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Insulin Resistance Exacerbates Alzheimer Disease via Multiple Mechanisms

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Alzheimer disease (AD) is a chronic neurodegenerative disease that accounts for 60–70% of dementia and is the sixth leading cause of death in the United States. The pathogenesis of this debilitating disorder is still not completely understood. New insights into the pathogenesis of AD are needed in order to develop novel pharmacologic approaches. In recent years, numerous studies have shown that insulin resistance plays a significant role in the development of AD. Over 80% of patients with AD have type II diabetes (T2DM) or abnormal serum glucose, suggesting that the pathogenic mechanisms of insulin resistance and AD likely overlap. Insulin resistance increases neuroinflammation, which promotes both amyloid β-protein deposition and aberrant tau phosphorylation. By increasing production of reactive oxygen species, insulin resistance triggers amyloid β-protein accumulation. Oxidative stress associated with insulin resistance also dysregulates glycogen synthase kinase 3-β (GSK-3β), which leads to increased tau phosphorylation. Both insulin and amyloid β-protein are metabolized by insulin degrading enzyme (IDE). Defects in this enzyme are the basis for a strong association between T2DM and AD. This review highlights multiple pathogenic mechanisms induced by insulin resistance that are implicated in AD. Several pharmacologic approaches to AD associated with insulin resistance are presented.

Keywords: Alzheimer's disease, insulin resistance, amyloid beta, tau, drug

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INTRODUCTION

Alzheimer disease (AD) is a chronic degenerative brain disease characterized by memory loss, cognitive impairment, and loss of activities of daily living (Jha et al., 2019). It is the most common form of dementia and the sixth leading cause of death in the United States (Wilson et al., 2012; Heron, 2013). An estimated 5.8 million Americans suffered from AD in 2020 and this number will triple to nearly 14 million people by 2060 (Matthews et al., 2019). There are no treatments that effectively stop or reverse AD progression, although some medications temporarily improve symptoms (Hsu and Marshall, 2017). Notably, the United States Food and Drug Administration (FDA) approved Aducanumab on June 7th, 2021, the first antibody for the treatment of AD which reduces amyloid plaques. However, this drug had previously failed to gain FDA approval, because initial analysis of clinical trial data did not show a significant improvement in patients' mental abilities. Phase IV trials are still required to verify its clinical benefits.

There are two major forms of AD: the sporadic (late-onset) form, which accounts for most cases, and the familial (early-onset) form, which is generally associated with the inheritance of genetic mutations (Bekris et al., 2010). While the cause of most AD cases is poorly understood (Reitz and Mayeux, 2014), genes encoding amyloid precursor protein (APP), presenilin 1 and presenilin 2 account for the majority of early-onset familial AD cases (Cheignon et al., 2018), whereas apolipoprotein E (APOE) is the main genetic risk factor in sporadic AD, especially *APOE−ε4* (Morris et al., 2014; Clark and Vissel, 2018).

The pathogenesis of AD is multifactorial (Crous-Bou et al., 2017). Accumulating studies indicate a strong association between type II diabetes (T2DM) and AD (Kang et al., 2017). Neuronal insulin signaling pathways are disrupted in both T2DM and AD and over 80% of AD patients have T2DM or display abnormal blood glucose levels (Zhao and Townsend, 2009). Observational studies demonstrate that T2DM nearly doubles the risk of AD and increases the likelihood of dementia (Leibson et al., 1997; Luchsinger et al., 2001; Xu et al., 2009). In addition, APOE4 and insulin resistance were found to impair cognitive function in a study of human E4-targeted replacement mice (Johnson et al., 2017). Multiple studies have also established that insulin resistance leads to the progression of two main pathological hallmarks of AD—senile plaques from extracellular deposition of amyloid β-protein and tau-based neurofibrillary tangles (NFT) (Ardura-Fabregat et al., 2017). Consequently, AD may be considered a type of metabolic disease, and the development of AD therapeutics may benefit from an understanding of the relationship between AD and insulin resistance (Kang et al., 2017).

