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Review article

Diabetes and Alzheimer's disease crosstalk

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ABSTRACT

Despite intensive research efforts over the past few decades, the mechanisms underlying the etiology of sporadic Alzheimer's disease (AD) remain unknown. This fact is of major concern because the number of patients affected by this medical condition is increasing exponentially and the existing treatments are only palliative in nature and offer no disease modifying affects. Interestingly, recent epidemiological studies indicate that diabetes significantly increases the risk of developing AD, suggesting that diabetes may play a causative role in the development of AD pathogenesis. Therefore, elucidating the molecular interactions between diabetes and AD is of critical significance because it might offer a novel approach to identifying mechanisms that may modulate the onset and progression of sporadic AD cases. This review highlights the involvement of several novels pathological molecular mechanisms induced by diabetes that increase AD pathogenesis. Furthermore, we discuss novel findings in animal model and clinical studies involving the use of anti-diabetic compounds as promising therapeutics for AD.

Contents

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, causing major progressive deficits in memory and cognitive function. Currently, over 35 million people worldwide are

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affected with the disease, including 5.4 million Americans, a number that is expected to double in the next 20 years as a consequence of a growing percentage of elderly in the overall human population (Hebert et al., 2001; Hebert et al., 2003; Hebert et al., 2013). From a public health perspective, AD imposes a severe financial and social cost that is expected to grow nearly five-fold in the ensuing decades (Alzheimer's Association, 2014). With existing AD treatments being palliative at best, and the number of patients and financial burden increasing exponentially, the need for efficacious therapeutics is becoming an urgent priority.

Neuropathologically, AD is characterized by the accumulation of senile plaques composed of amyloid-β (Aβ); neurofibrillary tangles (NFTs), formed mainly by hyperphosphorylation of tau protein; neuroinflammation and active gliosis; and significant synaptic and neuronal loss (Querfurth and LaFerla, 2010). AD can be categorized into two clinical subtypes, familial AD (fAD) and sporadic AD (sAD). Although both types of the disease (fAD and sAD) develop similar pathological phenotypes (e.g., plaques, tangles, synaptic impairments and neuronal loss), the factors triggering the neurodegenerative process are completely different. In fAD, the pathological buildup is caused by the presence of autosomal-dominant mutations in one of three genes: amyloid-β protein precursor (AβPP), presenilin-1 (PSEN1), or presenilin-2 (PSEN2) (Querfurth and LaFerla, 2010). However, the etiology underlying sAD, which represents the majority of AD cases (~98%), is complex and multi-factorial resulting from a combination of genetic, epigenetic, and lifestyle factors. Furthermore, the majority of sAD patients are elder subjects that commonly suffer from a variety of co-morbidities (e.g., stroke, stress, diabetes, seizures, osteoporosis, and renal disease) that can greatly add to the complexity underlying the pathogenesis of sAD and, therefore, may play an important role in the clinical course of the disease (Aubert et al., 2015; Doraiswamy et al., 2002; Magaki et al., 2014).

Over the past decade, multiple studies have been performed in animal models to understand the impact of these co-morbid medical conditions on AD pathogenesis and cognition (Abbondante et al., 2014; Baglietto-Vargas et al., 2015; Koike et al., 2011, 2010; Tran et al., 2011). Among the variety of co-morbidities, one of the most prevailing conditions affecting the human population is diabetes, and novel epidemiological studies indicate that diabetic patients have a significant risk of developing AD compared with healthy individuals (Arvanitakis et al., 2004; Fukazawa et al., 2013; Kopf and Frolich, 2009; MacKnight et al., 2002; Morris et al., 2014a; Ott et al., 1999). Furthermore, AD postmortem brain analysis have shown significant decreases in both insulin and insulin-like growth factor 1 (IGF-1) (Rivera et al., 2005), and ~80% of AD patients develop diabetes or glucose intolerance (Janson et al., 2004; Kroner, 2009). There have also been a number of animal studies that have observed correlations between altered body metabolism, weight, and changes in AD pathology, which we describe below and summarize in Tables 1 and 2. Additionally, there have been many clinical studies investigating the correlations between diabetes and cognitive dysfunction and between AD and altered insulin/glucose signaling. Some of these studies are summarized in Table 4. Overall, epidemiological, clinical, and animal studies suggest that a possible mechanistic relationship underlies these two important clinical disorders.

Diabetes is the most common metabolic disorder and is largely characterized by hyperglycemia, either because the pancreas does not produce enough insulin or because cells do not respond to it. Diabetes is also associated with several vascular disorders, including retinopathy, nephropathy, neuropathy, cardiovascular disease, and cognitive impairment (Umegaki, 2012). There are two major clinical subforms of diabetes: insulin-dependent diabetes (diabetes type 1, DT1), which accounts for 5–10% of total diabetic patients, and non-insulin-dependent diabetes (diabetes type 2, DT2), which accounts for the majority of the remaining diabetic patients. In addition, other types of diabetic conditions exist, such as gestational, monogenic diabetes, genetic syndrome, cases associated with disease of the exocrine pancreas, and cases induced by hormones or other drugs (Brands et al., 2005; Kharroubi and Darwish, 2015). There are currently over 176 million people worldwide affected by diabetes, which is estimated to reach 366 million by 2030 (Wild et al., 2004). The financial costs for supporting diabetes patients are estimated to be well over 174 billion dollars in the US alone, and the figure is expected to rapidly increase in the next decade.

Owing to the rapid growth in both diabetic numbers and the percentage of geriatrics in the overall population, identifying the clinical associations between diabetes and AD and elucidating the molecular mechanism that mediate their associations could provide protection from the profound medical and economical impact that these two disorders will have over the ensuing decades. An understanding of the links between diabetes and AD might offer novel approaches to modulating the onset and progression of either disorder. In this review, using both clinical and preclinical findings, we will highlight the possible mechanisms by which diabetes could increase AD pathogenesis and impair cognition. We will conclude the review with a discussion of the use of antidiabetic compounds as novel therapeutics for AD prevention.

2. Diabetes and β-amyloid pathogenesis

Amyloid plaques are primarily composed of amyloid-β (Aβ) and are a prominent pathological feature of AD. Aβ is a natural cleavage product consisting of 36–43 amino acids that it generates from the proteolysis of the amyloid precursor protein (APP) by the sequential enzymatic actions of beta-site amyloid precursor protein-cleaving enzyme 1 (BACE-1), a β-secretase, and a γ-secretase complex (LaFerla et al., 2007; Querfurth and LaFerla, 2010). Aβ has been demonstrated to be involved in several physiological processes, including synaptic plasticity, protein expression and neuronal survival (Multhaup et al., 2015; Pearson and Peers, 2006). However, an imbalance between the production and clearance of this peptide results in excess accumulation in the brain, which may be the initiation factor of AD onset. The hypothesis that an excess accumulation of Aβ underlies the onset of AD is known as the amyloid hypothesis and is supported by an accumulation of studies of genetic forms of Alzheimer's disease and Downs syndrome, as well as preclinical animal work (Hardy and Selkoe, 2002).

Aβ can spontaneously self-aggregate into multiple coexisting physical forms, a unique phenomenon of amyloids that is essential for their toxicity (Walsh and Selkoe, 2007). Classically, Aβ aggregates have been characterized by the presence of β-pleated sheet fibrils that arrange themselves into insoluble fibers and amyloid plaques (Kayed et al., 2003; Klein et al., 2001), however, intermediate assemblies (2–6 peptides) of Aβ oligomers can also coalesce in vivo. Early studies investigating the neurotoxicity of Aβ aggregates focused on β-pleated sheet-rich Aβ, however, accumulating evidence indicates that oligomers, and other intermediate aggregates, are the most neurotoxic forms of Aβ leading to impairs in long-term potentiation, causing synaptic dysfunction, neuronal loss and consequently memory deficits (Walsh and Selkoe, 2007).

In fAD cases, it is well documented that mutations in the genes for AβPP, PS1 or PS2 result in an increase in Aβ production and consequently accumulation (LaFerla et al., 2007; Querfurth and LaFerla, 2010). However, the etiology of the onset and progression of Aβ pathology in the sporadic form of AD is unknown. In this respect, novel clinical and animal model studies indicate that diabetes might be a contributing factor for the onset of overt Aβ pathology in sAD cases (Bomfim et al., 2012; de la Monte and Tong,

2014; Devi et al., 2012; Gasparini et al., 2002; Jolivalt et al., 2010; Schuh et al., 2011; Takeda et al., 2010; Talbot et al., 2012; Watson et al., 2003). Therefore, elucidating the molecular mechanism by which diabetes induces Aβ pathology will allow for the development of novel therapeutic strategies to delay or prevent AD. In the following section, we discuss several novel molecular mechanisms induced by diabetes that facilitate the development of Aβ pathology; some of the most important mechanisms are summarized in Fig. 1 and Table 1.

