A multi-center randomized proof-of-concept clinical trial applying [^{18}F]FDG-PET for evaluation of metabolic therapy with rosiglitazone XR in mild to moderate Alzheimer's disease. J Alzheimers Dis. 2010;22:1241–1256.

[268] Hanyu H, Sato T, Kiuchi A, et al. Pioglitazone improved cognition in a pilot study on patients with Alzheimer's disease and mild cognitive impairment with diabetes mellitus. J. Am. Geriatr. Soc. United States; 2009. p. 177–179.

[269] Hanyu H, Sato T, Sakurai H, et al. The role of tumor necrosis factor-alpha in cognitive improvement after peroxisome proliferator-activator receptor gamma agonist pioglitazone treatment in Alzheimer's disease. J. Am. Geriatr. Soc. United States; 2010. p. 1000–1001.

[270] Geldmacher DS, Fritsch T, McClendon MJ, et al. A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease. Arch Neurol.

2011;68:45–50.

[271] Sato T, Hanyu H, Hirao K, et al. Efficacy of PPAR-γ agonist pioglitazone in mild Alzheimer disease. Neurobiol Aging. 2011;32:1626–1633.

[272] Kellar D, Lockhart SN, Aisen P, et al. Intranasal Insulin Reduces White Matter Hyperintensity Progression in Association with Improvements in Cognition and CSF Biomarker Profiles in Mild Cognitive Impairment and Alzheimer's Disease. J Prev Alzheimer's Dis. 2021;8:240–248.

[273] Rosenbloom M, Barclay TR, Kashyap B, et al. A Phase II, Single-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Therapeutic Efficacy of Intranasal Glulisine in Amnestic Mild Cognitive Impairment and Probable Mild Alzheimer's Disease. Drugs Aging. 2021;38:407–415.

[274] Kellar D, Register T, Lockhart SN, et al. Intranasal insulin modulates cerebrospinal fluid markers of neuroinflammation in mild cognitive impairment and Alzheimer's disease: a randomized trial. Sci Rep. 2022;12:1346.

[275] Mullins RJ, Mustapic M, Chia CW, et al. A Pilot Study of Exenatide Actions in Alzheimer's Disease. Curr Alzheimer Res. 2019;16:741–752.

[276] Watson KT, Wroolie TE, Tong G, et al. Neural correlates of liraglutide effects in persons at risk for Alzheimer's disease. Behav Brain Res. 2019;356:271–278.

[277] Gejl M, Brock B, Egefjord L, et al. Blood-Brain Glucose Transfer in Alzheimer's disease: Effect of GLP-1 Analog Treatment. Sci Rep. 2017;7:17490.

[278] Solfrizzi V, Custodero C, Lozupone M, et al. Relationships of Dietary Patterns, Foods,

and Micro- and Macronutrients with Alzheimer's Disease and Late-Life Cognitive Disorders: A Systematic Review. J Alzheimers Dis [Internet]. 2017;59:815–849. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28697569.

[279] Bayer-Carter JL, Green PS, Montine TJ, et al. Diet intervention and cerebrospinal fluid biomarkers in amnestic mild cognitive impairment. Arch Neurol [Internet]. 2011;68:743–752. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21670398.

[280] Hughes TM, Craft S. The role of insulin in the vascular contributions to age-related dementia. Biochim Biophys Acta [Internet]. 2016;1862:983–991. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26657615.

[281] Pistollato F, Iglesias RC, Ruiz R, et al. Nutritional patterns associated with the maintenance of neurocognitive functions and the risk of dementia and Alzheimer's disease: A focus on human studies. Pharmacol Res [Internet]. 2018;131:32–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29555333.

[282] van den Brink AC, Brouwer-Brolsma EM, Berendsen AAM, et al. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diets Are Associated with Less Cognitive Decline and a Lower Risk of Alzheimer's Disease-A Review. Adv Nutr [Internet]. 2019;10:1040–1065. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31209456.

[283] Stephen R, Hongisto K, Solomon A, et al. Physical Activity and Alzheimer's Disease: A Systematic Review. J Gerontol A Biol Sci Med Sci [Internet]. 2017;72:733–739. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28049634.

[284] Jeong J-H, Koo J-H, Cho J-Y, et al. Neuroprotective effect of treadmill exercise against blunted brain insulin signaling, NADPH oxidase, and Tau hyperphosphorylation in rats fed a high-fat diet. Brain Res Bull [Internet]. 2018;142:374–383. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30081082.

[285] Ruegsegger GN, Vanderboom PM, Dasari S, et al. Exercise and metformin counteract altered mitochondrial function in the insulin-resistant brain. JCI insight [Internet]. 2019;4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31534057.