INSULIN RESISTANCE AND AD

Insulin is essential for metabolic homeostasis in the peripheral system (Tokarz et al., 2018), but has only been recognized for its role in regulating amyloid β-protein peptides and the generation of NFTs in the last few decades (Razay and Wilcock, 1994; Kroner, 2009). Under normal conditions, increased plasma glucose levels lead to stimulation of pancreatic β-cells to produce insulin, which decreases glucose levels. As blood glucose falls, counter-regulatory hormones including epinephrine, norepinephrine and cortisol from the adrenal glands arrest insulin-mediated glucose disposal. Insulin is then rapidly degraded in the liver, kidney and muscles by insulin degrading enzyme (IDE) (Watson and Craft, 2003). The pleiotropic biologic effects of insulin are mediated via binding and activating insulin receptors (IR) (Boucher et al., 2014), which are widely distributed in the periphery but selectively distributed in the central nervous system (CNS), including the cerebral cortex, hippocampus, hypothalamus and amygdala (Havrankova et al., 1978; Bosco et al., 2011; Soto et al., 2019). Insulin binding leads to a conformational change of the IR resulting in phosphorylation of intracellular IR substrate (IRS) proteins on tyrosine residues (Saini, 2010). Subsequently, IRS activates downstream pathways including mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K) (Gabbouj et al., 2019), which are important for mitogenic and metabolic functions (Plum et al., 2005).

However, in insulin resistance, cells fail to respond to insulin causing elevated blood glucose and effects on muscle, liver and brain (Kroner, 2009; Zhao and Townsend, 2009). Pancreatic β-cells produce more insulin in response to high blood glucose (hyperglycemia) resulting in hyperinsulinemia (high blood insulin), eventually leading to T2DM (Heydemann, 2016). Decreased levels of insulin and IR are found in the cerebrospinal fluid (CSF) of AD patients due to long-term peripheral hyperinsulinemia and decreased insulin transport across the blood-brain barrier (BBB) (Craft et al., 1998; Rivera et al., 2005; Steen et al., 2005; Gil-Bea et al., 2010; Stanley et al., 2016).

Accruing evidence shows that insulin facilitates memory and cognition under normal conditions (Watson et al., 2009; Tokarz et al., 2018) whereas chronic hyperinsulinemia impairs them (Lee et al., 2016). For instance, fructose-induced insulin-resistant rat models show impaired spatial learning in the water-maze test (Sachdeva et al., 2019). Moreover, intranasal insulin improves memory in humans (Benedict et al., 2008; Krug et al., 2010). Insulin resistance may accelerate the progression of senile plaques and NFTs via multiple mechanisms, resulting in cognitive decline, impaired long-term potentiation (LTP) and associated metabolic disease. A summary of the feed forward loop of insulin resistance and AD pathogenesis is provided in **Figure 1**.

Neuroinflammation Induced by Insulin Resistance in AD

The current consensus is that neuroinflammation plays a pivotal role in AD progression (Wang W. Y. et al., 2015), which is supported by results from APP transgenic mouse models in which injection of lipopolysaccharide (LPS, TLR4 activator) triggers neuroinflammation with two cellular hallmarks of AD in the brain, amyloid β-protein deposition (Lee et al., 2008; Go et al., 2016) and tau hyperphosphorylation (Kitazawa et al., 2005; Lee et al., 2010). Amyloid β-protein is the product of consecutive cleavage of APP by enzymes β-secretase (BACE) and γ-secretase. Processing of APP yields multiple forms of the protein; the 40 and 42 amino acid residue products are the most common forms (O'Brien and Wong, 2011). High levels of monomeric amyloid β-protein have a propensity to aggregate into fibrils and then plaques, resulting in neurodegeneration and induction of tau pathology (Mouchlis et al., 2020).

Inflammation is involved in activation of microglial cells, which are primarily responsible for amyloid β-protein phagocytosis. Microglia are brain-resident immune cells responsible for promoting phagocytotic clearance as well as providing trophic support to ensure tissue repair and cerebral homeostasis (Sarlus and Heneka, 2017). They also play a role in higher cognitive functions, such as learning and memory in the adult brain, and are involved in the pathogenesis of neurodegenerative diseases like AD. In the early stages of AD, activated microglia repair damaged tissue and decrease amyloid β-protein accumulation. However, chronic microglial activation induced by inflammation leads to release of inflammatory mediators and accumulation