2.1. Insulin and insulin-like growth factor resistance

Although, initial studies supported the concept that the brain is an insulin-insensitive organ (Hom et al., 1984; Seaquist et al., 2001), biochemical findings have demonstrated the presence of insulin, insulin receptors (IRs) and neuronal expression of insulin-sensitive glucose transporter 4 (GLUT-4) in the brain, therefore providing important evidence that the brain is a target organ for insulin (El Messari et al., 2002; Havrankova et al., 1978; Hill et al., 1986; Sankar et al., 2002). Moreover, new studies using positron emission tomography (PET) and ^{18}F-labeled fluorodeoxyglucose ([^{18}F] FDG) have shown evidence of the effect of insulin on brain metabolism. These studies have found that insulin stimulates brain glucose metabolism in patients with impaired glucose tolerance and that lowering insulin plasma concentrations below physiological fasting levels decreases brain glucose metabolism (Bingham et al., 2002; Hirvonen et al., 2011). Additionally, insulin and insulin-like growth factor-1 (IGF-1) signaling play a pleiotropic role in the organization and function of the brain, including neuromodulatory and neurotrophic roles (Cholerton et al., 2013; Correia et al., 2011; de la Monte and Tong, 2014; Kim and Feldman, 2012). Indeed, emerging evidence has suggested that insulin/IGF signaling plays a key role in synaptic plasticity by modulating cell membrane expression of excitatory and inhibitory receptors, regulating neurotransmitter expression (such as acetylcholine and norepinephrine), triggering signal transduction cascades (involved in gene expression required for long term consolidation), and increasing cortical cerebral glucose metabolism in brain regions important for learning and memory (Cholerton et al., 2013; Correia et al., 2011; de la Monte and Tong, 2014; Kim and Feldman, 2012). Furthermore, intranasal insulin administration improves memory function in both human and animal studies (Benedict et al., 2004, 2008; McNay et al., 2010). Overall, these works support the hypothesis that insulin and IGF signaling are important role in learning and memory processes.

Growing evidence supports the concept that insulin/IGF resistance is an important mediator of AD pathogenesis and cognitive deficits (Cholerton et al., 2013; Correia et al., 2011; de la Monte and Tong, 2014). In fact, relevant clinical studies in human AD patients have demonstrated that brain insulin resistance is an early and common feature of AD, with reduced insulin receptor expression and deficits in IGF-1 signaling (Hoyer, 2002; Rivera et al., 2005; Steen et al., 2005; Talbot et al., 2012). Indeed, brain insulin resistance is more severe in areas associated with cognitive performance, such as the hippocampus, which is also an area highly susceptible to AD pathogenesis (Talbot et al., 2012). Several mechanisms have been proposed to describe how insulin/IGF dysfunction might lead to Aβ pathogenesis. For example, a recent novel study showed that insulin alters AβPP processing by elevating the expression of BACE-1. The elevation of BACE-1 followed increased translational upregulation through the PERK-eIF2α phosphorylation pathway rather than more recognized transcriptional mechanisms, or changes in the GGA3- dependent lysosomal degradation (Devi et al., 2012). Moreover, in vitro studies have shown that insulin can increase extracellular Aβ levels by accelerating AβPP/Aβ trafficking from the endoplasmic reticulum and trans-Golgi network to the plasma membrane by inhibiting its degradation via insulin-degrading enzyme, a metalloprotease enzyme responsible for insulin degradation and the main soluble Aβ degrading enzyme at neutral pH (Gasparini et al., 2001; Pandini et al., 2013). Conversely, De Felice's group presented novel findings indicating that Aβ oligomers can inhibit insulin signaling via the JNK/TNFα pathway, inducing IRS-1 phosphorylation at multiple serine residues and inhibiting its physiological function (Bomfim et al., 2012; Clarke et al., 2015). Therefore, a positive feed-forward mechanism may exist between impaired insulin signaling and Aβ that may further exacerbate AD pathology.

Table 1
Diabetes promotes amyloid pathology (Abbreviations: intraperitoneal i.p.; intracerebroventricular i.c.v.). (Arancio et al., 2004; Devi et al., 2012; Ho et al., 2004; Jolivalt et al., 2010; Julien et al., 2010; Kim et al., 2013b; Lane et al., 2010; Leuner et al., 2012; Li et al., 2007; Liu et al., 2009a; Macauley et al., 2015; Takeda et al., 2010; Wang et al., 2014).

Animal model	Mechanism	Reference
TgmAPP/RAGE mice	RAGE is a cofactor for amyloid bet to induce spatial learning and memory deficits and impairments in synaptic markers	Arancio et al. (2004)
High fat diet (10% fat, 70% carb, and 20% protein) in Tg2576	High fat diet (HFD) promotes Aβ pathology in Tg2576 mice via modulation of γ-secretase activity and insulin degrading enzyme (IDE) activity	Ho et al. (2004)
Prediabetic type 2 BBZDR/Wor rats and type 1 BB/Wor rats	Phosphorylated tau and Aβ accumulation occurs in both diabetic scenarios (Type1 and 2), and associated with insulin resistance and hypercholesterolemia	Li et al. (2007)
C57BL6 mice (single i.p. injection of STZ, 150 mg/Kg)	Cerebral amyloid beta depositions observed in diabetes mice is attributed to upregulation of RAGE at the blood brain barrier	Liu et al. (2009a)
APP mice STZ (two consecutive i.p. injection of STZ, 90 mg/Kg)	Decreased insulin activity and increased GSK3b activity in diabetic APP mice is accompanied by increased tau phosphorylation and Aβ plaque accumulation	Jolivalt et al. (2010)
High fat diet (35%w/w) and 3xTg-AD mice	3xTg-AD mice exposed to diets rich in facts and low *n*-3:*n*-6 polyunsaturated fatty acid (PUFA) increases both amyloid-beta and tau pathology	Julien et al. (2010)
Sorcs1 hypomorphic mice and Ntg mice	Dysfunction of SorCS1 hypomorphic mice led to a increase in Aβ, demonstrating that SorCS1 contributes to the APP/Aβ disturbances associated with AD	Lane et al. (2010)
APP23 mice were crossed with ob/ob & NSY mice	Diabetes accelerates AD phenotype, inducing severe memory deficits and cognitive dysfunction via vascular inflammation	Takeda et al. (2010)
5xFAD mice STZ (two consecutive i.p. injection of STZ, 90 mg/Kg)	Insulin deficiency alters APP processing via translational upregulation of BACE1 with elevations in APP	Devi et al. (2012)
APP751SL animal model	Mitochondrion-derived ROS trigger Aβ production	Leuner et al. (2012)
5xFAD mice model	NButGT inhibits *O*-GlcNAcase activity and reducting Aβ production via lowered γ-secretase activity in 5xFAD mice	Kim et al. (2013b)
APP/PS1 mice	Diabetes (via STZ administration) increases amyloid pathology in APP/PS1 transgenic mice through AGEs/RAGE/Nf-KB pathway	Wang et al. (2014)
APPswe/PS1dE9 mice model	Hyperglycemia modulates Aβ levels through neuronal activity	Macauley et al. (2015)

2.2. Hyperglycemia

Elevated plasma glucose levels are a common pathological feature of diabetes patients, and recent epidemiological studies suggest that individuals with elevated blood glucose have an increased risk of developing dementia and a prompt conversion from mild cognitive impairment (MCI) to AD, suggesting that disrupted glucose homeostasis might play a causative role in AD onset and progression (Crane et al., 2013; Morris et al., 2014b; Umegaki, 2014).

Among the possible mechanisms underlying the association between glucose metabolism and AD, Dr. Holtzman's group has found that hyperglycemia modulates Aβ levels via neuronal activity (Macauley et al., 2015). They demonstrated, using glucose clamps and in vivo microdialysis techniques, that hyperglycemia increase Aβ levels via altering neuronal activity through K_{ATP} channels (Macauley et al., 2015). This study provides an important and valuable mechanistic link between glucose metabolism and AD and indicates that K_{ATP} channels could be a promising therapeutic approach for AD patients with metabolic problems.