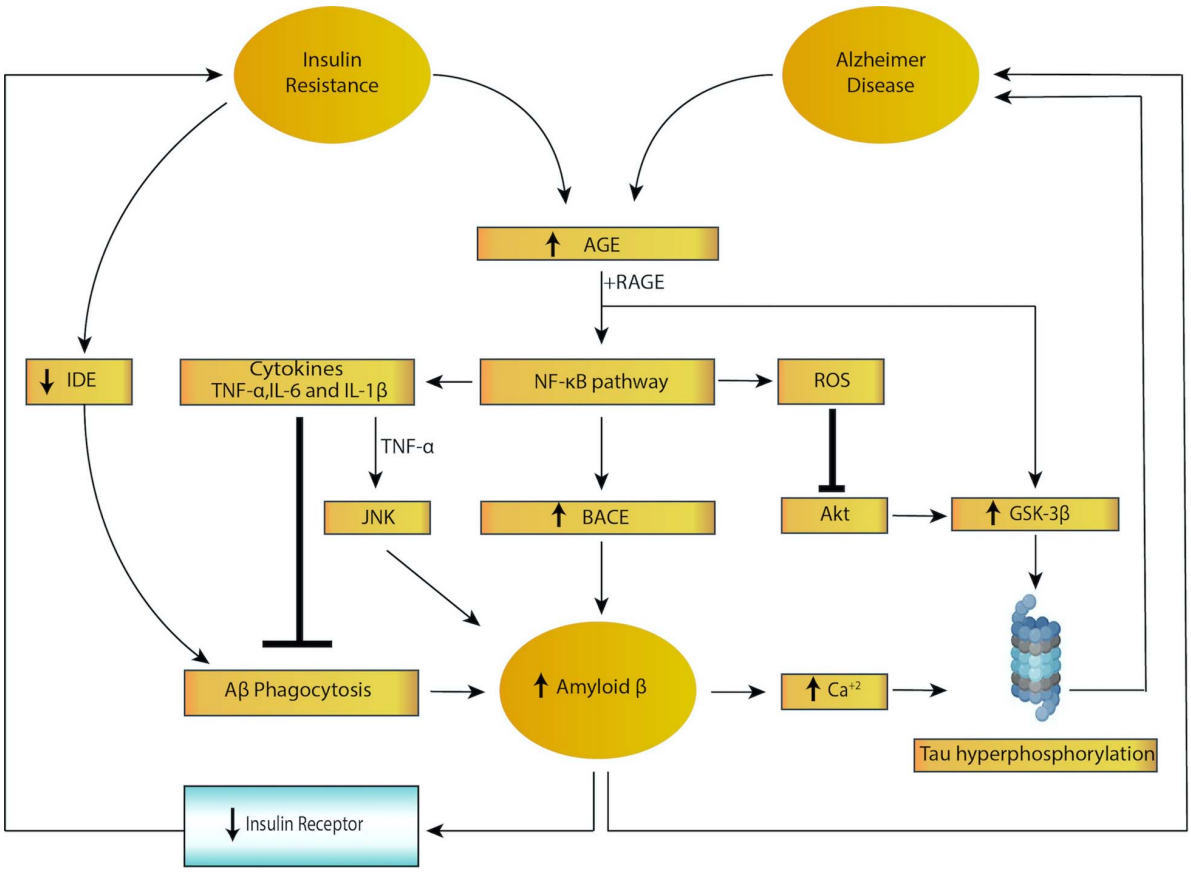

FIGURE 1 | Feed forward loop of insulin resistance and Alzheimer disease. Both insulin resistance and Alzheimer disease lead to activation of nuclear factor kappa B (NF-κB), increased cytokine secretion and increased reactive oxygen species (ROS) levels, triggering increased amyloid beta (amyloid β) and tau hyperphosphorylation. In addition, insulin resistance lowers levels of insulin degrading enzyme (IDE), resulting in impaired amyloid β phagocytosis. Higher levels of amyloid β, in turn, leads to decreased expression of the insulin receptor, which results in insulin resistance, creating a vicious cycle.

of danger-associated molecular patterns (DAMPs), which limits amyloid β-protein clearance, leading to more plaque accumulation, neuronal dysfunction and death (Clark and Vissel, 2015; Wang W. Y. et al., 2015; Brabazon et al., 2018). This hypothesis is supported by a longitudinal study showing increased levels of microglial activation in both mild cognitive impairment (MCI) and AD patients compared to controls, but a reduction in microglial activation following an initial peak in MCI patients (Fan et al., 2017). These data suggest that early microglial activation leads to a protective phenotype which can later turn into a pro-inflammatory picture due to failure of amyloid β-protein clearance and progressive neuronal damage.