Furthermore, abnormal glucose metabolism stimulates glycation reactions that lead to the formation of advanced glycation end-products (AGEs). AGEs are produced by complex non-enzymatic reactions between sugars, free amino groups of proteins, lipids, and nucleic acids (Sims-Robinson et al., 2010; Singh et al., 2001). Moreover, immunohistochemical analysis in postmortem human brains reveal that AGEs are associated with both Aβ plaques and NFTs (Dei et al., 2002; Valente et al., 2010); interestingly, AD patients with diabetes (ADD) show even higher levels of AGEs compared with non-diabetic AD subjects (Valente et al., 2010). Taken together, these studies suggest a pathological synergism between AD and diabetes that occurs through an AGE-dependent mechanism (Dei et al., 2002; Valente et al., 2010). In this respect, several studies have revealed that diabetes might promote AD pathogenesis by modulating the AGEs/RAGE/NF-κB pathway (Arancio et al., 2004; Deane et al., 2003; Liu et al., 2009a; Takeda et al., 2010). In addition, another study led by Dr. Song indicates that high glucose levels promote Aβ generation directly by inhibiting the degradation of the AβPP protein (Yang et al., 2013).

Overall, multiple mechanisms suggest that high glucose levels might promote AD pathogenesis, and strategies focused to control and diminish glycemic levels might be beneficial preventives strategies to delay AD onset and progression and reduce the incidence of AD in diabetic patients.

2.3. O-*GlcNAcylation*

O-GlcNAcylation is a ubiquitous nucleocytoplasmic postranslation modification whose primary function is to modulate cellular signaling and transcriptional regulatory pathways in response to nutrients and cellular stress (Hart et al., 2011). Notably, *O*-GlcNAcylation is regulated by intracellular glucose metabolism, and in AD patients, levels of *O*-GlcNAcylation are significantly reduced compared with observed for controls (Zhu et al., 2014). Several studies have demonstrated that AβPP is modified by *O*-GlcNAcylation, and increases in *O*-GlcNAcylation levels can reduce Aβ production by lowering γ-secretase activity, although other possible mechanisms induced by *O*-GlcNAcylation may regulate Aβ levels (Jacobsen and Iverfeldt, 2011; Kim et al., 2013b; Yuzwa et al., 2014; Zhu et al., 2014).

2.4. Oxidative stress and mitochondrial dysfunction

Oxidative stress is a harmful condition resulting from an imbalance in the production and accumulation of potentially harmful free radicals (including reactive oxygen species (ROS) and reactive nitrogen species (RNS)) when the metabolic activity of cells exceeds their antioxidant capacity. The accumulation of high levels of ROS or RNS species can affect a range of biomolecules, including proteins, lipids and nucleic acids, compromising cell integrity and function and leading to cell death (Cobb and Cole, 2015; Radi et al., 2014).

Elevated levels of ROS and RNS have been detected in both diabetic and AD patients compared with those of healthy controls, suggesting that oxidative stress may be an important hallmark in both diseases (Butterfield et al., 2007; Giugliano et al., 1996; Pratico and Sung, 2004; Reddy et al., 2009). In diabetes, it is now well accepted that oxidative stress plays an important role in the development of this pathological condition, and many different potential mechanisms are implicated in the induction of increased oxidative stress, such as auto-oxidation of glucose, impaired antioxidant defense enzymes, metabolic abnormalities initiated by elevated levels of glucose and mitochondria damage (Brownlee, 2005; Kowluru and Mishra, 2015; Nikooyeh and Neyestani, 2015). Furthermore, oxidized proteins and lipids are elevated in the brain and CSF of AD patients compared with healthy controls, and mounting evidence indicates that this oxidative damage might occur early in the development of AD as observed in MCI patients (Brownlee, 2005; Kowluru and Mishra, 2015; Nikooyeh and Neyestani, 2015). Therefore, the hypothesis that oxidative stress serves as a link between diabetes and AD is currently under examination by several research groups (Moreira, 2012; Reddy et al., 2009). Recent studies have provided some insight into the possible mechanism by which oxidative stress may increase Aβ pathology, such as via stimulating AβPP gene expression or by modulating its processing via modulating γ- and β-secretase (Cai et al., 2011; Jo et al., 2010; Oda et al., 2010; Tamagno et al., 2012).

Mitochondria abnormalities have also been proposed as a potential link between diabetes and AD (Moreira et al., 2007). In diabetic patients, several abnormalities associated with mitochondria biology have been observed, including altered mitochondrial morphology, increased intracellular calcium levels, deficiency in bioenergetics and antioxidant capacity (Anello et al., 2005; Edwards et al., 2010; Fernyhough et al., 2010; Kelley et al., 2002; Mastrocola et al., 2005; Moreira et al., 2003, 2005). Additionally, mitochondria dysfunction occurs in AD patients, and several possible mechanisms have been proposed to underlie the impairments in mitochondria function in AD, such as affecting cytochrome c oxidase of the respiratory chain, mitochondria membrane potential, ATP production, and fusion/fission interactions (Bosetti et al., 2002; Cardoso et al., 2004; Hirai et al., 2001; Swerdlow and Kish, 2002; Valla et al., 2006; Wang et al., 2008). Because of the strong evidence indicating that Aβ can accumulate in mitochondria, multiple studies have focused on determining how Aβ affects mitochondrial function. These studies have revealed that mitochondrial abnormalities induced by Aβ include mitochondrial swelling, apoptosis, opening of mitochondrial transition pores (mPTPs) and increases in ROS production and therefore conclude that Aβ leads to severe structural and functional abnormalities in mitochondria (Cabezas-Opazo et al., 2015; Casley et al., 2002; Crouch et al., 2005; Jafari et al., 2015; Kaminsky et al., 2015; Kumar and Singh, 2015; Picone et al., 2014; Pinho et al., 2014; Ronnback et al., 2015; Ye et al., 2015). Furthermore, in work conducted in the Müller Lab exploring whether mitochondria-derived ROS has an effect on Aβ production (Leuner et al., 2012), the authors used specific inhibitors of the respiratory chain, rotenone and antimycin, and demonstrated an increase in Aβ levels that was dependent on mitochondria ROS concentrations. In addition, the Müller Lab used antioxidant compounds that prevented mitochondrial dysfunction and reduced the formation of Aβ (Leuner et al., 2012). Overall, these observations suggest there exists a vicious cycle between oxidative stress, mito-

chondrial impairment and Aβ levels that could be an important link between diabetes and AD.

2.5. Other molecular mechanisms that modulate Aβ pathology

Lipotoxicity is an important pathological feature of diabetes patients that occurs as a result of excess production of free fat acids (FFAs) (Cholerton et al., 2013; Correia et al., 2011; de la Monte and Tong, 2014). Interestingly, several clinical studies indicate that AD brains contain elevated levels of saturated FFAs compared with the brains of healthy subjects and in patients with metabolic syndrome (Fonteh et al., 2014; Karmi et al., 2010; Roher et al., 2002). Moreover, epidemiological findings suggest that the consumption of saturated FFAs might increase the risk of developing AD (Takechi et al., 2010). This hypothesis is supported by studies using AD animal models fed high-fat diets, which have shown that a diet rich in saturated FFAs can accelerate AD-like pathology (Barron et al., 2013; Hohsfield et al., 2014; Julien et al., 2010; Knight et al., 2014; Vandal et al., 2014). Novel findings suggest that saturated FFAs can modulate AD pathology through several potential mechanisms, including an inhibitory effect of IDE, which can then lead to reduced Aβ clearance, by modulating AβPP processing via activation of the STAT3/BACE1/presenilin-1 and by stimulating pro-inflammatory process via the production of excess TNFα signaling (Liu et al., 2013a,b). Furthermore, some genetic risk factors may also link diabetes to AD onset, such as deficiencies in SORCS1 (a diabetic quantitative trait associated gene), which have been linked to increased Aβ generation in mice and might be a common genetic risk factor underlying Aβ pathogenesis (Lane et al., 2010, 2013).

2.6. Aβ and synaptic impairments

Accumulating evidence indicate that synaptic loss is a critical event in the pathophysiology of AD and is the best predictor of clinical symptoms and disease progression (Selkoe, 2002; Sze et al., 1997; Terry et al., 1991). Various lines of evidence suggest that Aβ plays a causal role in synaptic dysfunction in AD, therefore affecting brain neuronal networks (Mucke and Selkoe, 2012; Palop and Mucke, 2010; Querfurth and LaFerla, 2010). Consequently, over the past two decades, many efforts have focused on elucidating the role and effect of Aβ on synaptic function. Interestingly, Aβ exerts a critical physiological role in synaptic transmission, and the production of Aβ is modulated by neuronal activity, i.e., increased neuronal activity enhances Aβ production, whereas low neuronal activity has the opposite effect (Cirrito et al., 2005; Kamenetz et al., 2003). However, under conditions in which Aβ levels are in excess, as occurs in AD, the potential for detrimental effects in synaptic function and consequently impaired cognition are increased. Along these lines, several groups have shown that elevate levels of Aβ impair glutamatergic and GABAergic transmission and cause synaptic loss (Hsia et al., 1999; Kamenetz et al., 2003; Mucke et al., 2000; Ulrich, 2015). The Aβ-dependent effects on synaptic function are suggested to be mediated by the modulation of several synaptic receptors, including α7-nAChRs, NMDARs, and $GABA_AR$, via blocking glutamate uptake at synapses, by the impairment of insulin signaling, and other multiple synaptic downstream targets such as calcineuring-STEP-cofilin, p38MAPK, GSK3β and Fyn signaling pathways (Bomfim et al., 2012; Chabrier et al., 2012, 2014; Li et al., 2009; Shankar et al., 2007; Snyder et al., 2005; Tackenberg and Brandt, 2009; Wang et al., 2004). As described above, diabetes may trigger Aβ pathogenesis via various mechanisms; therefore, it is possible that one of the key players through which diabetes may affect synaptic function and neuronal transmission in the central nervous system (CNS) is Aβ. Hence, additional studies focused on this aspect would be interesting to elucidate the plausible contribution of Aβ to cognitive deficits induced by diabetes.

3. Diabetes and tau pathology

The microtubule-associated protein tau (MAPT) is a cytoskeleton protein expressed predominantly by neurons and is localized mainly in the axonal compartment. Under physiological conditions, tau is a highly soluble and natively unfolded protein that interacts with tubulin and plays a key role in microtubule assembly and stability (Avila et al., 2004; Weingarten et al., 1975). Furthermore, tau plays an essential role in the balance of microtubule-dependent axonal transport of organelles and biomolecules (Dixit et al., 2008; Stokin et al., 2005). Tau is regulated during both normal homeostasis and in stress-induced responses by an array of posttranslational modifications that include glycosylation, ubiquitination, glycation, nitration, oxidation, cleavage or truncation, and polyamination and sumoylation (Martin et al., 2011; Medeiros et al., 2011). Under pathological conditions, such as those associated with AD and other tauopathies, tau is excessively phosphorylated, cleaved, glycosylated, etc., which leads to its pathological accumulation. This accumulation in turn results in the disruption of the microtubules, altering postsynaptic physiology and leading to synaptic dysfunction and cognitive deficits (Ittner et al., 2010; Johnson and Stoothoff, 2004; Querfurth and LaFerla, 2010). Unfortunately, the underlying factors responsible for the formation of tau lesions in sAD patients remain unclear. Interestingly, recent evidence obtained from human and animal models as shown that diabetes can promote aberrant tau modification (Asano et al., 2007; Clodfelder-Miller et al., 2006; Grunblatt et al., 2007; Jolivalt et al., 2010, 2008; Jung et al., 2013; Ke et al., 2009; Kim et al., 2013a, 2009; Leboucher et al., 2013; Li et al., 2007; Liu et al., 2004, 2009b, 2011; Ma et al., 2013; Planel et al., 2007; Qu et al., 2011; Sutherland et al., 1993; Taniguchi et al., 2006). Because tau is regulated predominantly through posttranslational modifications, understanding how diabetes can alter these modifications is of great interest and may lead to the design of strategies to prevent the disruption and aggregation of tau and mitigate cognitive and synaptic deficits. Several of the most important findings obtained from animal models are summarized in Table 2 and described in Fig. 1.

3.1. Post-translational modifications of tau

3.1.1. Tau phosphorylation

Phosphorylation is the most common, and most extensively studied, tau post-translational modification (Martin et al., 2011). The degree of tau phosphorylation is inversely proportional to tau's affinity for microtubules and can result in neuronal cytoskeleton destabilization and impaired axonal transport, which in turn can lead to synaptic impairment and progressive neurodegeneration once a pathological threshold is reached (Spires-Jones et al., 2009). Interestingly, several preclinical studies have shown that modeling either type 1 or type 2 diabetes in rodents results in an increase in tau phosphorylation versus normal controls animals (Abbondante et al., 2014; Clodfelder-Miller et al., 2006; Grunblatt et al., 2007; Ke et al., 2009; Kim et al., 2009; Ma et al., 2013; Planel et al., 2007; Qu et al., 2011). Several mechanisms have been suggested to underlie tau hyperphosphorylation induced by diabetes. Among these, growing evidence suggests that insulin signaling is one of the most significant mechanisms (de la Monte, 2012; Yang and Song, 2013). Impaired insulin-signaling results in a significant decrease in phosphatidylinositol-3-kinase (PI3K) and Akt, and Wnt/β-catenine pathway signaling and a subsequent increase in the activation of glycogen synthase kinase (GSK3β), which leads to tau hyperphosphorylation and self-aggregation (de la Monte, 2012;

Table 2
Diabetes induces tau pathology (Abbreviations: intraperitoneal i.p.; intracerebroventricular i.c.v.). (Abbondante et al., 2014; Clodfelder-Miller et al., 2006; Deng et al., 2009; Jolivalt et al., 2008; Jung et al., 2013; Ke et al., 2009; Kim et al., 2013a, 2009; Leboucher et al., 2013; Ma et al., 2013; Papon et al., 2013; Planel et al., 2007; Qu et al., 2011).

Animal model	Mechanism	Reference
Single STZ injection (i.p) of 150 mg/Kg in Ntg mice	Type 1 diabetes induced by STZ injection significantly decreased protein phosphatase 2A activity, which lead to high levels of tau hyperphosphorylation	Clodfelder-Miller et al. (2006)
Single STZ injection (i.p) of 200 mg/kg in Ntg mice	Insulin dysfunction induced tau hyperphosphorylation via two mechanisms (hypothermia, and through the inhibition of phosphatase activity)	Planel et al. (2007)
Two consecutive STZ injections of 90 mg/kg, i.p in Swiss Webster rats and db/db mice	Insulin deficiency induced tau hyperphosphorylation via the IR/AKT/GSK3 pathway	Jolivalt et al. (2008)
Single STZ injection (i.p) of 200 mg/kg in pR5 mice	STZ induced Type 1 diabetes accelerated the onset of tau pathology, and increased its overall severity	Ke et al. (2009)
STZ injection (i.p and 50 mg/kg; 5 consecutive days) in Ntg and db/db mice	Insulin deficiency may be a major contributing factor for type 1 diabetes to induced tau hyperphosphorylation, while in type 2 diabetes, hyperglycemia-mediated tau cleave	Kim et al. (2009)
I.C.V. administration of STZ (1.5 mg/kg at each site) in Ntg mice	Impaired insulin signaling induced an overactivation of GSK-3 kinase, and the downregulation of *O*-GlcNAcylation, which resulted in tau and neurofilament hyperphosphorylation, and neurofibrillary degeneration	Kim et al. (2009)
Single STZ injection (i.p) of 55 mg/kg in Ntg mice	STZ-induced hyperglycemia altered the Akt/GSK-3/PP2A cascade, and leads to the development of abnormal tau phosphorylate forms	Qu et al. (2011)
OLETF rats	T2D leas to increased polyubiquitinated *p*-tau via decreased p62 transcription	Jung et al. (2013)
Ob/ob mice	Hyperglycemia, induced by T2DM, was found to be a key factor that leads to overt tau cleave via activation of caspase-3	Kim et al. (2013a)
THY-Tau22 transgenic model mice given high-fat diet (20 weeks)	Diet-induced obesity exacerbated tau phosphorylation and cognitive impairment in tau transgenic mice, independently from peripheral/central insulin resistance	Leboucher et al. (2013)
Single STZ injection of 30 mg/Kg, i.p or high-fat and high-carbohydrate diet (8 weeks) in a T2D rat model	T2D onset lead to increased tau pathology, via insulin signaling impairments linked to increased activated mTOR	Ma et al. (2013)
Non-obese diabetic (NOD) mouse model	Induced insulin dysfunction in NOD mice lead to the development of Alzheimer's-like tau pathology, which was likely due to the deregulation of phosphatase 2A (PP2A)	Papon et al. (2013)
Single STZ injection (i.p) of 150 mg/kg in Ntg and TauKO mice	Chemically induced Type 1 diabetes resulted in tau dependent cognitive and synaptic deficits	Abbondante et al. (2014)

Yang and Song, 2013). Additionally, several studies have shown that impairments in insulin signaling might alter the activation of several other kinases that regulate tau, including p38 mitogen-activated protein kinase (p38 MAP) and c-Jun N-terminal Kinase (JNK) (Clodfelder-Miller et al., 2006). Furthermore, phospho-tau levels are also regulated by phosphatase activity, such as the well-characterized phosphatase 2A (PP2A), and several findings suggest that insulin deficiency reduces the activity of PP2A, which then leads to an increase in tau hyperphosphorylation (Clodfelder-Miller et al., 2006; Papon et al., 2013). Finally, both human primary neuronal cultures and animal studies demonstrate that insulin and IGF-1 reduce tau phosphorylation and promote tau binding to microtubules through inhibition of GSK3β (Hong and Lee, 1997). Together, these studies suggest that insulin and IGF-1 regulate the level of tau phosphorylation, and therefore, disruption in proper insulin and IGF-1 signaling could play an important role in the onset and progression of tau pathogenesis.