Insulin resistance results in microglial activation and inflammation (McCaulley and Grush, 2017) by inducing the activation of resting (ramified) microglia and changes in cellular morphology, surface phenotype, secretary mediators and proliferative responses (Sarlus and Heneka, 2017). One common molecular pathology shared by insulin resistance and AD is increased levels of advanced glycation end products (AGEs) (Zhao and Townsend, 2009). Binding of AGEs to their cellular receptors (RAGE) not only upregulates glycogen synthase kinase 3β (GSK-3β), causing tau hyperphosphorylation (Peng et al., 2007; Li et al., 2012a,b), but also activates the NF-κB pathway, which produces reactive oxygen species (ROS) and pro-inflammatory cytokines [interleukin (IL)-6, IL-1β, TNF] (Kandimalla et al., 2017). These cytokines are observed to increase accumulation of amyloid β-protein in AD by two mechanisms: (1) increased levels of pro-inflammatory cytokines inhibit phagocytosis of amyloid β-protein in AD brains thereby hindering the removal of plaque by resident microglia; (2) TNF has been shown to upregulate the production of amyloid β-protein via activation of the c-Jun N-terminal kinase (JNK)-dependent MAPK pathway, which promotes phosphorylation and cleavage of APP (Liaoi et al., 2004; McAlpine and Tansey, 2008; Colombo et al., 2009; Montgomery et al., 2011; Cheng et al., 2014; Ahn et al., 2016; Decourt et al., 2017; Zhang et al., 2019). In addition, activation of the NF-κB pathway further increases BACE expression, resulting in increased production of amyloid β-protein (Guglielmotto et al., 2012; Cai et al., 2016). High levels of amyloid β-protein cause

IR downregulation via internalization, desensitization or direct substrate competition, which ultimately turn into insulin resistance (Xie et al., 2002; Mullins et al., 2017). Moreover, amyloid β-protein triggers Ca^{2+} influx, which not only causes hyperphosphorylation of tau protein (Bosco et al., 2011) via GSK-3β, but also inhibits IR tyrosine kinase signaling. The increased levels of Ca^{2+} stimulate Ca^{2+}-dependent serine/threonine protein kinases (PKC, Akt), which phosphorylate IRs and insulin resistance substrate (IRS) and thus negatively regulate IRs in the brain (Zhao and Townsend, 2009). Taken together, insulin resistance, neuroinflammation and exacerbation of amyloid β-protein and tau form a feed-forward loop in AD pathogenesis. Imbalance induced by any of these factors will facilitate AD progression, resulting in neurotoxicity, neurodegeneration and induction of a negative effect on IRs.

Oxidative Stress Induced by Insulin Resistance in AD

Growing evidence suggests that insulin/insulin-like growth factor (IGF) signaling is strongly associated with oxidative stress. Brain insulin/IGF resistance may contribute to impairments in glucose utilization and disruption of energy metabolism, resulting in production of ROS, DNA damage and mitochondrial dysfunction, eventually causing pro-apoptosis, pro-inflammation and amyloid β-protein cascades (de la Monte, 2014). Imbalance between the production of ROS and antioxidant defenses leads to oxidative stress which not only damages cells but also alters signaling pathways (Hurrle and Hsu, 2017). Oxidative stress has been implicated in AD and several studies have reported that it plays an important role in tau hyperphosphorylation and APP-amyloid β-protein accumulation (Huang et al., 2016).

Tau protein, a major microtubule-associated protein in the brain, functions mainly to maintain the stability of microtubules in neurons and other cells as well as facilitate cell differentiation and polarization (Mouchlis et al., 2020). According to the tau hypothesis, hyperphosphorylated tau pairs with other strands of tau protein and then forms NFT in neuronal cell bodies, which eventually induces microtubule dysregulation (Iqbal et al., 2005), causing impaired communication between neurons and even cell death (Bosco et al., 2011; Kametani and Hasegawa, 2018). As mentioned above, insulin resistance causes production of ROS via the activation of the AGE/RAGE pathway, inducing various stress sensitive signaling pathways, such as NF-κB, JNK/SAPK, p38 MAPK, and Akt pathway in particular (Rains and Jain, 2011). Increased oxidative stress inactivates the Akt pathway, concomitantly to downstream activation of GSK3 and subsequent hyperphosphorylation of tau protein (Bloch-Damti and Bashan, 2005; Hambright et al., 2015; Zhao et al., 2017; Ciotti et al., 2020).