In addition to insulin, other factors induced by diabetes might play an important role in tau pathogenesis, such as advanced glycation end-products (AGEs) (Sims-Robinson et al., 2010; Singh et al., 2001). Abnormal glucose metabolism contributes to the formation of AGEs, and indeed, AGEs accumulate during normal aging, but their accumulation is greatly accelerated under diabetic conditions (Singh et al., 2001). Interestingly, postmortem human brain analysis have revealed that AGEs are found within NFTs (Dei et al., 2002; Valente et al., 2010). However, a critical question that remains to be answered is how higher AGE levels contribute to exacerbated tau phosphorylation. In this regard, several studies suggest that AGEs induce tau hyperphosphorylation, as subsequently synaptic and cognitive deficits, through RAGE-mediated GSK-3 activation (Li et al., 2012a,b). Thus, targeting the RAGE/GSK-3 pathway could be a promising therapeutic strategy for preventing tau hyperphosphorylation and synaptic impairments in response to increased AGE levels. Moreover, recent findings also indicate that diabetes increases the hyperphosphorylation of tau through impairment of the protein degradation system involved in the downregulation of the protein p62 (Jung et al., 2013). The p62 protein delivers polyubiquitinated tau protein to the proteasome and autophagosome for degradation via Rpt1 and LC-3II, respectively (Wang and Mandelkow, 2012), and thus, deficiencies in p62 may inhibit the degradation of polyubiquitinated p-tau proteins. Overall, several mechanisms induced by diabetes, including insulin deficiency, AGE elevation, and impairments in the protein degradation system, contribute to tau hyperphosphorylation and consequently may further promote the exacerbation of AD pathology and cognitive deficits (Spires-Jones et al., 2009).

3.1.2. *Tau truncation*

The truncation of tau is another important posttranslational modification that is under intensive research. Currently, several studies have reported on the impact of this posttranslation modification in relation to the neurodegenerative events that occur in several disorders, including AD (Farias et al., 2011; Martin et al., 2011). Tau truncation is suggested to enhance the capacity of tau to aggregate and promote the formation of NFTs in AD (Hanger and Wray, 2010; Martin et al., 2011). Tau can be cleaved by a variety of proteolytic enzymes, including caspases, calpains, thrombin, cathepsins and puromycin-sensitive aminopeptidase (PSA), and tau-truncated fragments appear to lack both the N- and C-termini of tau (Hanger and Wray, 2010; Martin et al., 2011). With respect to diabetes, a novel study by Feldman and collaborators revealed that in an animal model of type 2 diabetes, tau is highly cleaved, which may subsequently contribute to the formation of tau accumulation (Kim et al., 2009). Moreover, in another study by the Feldman Group, the researchers found that hyperglycemia is a major factor that induces tau cleavage, which is partially mediated through caspase activation (Kim et al., 2013a). Taken together, these studies indicate that diabetes induces the formation of tau-truncated fragments that may contribute to the increased incidence of AD in diabetic patients. However, further studies outlining the mechanisms by which tau truncation contributes to diabetes-induced cell damage, synaptic and cognitive deficits are greatly needed.

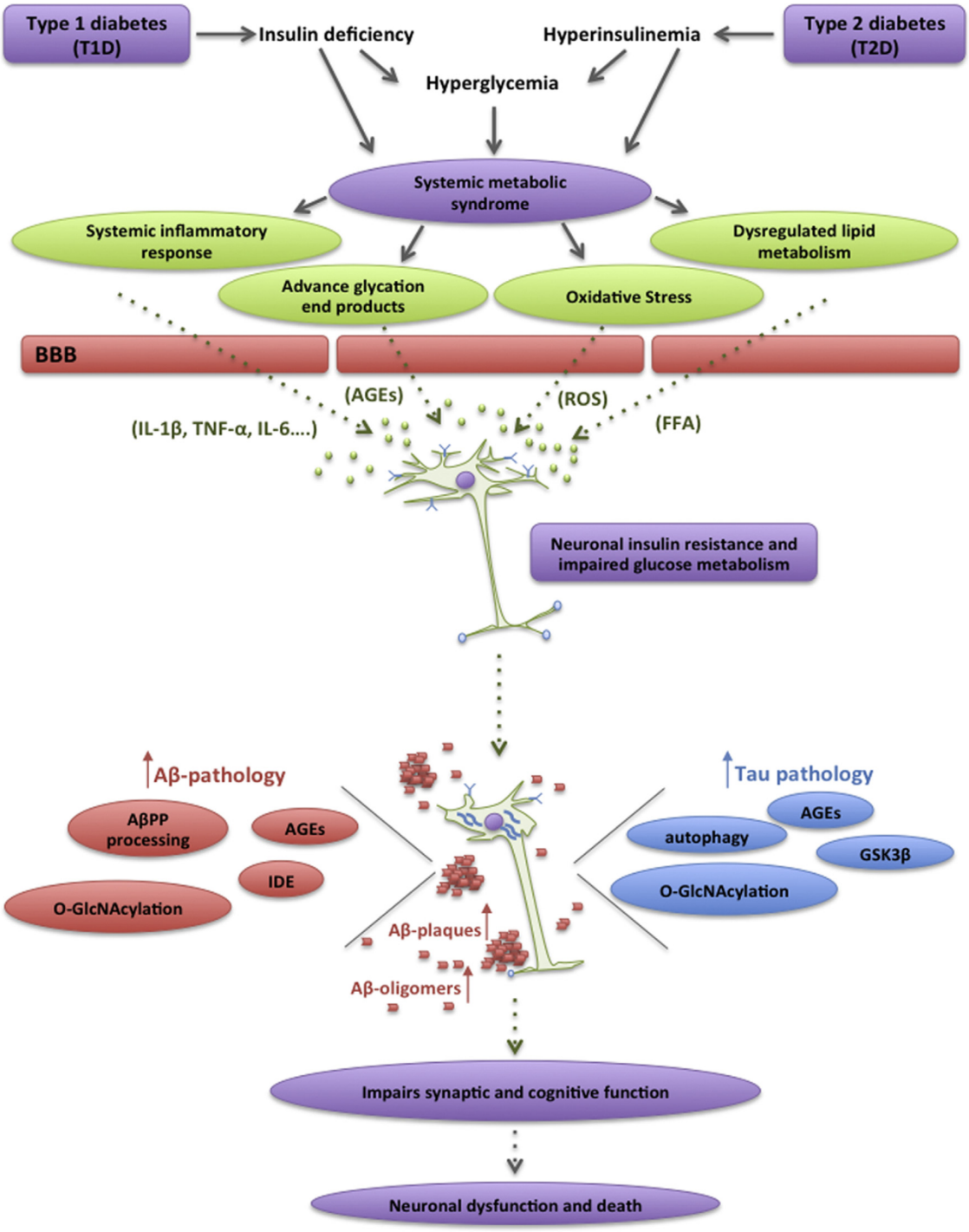

Fig. 1. Overview of multiple molecular mechanisms by which diabetes (types 1 and 2) triggers AD pathogenesis. Here, we present a summary of multiple possible mechanisms induced by diabetes that might participate as a molecular trigger for AD pathogenesis in the brain. Several of these pathogenic processes are more predominant in one type of diabetes versus the other type. For example, insulinemia and hyperglycemia are predominant pathogenic process by which type 1 diabetes might accelerate AD pathogenesis, although oxidative stress and the production of advance glycation end-products also might play an important role. In type 2 diabetes, in addition to hyperglycemia, chronic inflammation, oxidative stress and dysregulated lipid metabolism might trigger important downstream mechanisms that induce both Aβ and tau pathology, as presented in the figure. Among these downstream processes induced by type 1 and 2 diabetes, insulin resistance, altering APP processing, triggering the glycogen synthase kinase-3 beta (GSK3β), reducing the levels of insulin degrading enzyme (IDE), increasing the formation of advanced glycation end-product (AGEs), affecting autophagy and the *O*-GlcNAcylation process might trigger the production and accumulation of both Aβ and tau pathology. Therefore, the accumulation of Aβ and tau may further exacerbate the adverse effects on synaptic and cognitive function and consequently induce cell death.

3.1.3. *Tau glycosylation*

Glycosylation is the result of a covalent attachment of oligosaccharides to a protein or lipids. There are two main types of glycosylation that occur with respect to the tau protein: *O*-glycosylation (in which sugars are linked to the hydroxyl groups of serine or threonine residues) and *N*-glycosylation (in which sugars are linked to the amine group of the asparagine side chain of proteins) (Dias and Hart, 2007). Interestingly, several studies have shown that impairments in glucose metabolism down-regulate *O*-GlcNAcylation levels and subsequently facilitate the formation

of abnormal tau hyperphosphorylation (Deng et al., 2009; Liu et al., 2004). Although it is not well known how the degree of *O*-GlcNAcylation can affect the formation of tau phosphorylation, it is hypothesized that competition between *O*-GlcNAcylation and phosphorylation for occupancy of serine/threonine sites of tau might be the primary factor (Hart et al., 2011). Indeed, tau has at least 12 *O*-GlcNAcylation sites that are inversely correlated with phosphorylation status (Dias and Hart, 2007). Thus, a reduction of *O*-GlcNAcylation, induced by alterations in the glucose metabolism, might facilitate the generation of excess phosphogroups to serine/threonine sites in tau and consequently lead to a hyperphosphorylated tau state.

Overall, these findings indicate that diabetes significantly alters multiple physiological processes (including hyperphosphorylation, truncation and glycosylation) that can result in an increase in tau pathology and affect neuronal survival, synaptic function and cognition. In addition, it remains to be determined whether diabetes can also enhance the degree of other post-translational modifications of tau, such as ubiquitination, nitration, polyamination and sumoylation, further solidifying its role as an important comorbid contributor to AD pathogenesis.

3.2. Tau and synaptic impairments

As previously described, tau is a cytoskeleton protein that exerts a crucial effect on the balance of microtubule-dependent axonal transport of organelles and biomolecules (Dixit et al., 2008; Stokin et al., 2005). However, in pathological conditions such as AD, tau might be a key factor that impairs synaptic function. In this regard, recent significant findings have provided substantial insight into the synaptotoxic role of tau (Hoover et al., 2010; Ittner et al., 2010; Palop et al., 2011; Roberson et al., 2007). One of these possible mechanisms involves an interaction with the Src kinase Fyn. Tau can bind to Fyn via its amino-terminal projection domain (PD), and Fyn, normally found accumulated in the postsynaptic compartment, then phosphorylates the NR subunit 2 (NR2) and stabilizes the interaction of the NR complex with the postsynaptic density protein 95 (PSD-95) (Ittner et al., 2010). This stabilization links NRs to synaptic excitotoxic downstream signaling (Salter and Kalia, 2004). Another possible mechanism linking tau pathology to synaptic dysfunction involves tau-mediated defects in axonal transport based on the alteration of microtubule stabilization and/or via its differential regulation of motor proteins (including dynein and kinesin) (Dixit et al., 2008; Palop et al., 2011). Thus, disruption of cellular transport might cause synapse degeneration and ultimately neuronal degeneration, leading to disrupted neural circuits and cognitive impairments (Spires-Jones et al., 2009). Nevertheless, the exact pathological mechanism by which tau causes synaptic toxicity is not yet fully understood, and further investigation is necessary to address the pathogenic role of tau in synaptic and cognitive function in diabetes and AD (Palop et al., 2011).

Overall, the studies described above show that tau can exert a critical effect on synaptic function. Because diabetes promotes aberrant tau modifications (Asano et al., 2007; Clodfelder-Miller et al., 2006; Grunblatt et al., 2007; Jolivalt et al., 2010; Jolivalt et al., 2008; Jung et al., 2013; Ke et al., 2009; Kim et al., 2013a, 2009; Leboucher et al., 2013; Li et al., 2007; Liu et al., 2004, 2009b, 2011; Ma et al., 2013; Planel et al., 2007; Qu et al., 2011; Sutherland et al., 1993; Taniguchi et al., 2006), our laboratory hypothesized that diabetes might cause synaptic deficits via tau-dependent mechanisms. To address this hypothesis, we utilized a combined pharmacological and genetic approach by treating tau knock-out (tauKO) with streptozotozin (STZ), rendering a valuable model for studying DT1. Our findings reveal that DT1 impairs cognition via a tau-dependent mechanism, and genetically ablating tau prevents both synaptic and cognitive deficits (Abbondante et al., 2014). Therefore, our results provide new insights into the relevance of tau as a key mediator of the induction of synaptic and cognitive impairments induced by diabetes (Abbondante et al., 2014). However, DT1 accounts for a small proportion of diabetes cases, and further studies will be necessary to determine whether tau plays an equally relevant role in DT2-mediated synaptic and cognitive deficits. Taken together, our study lends strong support to the hypothesis that tau represents a critical link that underlies the interaction between diabetes and AD, and thus, tau represents a promising molecular target for the development of future drugs for treating and/or preventing cognitive deficits in patients with AD and diabetes.

4. Diabetes and chronic inflammation

Inflammation is a fundamental physiological process that occurs in response to the presence of infection or as a reaction to tissue injury (Heneka et al., 2015; Heppner et al., 2015; Querfurth and LaFerla, 2010; Wyss-Coray, 2006; Wyss-Coray and Rogers, 2012). The response is primarily localized and characterized by the infiltration and activation of immune cells due to the generation of inflammatory mediators. Both clinical and preclinical studies have provided evidence that inflammatory pathways are activated in diabetes and AD (Donath, 2014; Donath and Shoelson, 2011; Heneka et al., 2015; Heppner et al., 2015; Querfurth and LaFerla, 2010; Wyss-Coray, 2006; Wyss-Coray and Rogers, 2012).

The contribution of inflammation to the progression of AD has been recognized for over a decade. Indeed, elevated levels of several mediators of the innate immune response, such as components of the complement system and pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), are increased in the AD brain (Akiyama et al., 2000). Additionally, reactive glia are a common feature of the AD brain, with both microglia and astrocytes observed surrounding Aβ plaques, and the dominant source of innate immune mediator production in the brain (Querfurth and LaFerla, 2010). The inflammatory response found in AD is largely considered a response to the deposition of Aβ because a number of studies have demonstrated the activation of the innate immune system in response to various forms of Aβ (Dhawan et al., 2012; Lue et al., 2001), although other inflammatory triggers have also been associated with inflammation within the AD brain.

The pathogenesis of diabetes mellitus, particularly DT2, has also been highly associated with excess immune system activation. Several studies have documented elevated levels of specific acute phase inflammatory products, including interleukin-6 (IL-6) and C-reactive protein, in the blood of DT2 patients (Freeman et al., 2002; Pradhan et al., 2001). As such, accumulating preclinical evidence suggests a strong correlation between overt systemic immune activation and insulin resistance (Pickup et al., 1997). For example, studies involving obese animal models have demonstrated a direct link between the immune mediator TNF-α and the onset of obesity-linked insulin resistance, with high levels of the mediator being overexpressed within adipose tissue (Hotamisligil et al., 1994; Hotamisligil et al., 1993).

To investigate overt inflammation as a potential link between diabetes and AD, Takeda et al. created a dual model of DT2 by crossing an AD transgenic model with the ob/ob obesity mouse model, or the NSY DT2 mouse model. The results from one such study showed increased levels of cerebrovascular inflammation, along with vascular Aβ, in AβPP/ob/ob mice (Takeda et al., 2010). More specifically, the authors reported an increase in the expression of the receptor for advanced glycation end-product (RAGE) in microvessels, which was observed before the deposition of any cerebral Aβ. Increases in the ligands for RAGE and AGEs represent

a feature commonly observed in both AD and DT2 patients (Sasaki et al., 2001; Valente et al., 2010). Furthermore, the authors also found elevated levels of TNF-α and IL-6 within brain microvessels of the double transgenic AβPP/ob/ob mice. A similar increase in IL-6 was observed in AβPP/NSY mice after being on a high-fat diet. Corroborating the results observed in AβPP/NSY mice, other studies have found that AD mice kept on a high-fat diet show signs of increasing overt inflammation. In one study, in which 3xTg-AD mice were given a high-fat diet, a significant increase in microgliosis was observed after a 9-month treatment regimen (Knight et al., 2014). As such, the results from preclinical assessments of AD and diabetes models support a crucial role for inflammatory pathway activation in the pathogenesis of both diseases, and cross-analysis using a dual model approach shows a significant interaction between AD and diabetes in areas specific to immune system function.