Insulin resistance is also involved in APP-amyloid β-protein accumulation. APP-amyloid β-protein toxic fibrils, in turn, impair insulin signaling by downregulating IRs (Lee et al., 2013). Metal ions, such as zinc and copper bind to amyloid β-protein peptides and catalyze the production of ROS, which causes oxidative damage affecting both amyloid β-protein peptide and surrounding biomolecules, such as proteins and lipids (Cheignon et al., 2018). Both tau hyperphosphorylation and amyloid β-protein accumulation contribute to the positive feedback mechanism that exacerbates insulin/IGF resistance through increased oxidative stress, neurotoxicity and synaptic dysfunction (Lee et al., 2013).

Decreased Degradation of Amyloid β-Protein Induced by Insulin Resistance via IDE

Insulin is inactivated by IDE, also known as insulin protease (Manolopoulou et al., 2009; Song et al., 2018). IDE is widely distributed in many organs including liver, pancreas, brain and in diverse cellular compartments (Hulse et al., 2009). Accumulating studies have expanded the list of substrates and potential physiological roles of IDE, which includes degradation of multiple bioactive peptides, such as glucagon, IGF-2, and amyloid β-protein (Tang, 2016).

Amyloid β-protein forms various oligomers, leading to fibrils that then aggregate into plaques (Chen et al., 2017), which interrupt normal brain functions. Furthermore, soluble oligomeric forms of amyloid β-protein are the primary toxic species (Haass and Selkoe, 2007; Selkoe and Hardy, 2016) that have been shown to cause synaptic damage and neuronal cell death in both an APP knock-out mouse model and post-mortem human brains from patients with AD (Ding et al., 2019; Rolland et al., 2020). IDE is able to degrade both extracellular and intracellular amyloid β-protein, which protects against formation of these toxic oligomers. In addition, IDE functions as a "dead-end chaperone," preventing formation of toxic α-synuclein aggregates which can form a stable complex with amyloid β-protein (Sharma et al., 2015). α-synuclein is implicated in the pathophysiology of AD because high levels of α-synuclein are detected in the CSF of patients with MCI and AD (Twohig et al., 2018; Twohig and Nielsen, 2019).

Because insulin and amyloid β-protein are competing substrates for IDE, IDE defects are not only involved in the development of AD but also the basis for a strong association between T2DM and AD. Hyperinsulinemia may downregulate insulin uptake across the BBB and reduce levels of insulin in the brain because of saturation at supraphysiological levels (Reitz and Mayeux, 2014). This may result in decreased levels of IDE (Abdul-Hay et al., 2011; Protzek et al., 2016; Kang et al., 2017), causing decreased degradation of amyloid β-protein and increased deposits of amyloid β-protein (Li et al., 2018). In addition, increased levels of IDE are detected in post-mortem human brains from patients with moderate stage AD (Braak 3–4) whereas significantly reduced level of IDE are found in severe AD (Braak 5–6) (Delikkaya et al., 2019), suggesting that IDE is affected by insulin deficiency and insulin resistance in the early and moderate stages of AD. The development of IDE modulators may be a novel therapeutic approach to both T2DM and AD (Pivovarova et al., 2016).

TABLE 1 | Various potential treatments for Alzheimer's disease with insulin resistance.

Drug		Classification	Benefits
Anti-diabetic drugs	Metformin	Biguanide	First-line medication for T2DM; anti-inflammation; ↓ Aβ aggregation
	Liraglutide	GLP-1 agonist	↑ Insulin secretion; ↓ Aβ accumulation and ↓ tau hyperphosphorylation
	Intranasal insulin	–	Crosses BBB, improves cognitive functions and memory
Anti-inflammatory drugs	Tolfenamic Acid	Fenamate NSAIDs	Anti-inflammation via inhibition of NF-κB pathway; cognition enhancement via↓ Aβ and tau phosphorylation
	Mefenamic Acid	Fenamate NSAIDs	Anti-inflammation via inhibition of NLRP3 inflammasome; improve Aβ-induced learning and memory impairments
	Etanercept	TNF-α inhibitors	Anti-inflammation; ↓ Aβ to ↓ risk of AD
Antioxidant drugs	Vitamin C and E	Antioxidant	↓ Neuronal loss and Aβ; ↓ oxidative stress and tau-induced neurotoxicity
Thiazolidinediones (TZDs)	Rosiglitazone	–	↑ Insulin sensitivity; ↓ Aβ levels; improves cognitive functions
	Pioglitazone	–	↑ Insulin sensitivity; ↓ Aβ levels via downregulation of APP and BACE1

POTENTIAL TREATMENTS OF INSULIN RESISTANCE IN AD

Potential drug therapies for AD based on the association between insulin resistance and AD are listed in **Table 1**.