5. Structural changes in brain regions associated with learning and memory processes in diabetes and Alzheimer's disease

Regions of the brain associated with learning and memory can be disrupted by acute exposure to pathological factors or show a gradual decline in functionality and alterations in structure with age (Hakun et al., 2015; Sacktor et al., 2002; Salthouse, 2010). However, both diabetes and AD have been shown to produce robust changes in brain regions associated with learning and memory well beyond what would be expected from normal aging (summarized in Table 3). Indeed, many brain structures involved in learning and memory formation, such as the hippocampus and entorhinal cortex, contain a high density of insulin receptors. Obstruction of insulin signaling within these regions can result in cognitive dysfunction due to disruptions in learning and memory formation (Dou et al., 2005; Zhao and Alkon, 2001). Furthermore, epidemiological studies using neuroimaging techniques have shown that diabetes is associated with reduced hippocampal and cortical volume (Moran et al., 2013; Roberts et al., 2014). Diabetes is not associated with only structural changes in the brain, however, because diabetic patients have also been shown to develop functional deficits in neuronal connectivity within brain areas susceptible to AD (Chen et al., 2014; Hoogenboom et al., 2014). In a study by Cui et al., diabetic patients exhibited decreased spontaneous brain activity within the postcentral gyrus (Cui et al., 2014). In another study by Marder et al., researchers used functional MRI during a series of encoding and recognition cognitive tasks to demonstrate that diabetic patients show reduced activation of the dorsolateral prefrontal cortex during learning encoding (Marder et al., 2014). Together, these studies suggest that the pathology associated with diabetes can lead to neuronal loss within areas of the brain associated with AD pathology, as well as cause aberrant functional connectivity between pathways critical to cognition.

Table 3
Structural changes in diabetic and AD brain patients. (Abbreviations: AD = Alzheimer's disease; AGEs = Advanced glycation end-product; APOE = apolipoprotein E; DM = Diabetes mellitus; FA = Fatty acids; IGF = Insulin-like growth factor; IRS = Insulin receptor substrate; MCI = Mild cognitive impairment; PUFA = Polyunsaturated fatty acids; T2DM = Type 2 diabetes mellitus.) (Arvanitakis et al., 2004; Craft et al., 2012; Crane et al., 2013; Fonteh et al., 2014; Fukazawa et al., 2013; Hsu et al., 2011; Janson et al., 2004; Liu et al., 2009b; MacKnight et al., 2002; Morris et al., 2014b; Ott et al., 1999; Steen et al., 2005; Talbot et al., 2012; Valente et al., 2010; Wahlqvist et al., 2012).

Patient/sample #	Study conclusion	Reference
126	A diabetes attributable risk for dementia of 8.8% suggests that diabetes may have contributed to the clinical syndrome in a substantial proportion of all dementia patients	Ott et al. (1999)
5574	No association between DM and incident of AD, even though diabetes was associated with incident vascular cognitive impairment	MacKnight et al. (2002)
824	Diabetes mellitus may be associated with an increased risk of developing AD and may affect cognitive systems differentially	Arvanitakis et al. (2004)
238	These data support the hypothesis that patients with AD are more vulnerable to type 2 diabetes and the possibility of linkage between the processes responsible for loss of brain cells and beta-cells in these diseases	Janson et al. (2004)
54	Reduced CNS expression of genes encoding insulin, IGF-I, and IGF-II, as well as the insulin and IGF-I receptors, suggests that AD may represent a neuro-endocrine disorder that resembles a distinct from DM	Steen et al. (2005)
511	Exploratory analyses suggested that APOE epsilon4 non-carriers exhibited cognitive and functional improvement in response to rosiglitazone, whereas APOE epsilon4 allele carriers showed no improvement and some decline was noted	Risner et al. (2006)
36	These results suggest that T2DM may contribute to the increased risk for AD by impairing brain glucose uptake/metabolism and, consequently, down-regulation of *O*-GlcNAcylation, which facilitates abnormal hyperphosphorylation of tau	Liu et al. (2009b)
31	The results suggesting that AGEs may promote the generation of an oxidative stress vicious cycle, which can explain the severe progression of patients with both DM and AD	Valente et al. (2010)
127,209	T2DM increases the risk of dementia more than 2-fold. Treatment with sulfonylureas may decrease the risk of dementia, as does metformin; together, these 2 treatments decrease the risk of dementia in T2DM patients by 35% over 8 years	Hsu et al. (2011)
104	The results support longer trials of intranasal insulin therapy for patients with amnestic mild cognitive impairment and patients with AD	Craft et al. (2012)
138	Brain insulin resistance in AD patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline	Talbot et al. (2012)
762,753	The incident AD risk is increased by 2.6-fold in T2DM, and the combination of sulfonylurea and metformin minimizes this risk	Wahlqvist et al. (2012)
2,067	The results suggest that higher glucose levels may be a risk factor for dementia, even among persons without diabetes	Crane et al. (2013)
175	The clinical features of subjects with AD associated with DM may differ depending on brain imaging patterns. Among them, there may be a dementia subgroup with characteristics predominately associated with DM-related metabolic abnormalities	Fukazawa et al. (2013)
139	Altered FA levels reflect the importance of abnormal metabolism and oxidative pathways in AD, and suggests that disturbed PUFA metabolism contributes to AD pathology	Fonteh et al. (2014)
264	Subjects with normal glycemia at baseline had less functional and global cognitive decline over 2 years than subjects with impaired glycemia. Subjects with normal glycemia also lost less whole brain volume and exhibited lower conversion from MCI to AD	Morris et al. (2014a,b)

Although the degree to which diabetes can affect brain structure and functionality remains unclear, AD onset and progression have been strongly linked to changes in brain structure and functionality. A number of studies have mapped the dynamic spreading of neuronal loss within the brains of AD patients. The loss, preferentially affecting frontal-temporal and limbic cortices, has been long associated with the buildup of Aβ and tau pathology (Devanand et al., 2012; Thompson et al., 2003). AD is also associated with functional deficits in neuronal networks important for learning and memory. These functional abnormalities are first present in MCI, affecting temporal cortical regions, the posterior cingulate cortex, and the hippocampal formation, and spread to additional regions as the disease progresses (Chhatwal and Sperling, 2012; Putcha et al., 2011; Rombouts et al., 2005). Thus, based on neuroimaging studies in human patients over the years, a detailed map of the pattern of the functional and structural changes that occur as AD progresses has been well established. What remains to be determined are the factors that initiate the observed neurodegenerative changes and whether the functional and structural changes elicited by diabetes may contribute along with more classically recognized AD pathology.

Few studies have focused on the direct association between diabetes-mediated brain atrophy and subsequent conversion to MCI or AD based on neuroimaging. One such study by Dr. Fukazawa's lab reported that a dementia subgroup within AD patients presented characteristics predominantly associated with diabetes-related metabolic abnormalities (Fukazawa et al., 2013). Whether this subgroup represents a direct effect by diabetes remains unknown, and further study is needed to determine the degree to with brain deficits elicited by diabetes might initiate or exacerbate the pathology of AD.

6. Anti-diabetic agents as a treatment for Alzheimer's disease

Given the extensive preclinical evidence demonstrating a causative link between insulin signaling dysfunction and select pathological mechanisms of AD, one could hypothesize that a drug designed to combat diabetes could potentially be useful in treating AD. Indeed, several epidemiological studies have examined the effect of anti-diabetic drug treatment on individuals with both AD and DT2.

One of the most commonly used anti-diabetic drugs is metformin. Metformin acts by reducing serum glucose levels via several different mechanisms but most notably through non-pancreatic mechanisms that do not greatly increase the amount of insulin secretion (Kickstein et al., 2010; Kirpichnikov et al., 2002). In two recent epidemiological studies comparing patients with DT2 who received metformin and sulfonylurea (another common anti-diabetic drug that works by stimulating beta-cells to release more insulin) with patients who received no anti-diabetic treatment, the metformin and sulfonylurea combined regimen was found to greatly decrease the risk of dementia onset (Hsu et al., 2011; Wahlqvist et al., 2012). In contrast, metformin treatment alone was found to increase the risk of AD onset in a separate epidemiological study (Imfeld et al., 2012). Metformin treatment is not without complication; prolonged use has been associated with some side effects (Kahn et al., 2006). As such, more research looking into the effectiveness of metformin on AD outcome is needed.

As previously mentioned, intranasal insulin administration can improve memory function in both human and animal studies, particularly hippocampal associated memory because the hippocampus contains a high density of insulin receptors (Benedict et al., 2004, 2008; McNay et al., 2010). Based on the observation that individuals suffering from AD have detectable disruptions in brain insulin signaling, several studies have tested intranasal insulin as

Table 4
Anti-diabetic compound as a treatment for AD (Abbreviations: intraperitoneal i.p.; subcutaneous s.c.). (Bomfim et al., 2012; Chen et al., 2015; Gao et al., 2014; Hansen et al., 2015; Kickstein et al., 2010; Kosaraju et al., 2013a,b; Long-Smith et al., 2013; McClean and Holscher, 2014a,b; Parthsarathy and Holscher, 2013; Vandal et al., 2014).

Animal Model	Mechanism	Reference
Human tau mice and metformin (2.5 mM)	Metformin induces protein phosphatase 2A (PP2A) activity and reduces tau phosphorylation at PP2A-dependant epitopes, independent of AMPK activation	Kickstein et al. (2010)
APP/PS1 mice and Exendin-4 (25 nmol/kg, i.p. injections for 8 weeks)	The anti-diabetic agent, exendin-4 (exenatide), decreases hippocampal IRS-1pSer and activated JNK levels, thereby preventing Alzheimer's-associated Aβ oligomers induced impaired IRS-1 signaling, and subsequently improving cognition	Bomfim et al. (2012)
APPswe/PS1dE9 and Liraglutide (25 nmol/kg, i.p. injection for 8 weeks)	Liraglutide treatments significantly decrease the levels of IRS-1pS(616), amyloid plaques load and glia cells associated to amyloid loads (astrocytes and microglia)	Long-Smith et al. (2013)
Intracerebral-ventricular STZ injection (3 mg/kg) and geniposide (50 μM)	Geniposide treatment reduced tau phosphorylation via reduction of GSK3β, and prevented STZ-induced spatial learning deficits	Gao et al. (2014)
Intracerebral STZ injection (3 mg/kg twice) and Vildagliptin (2.5, 5 and 10 mg/kg injections for 30 days)	Vildagliptin treatments lower STZ-induced amyloid load, tau phosphorylation, and inflammation in the brain, reversing STZ-associated cognitive deficits	Kosaraju et al. (2013a,b)
Intracerebral-ventricular STZ injections (3 mg/kg twice) and Saxagliptin treatment (0.25, 0.5 and 1 mg/kg for 60 days)	Saxagliptin, a DPP-4 inhibitor, mitigates Aβ, tau phosphorylation and inflammatory markers, resulting in marked reversal in behavioral and cognitive deficits associated with AD	Kosaraju et al. (2013a,b)
APPswe/PS1dE9 mice treated with liraglutide (25 nmol/kg, i.p. for 2 months)	Liraglutide reverse synaptic and memory deficits and reduce Aβ plaque load in APPswe/PS1dE9 mice by increasing degrading enzyme levels (IDE)	McClean and Holscher (2014a,b)
APP/PS1 mice and liraglutide (25 nmol/kg, injected i.p. for 37 days)	Acute and chronic treatments of liraglutide increase neurogenesis in APP/PS1 mice	Parthsarathy and Holscher (2013)
3xTg-AD mice treated with high-fat diet and insulin	Insulin reverse high-fat diet induced Aβ accumulation and improves cognition in 3xTg-AD	Vandal et al. (2014)
APPse/PS1dE9 mice treated with Pioglitazone (10 mg/kg for 7 days)	Pioglitazone improve cognitive and synaptic function in APPswe/PS1dE9 transgenic mice by inhibition of cyclin-dependent kinase 5 (cdk5) activity	Chen et al. (2015)
SAMP8 mice and Liraglutide (100 or 500 μg/kg/day, s.c. for 4 months)	Liraglutide improve cognition and prevent hippocampal neuronal loss in a senescence-accelerated mouse model of Alzheimer's disease	Hansen et al. (2015)
APPswe/PS1dE9 mice treated with lixisenatide (1 or 10 nmol/kg, i.p. injection for 10 weeks)	Lixisenatide restore cognitive and synaptic function in APPswe/PS1dE9 mice by reducing Aβ pathology and inflammatory response	McClean and Holscher (2014a,b)

a potential therapy for AD (Benedict et al., 2011). In a study by Reger et al., the authors found that a single intranasal administration of insulin had a positive effect on declarative memory recall in apolipoprotein epsilon 4 (APOε4) negative AD patients and no improvement in APOε4 positive AD patients (Reger et al., 2006). In a separate pilot clinical trial, 40 AD patients and 64 MCI patients were treated with either intranasal insulin or vehicle for a period of 4 months. Comparisons between subjects revealed improved delayed memory and cognitive function in insulin-treated subjects (Craft et al., 2012). Such findings indicate that intranasal insulin could be a promising therapeutic for AD patients, particularly those with an APOε4 negative genotype.

Another class of anti-diabetic drugs is the peroxisome proliferator-activated receptor-γ (PPARγ) agonists. Peroxisome proliferator activated receptors are a subfamily of nuclear receptors that regulate gene expression in response to ligand binding, and to date, three isoforms have been identified (Berger and Moller, 2002). The third isoform, PPARγ, is expressed most abundantly in adipose tissue and is the target of a group of drugs known as the thiazolidinediones, which are approved for use as a glucose-lowering therapy for patients with DT2. Thiazolidinediones have also been studied as a potential treatment for AD. In a study by Watson et al., AD patients were given 4 mg daily of the thiazolidinedione rosiglitazone for a period of 4 or 6 months. Compared with control subjects, rosiglitazone-treated patients showed improved performance in memory recall and selective attention tasks (Watson et al., 2005). In a second study involving more than 500 AD patients, a 6-month treatment with 8 mg rosiglitazone was found to provide a significant improvement in cognitive performance, particularly in APOε4 negative individuals (Risner et al., 2006). Unfortunately, thiazolidinedione treatment has been associated with increased edema and congestive heart failure, and therefore, the current drug structures must be modified to reduce these negative side effects before further testing on AD patients can be conducted.

Moreover, multiple studies involving preclinical AD models have shown that several anti-diabetic drugs (Liraglutide, lixisenatide, exenatide, luteolin, pioglitazone, vidagliptin, etc.) diminish AD pathology and restore synaptic and cognitive function (summarized in Table 4) (Bomfim et al., 2012; Chen et al., 2015; Gao et al., 2014; Hansen et al., 2015; Kickstein et al., 2010; Kosaraju et al., 2013a,b; Long-Smith et al., 2013; McClean and Holscher, 2014a; McClean and Holscher, 2014b; Parthsarathy and Holscher, 2013; Vandal et al., 2014). Overall, these studies support the idea that both diabetes and Alzheimer's share multiple neuropathological mechanisms and that the use of anti-diabetic compounds represent a promising therapeutic strategy for AD patients.

7. Conclusion

The correlation between reduced glucose metabolism, as measured by PET using flurodeoxyglucose, and the onset of mild cognitive impairment (MCI) has been known for over a decade (Friedland et al., 1983; Mosconi, 2005). This association is so strong that AD is sometimes referred to as type 3 diabetes (Kroner, 2009). Similar reductions in brain glucose metabolism are an indication of insulin signaling dysfunction, which is a common feature of diabetic patients, particularly those with DT2. DT2 is also associated with impairments in cognitive function, although the mechanisms underlining DT2-mediated cognitive dysfunction are not fully understood. Extensive evidence suggests that patients with DT2 are at an increased risk of developing AD. Indeed, a number of clinical studies have found that more than three-fourths of AD patients have pre- or full DT2 (Janson et al., 2004). Therefore, over the past two decades, significant effort has been dedicated to identifying common pathological molecular mechanisms between AD and diabetes, particularly DT2, with the goal of better understanding the onset and development of both diseases.

Although epidemiological studies have been crucial in identifying potential links between diabetes and AD, animal models have proven to be valuable tools in elucidating the complex interactions between potential disease mediators. For instance, several factors that link diabetes to AD and vice versa have been identified, including, oxidative stress, formation of advanced glycation end-products (AGEs), and overt immune system activation. These factors represent common targets for both diseases. Therefore, some researchers have already begun to test anti-diabetic medications as potential AD therapeutics. As such, anti-diabetic approaches such as intranasal insulin delivery and anti-diabetic drugs such as PPARγ agonist have been tested in some pilot clinical studies. Although some gains have been made, several hurdles still remain to be cleared before an effective insulin-sensitizing treatment strategy for AD is realized.

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