Anti-diabetic Drugs

Metformin, a biguanide antihyperglycemic agent which is the first-line medication for T2DM, attenuates inflammation, reduces risk of metabolic syndrome (Li et al., 2015) and may decrease risk of dementia and improve cognitive function. A meta-analysis showed that metformin was beneficial to diabetes patients with dementia or AD (Lin et al., 2018). Interestingly, T2DM patients with long-term use of metformin have been reported to slightly increase the risk of AD (Imfeld et al., 2012) due to metformin-induced vitamin B12 deficiency (Aroda et al., 2016; Campbell et al., 2018). Vitamin B12 deficiency has been reported to increase risk of AD, although the mechanism behind this association is uncertain (Abyad, 2002; Health Quality Ontario., 2013).

Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is used to treat T2DM and obesity by increasing insulin release from the pancreas as well as decreasing excessive glucagon release (Femminella et al., 2019). Recent studies have indicated that liraglutide may attenuate cognitive impairment. *In vitro* investigation has shown that liraglutide regulates neuronal insulin signaling and BACE-1 activity to suppress accumulation of amyloid β-protein and hyperphosphorylation of tau protein (Jantrapirom et al., 2020). Also, it prevents loss of brain insulin receptors and synapses and reverses cognitive impairment induced by amyloid β-protein oligomers in mouse hippocampi (Batista et al., 2018).

Intranasal insulin provides a potential pharmacological strategy to treat AD. Although there are different routes of administration for insulin, such as subcutaneous, intramuscular, and oral (Henkin, 2010), intranasal insulin has the advantage of penetrating the BBB and accessing the CNS because of the direct neuroanatomical connections between the olfactory nerves and the brain (de la Monte, 2013) which are beneficial for treating neurodegenerative and psychiatric disease (Hanson and Frey, 2008). More and more clinical studies have shown that intranasal insulin effectively improves cognitive function and memory (Benedict et al., 2008; Hallschmid et al., 2008; Krug et al., 2010), although a newly released study contradicts this finding (Craft et al., 2020). Thus, more direct experimental and clinical evidence are needed to investigate the safety and efficacy of intranasal insulin.

Anti-inflammatory Drugs

In 2020, 18% of agents in Phase III trials and 15% of agents in Phase II trials targeted inflammation to treat AD (Cummings et al., 2020). This is because a number of epidemiologic studies have reported that anti-inflammatory medication lowers the risk of cognitive impairment and AD. Although the effect of non-steroidal anti-inflammatory drugs (NSAIDs) in AD is under debate (Wang J. et al., 2015; Zhang et al., 2018), fenamate NSAIDS have aroused people's attention. These compounds selectively inhibit the NLRP3 inflammasome, which is implicated in inflammatory diseases including AD and T2DM, via the inhibition of volume-regulated anion channels (VRACs). The anti-inflammatory effects of two drugs in this class, tolfenamic acid and mefenamic acid, showed benefits in a 3 × TgAD transgenic model of AD (Daniels et al., 2016).

TNF is a key pro-inflammatory cytokine involved in insulin resistance, systemic inflammation and upregulation of amyloid β-protein, which further affects tau hyperphosphorylation (Clark and Vissel, 2015, 2016). Considering the importance of TNF in T2DM and AD pathogenesis, are TNF inhibitors a promising approach to treat AD or AD with T2DM? Although insufficient data are available, TNF inhibitors have been shown to produce cognitive improvements and lower the risk of AD in clinical trials of infliximab and adalimumab (Shi et al., 2011; Zhou et al., 2020). Etanercept, a specific anti-TNF biological in wide clinical use (Clark and Vissel, 2021), has been reported to attenuate neuroinflammation and improve cognitive function in murine models of traumatic brain injury (Chio et al., 2010) and Japanese encephalitis virus (Ye et al., 2014) and in clinical studies (Chen et al., 2010). However, further investigations to evaluate the use and specificity of these agents for dementia needs to be conducted.

Antioxidant Drugs

Oxidative stress is involved in the pathogenesis of both AD and T2DM. Vitamins C and E, potent antioxidants, are believed to lower the risk of AD and dementia (Lam et al., 2016). This hypothesis is supported by a cohort study which showed a significant protective effect of combined vitamin C and E supplements on cognitive functions in elderly men (Masaki et al., 2000). Another study with 4,740 participants also showed that long-term use of vitamin C and E supplements in combination helped to reduce the incidence of AD (Zandi et al., 2004). In addition, lower plasma levels of vitamin C and E were detected in patients with MCI compared to controls (Rinaldi et al., 2003). However, other studies indicated that vitamins C and E did not reduce the risk of developing AD and vitamin E supplementation had no significant effect on the amyloidotic phenotype if the amyloid plaques were already deposited (Feng and Wang, 2012).

Thiazolidinediones (TZDs)

The peroxisome proliferator-activated receptor-γ (PPAR- γ), highly expressed in adipose tissue, has a pivotal role in regulating carbohydrate, protein, and lipid metabolism and inflammatory responses (de la Monte, 2017). Thiazolidinediones (TZDs) are synthetic PPAR- γ agonists and potent insulin sensitizers, approved to treat T2DM. TZDs are now considered an attractive treatment of AD because of their potential benefit in cognitive function and memory (Khan et al., 2019). Here, we discuss two prototype TZDs—rosiglitazone and pioglitazone.

Rosiglitazone not only increases insulin sensitivity but also regulates APP processing, leading to reduced plasma amyloid β-protein levels (Pardeshi et al., 2017). Rosiglitazone upregulates IDE levels and downregulates amyloid β-protein levels in a mixed transgenic APPSwe/PS1 mouse model exhibiting both AD and T2DM (Li et al., 2018). Patients with mild to moderate AD in clinical trials were found to significantly improve cognitive function when administrated rosiglitazone (Watson et al., 2005; Risner et al., 2006). However, a phase III trial of rosiglitazone showed no significant effect on cognition (Gold et al., 2010) and rosiglitazone had no effect on the risk of dementia in T2DM patients (Tseng, 2019).

Pioglitazone has been found to increase insulin sensitivity, downregulate levels of hippocampal amyloid β-protein oligomer and decrease pro-cognitive effects in insulin-resistant rats (Yin et al., 2013; Gad et al., 2015). Furthermore, pioglitazone improved cognitive performance in some patients with AD and T2DM (Hanyu et al., 2009; Sato et al., 2011). However, the adverse effects of TZDs, including edema and congestive heart failure, are major limitations for their use in the treatment of dementia and AD (Campbell et al., 2018).

DISCUSSION

AD is a well-known neurodegenerative disorder, which afflicts millions of people worldwide and places a huge financial burden on society (Jia et al., 2018). For decades, treatments targeting amyloid β-protein based on the amyloid-cascade hypothesis and oligomer-cascade hypothesis have failed (Morris et al., 2014, 2018; Panza et al., 2019). The FDA's approval of the amyloid β-antibody Aducanumab reflects a promising achievement in AD therapy despite uncertainty about this drug's clinical benefits and adverse reactions. Apart from amyloid targets, in 2020, according to the FDA registry, there were over 50 agents in clinical trials targeting tau protein, inflammation and metabolism (Cummings et al., 2020). Therefore, novel approaches based on recent insights into this disease are needed.

The role of insulin in AD pathogenesis has only recently gained attention. Insulin resistance may not be the primary cause of AD but it definitely exacerbates AD progression (Clark and Vissel, 2018). In this review, we summarize the mechanisms whereby insulin resistance worsens amyloid β-protein accumulation and tau hyperphosphorylation, including activation of neuroinflammation, activation of oxidative stress and downregulation of IDE. We highlight how insulin resistance and AD form a feed-forward loop in which insulin resistance increases the risk of AD and AD, in turn, exacerbates insulin resistance. Targeting insulin resistance may be a breakthrough strategy to treat AD and may avoid the pitfalls of past treatments targeting amyloid β-protein and tau protein. This review adds to the literature linking insulin resistance and AD by extending insights in this area to update the list of drug candidates that can be repurposed for AD. Further research into the mechanism of the metabolic drivers of AD is needed to identify novel therapeutic approaches for this devastating disease.

AUTHOR CONTRIBUTIONS

ZW and JK wrote the first draft of the manuscript. SR conceived the idea for the article and edited the manuscript. All authors contributed to the article and approved the submitted version.

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