

## REVIEW ARTICLE

# Neurodegeneration in type 2 diabetes: Alzheimer's as a case study

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**Abstract**

**Introduction:** Rigorous research in the last few years has shown that in addition to the classical mechanism of neurodegeneration, certain unconventional mechanisms may also lead to neurodegenerative disease. One of them is a widely studied metabolic disorder: type 2 diabetes mellitus (T2DM). We now have a clear understanding of glucose-mediated neurodegeneration, mostly from studies in Alzheimer's disease (AD) models. AD is recognized to be significantly associated with hyperglycemia, even earning the term "type 3 diabetes." Here, we review first the pathophysiology of AD, both from the perspective of classical protein accumulation, as well as the newer T2DM-dependent mechanisms supported by findings from patients with T2DM. Secondly, we review the different pathways through which neurodegeneration is aggravated in hyperglycemic conditions taking AD as a case study. Finally, some of the current advances in AD management as a result of recent research developments in metabolic disorders-driven neurodegeneration are also discussed.

**Methods:** Relevant literatures found from PubMed search were reviewed.

**Results:** Apart from the known causes of AD, type 2 diabetes opens a new window to the AD pathology in several ways. It is a bidirectional interaction, of which, the molecular and signaling mechanisms are recently studied. This is our attempt to connect all of them to draw a complete mechanistic explanation for the neurodegeneration in T2DM. Refer to Figure 3.

**Conclusion:** The perspective of AD as a classical neurodegenerative disease is changing, and it is now being looked at from a zoomed-out perspective. The correlation between T2DM and AD is something observed and studied extensively. It is promising to know that there are certain advances in AD management following these studies.

**KEYWORDS**

Alzheimer's disease, neurodegeneration, type 2 diabetes mellitus, type 3 diabetes

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## 1 | INTRODUCTION

Neurodegenerative diseases are generally characterized by cellular accumulation of misfolded proteins, ROS production due to mitochondrial dysfunction, and disruption of the autophagy machinery in neuronal cells. Alzheimer's disease (AD) despite being a neurodegenerative disease with a well-explored disease pathology is still of much interest to researchers. Conventional mechanisms of neurodegeneration in patients with AD include beta-amyloid (A $\beta$ ) plaque accumulation and tau protein neurofibrillary tangles formation in the brain, eventually leading to dementia and other behavioral problems, and ultimately to death. For a long time, these mechanisms were the focus of AD research, leading to a growing hope that effective drugs against AD would be discovered soon. Now, we understand that the changes leading to AD are also aging-related, genetic and inheritable, and thus are not easily reversible. Recent progress in AD research has demonstrated that there are several other external factors widely causing the emergence of AD pathologies, such as obesity, diabetes, brain injury, neurotoxicity, and infections (Dosunmu, Wu, Basha, & Zawia, 2007; Pugazhenthii, Qin, & Reddy, 2017). Although it has been more than a decade since the idea of diabetes mellitus as a causal disorder of many neuronal diseases originated, this link has been less explored (Seaquist, 2010). This oversight is likely due to inadequate methodologies and lack of appropriate testable models. Recently, this idea has gained momentum since increased AD pathology has been observed in AD patients with T2DM (Mehla, Chauhan, & Chauhan, 2014). These unconventional modes of AD emergence are likely to be lifestyle-related and may be controlled and even reversed if correctly targeted. Therefore, it is essential to focus research on the relationship between metabolic disorders and neuronal alterations resulting from such disorders, in order to unravel the molecular mechanisms behind it (Calvo-Ochoa & Arias, 2015). Here, we provide a concise review of diabetes-associated mechanisms of neurodegeneration and cognitive impairment, with an emphasis on the pathophysiology of AD.

## 2 | PATHOPHYSIOLOGY OF AD

### 2.1 | Classical AD pathology

Alzheimer's disease has been recognized as a deadly neurological disease since its discovery at the beginning of the 20th century by Dr. Alois Alzheimer and continues to be a significant neurodegenerative disease without a cure. It is a prominent cause of dementia in elderly people all over the world. According to the World Alzheimer Report 2015, there are approximately 46.8 million people worldwide diagnosed with dementia. In AD, irreversible neurodegeneration causes severe damage to the brain tissue and a reduction in size of the brain (Bernardes et al., 2017; Hannah, 1936). The term neurodegeneration refers to the progressive death of neurons due to multiple causes, some of which are widely explored as in the case of AD. Classically, AD is characterized by the accumulation of protein

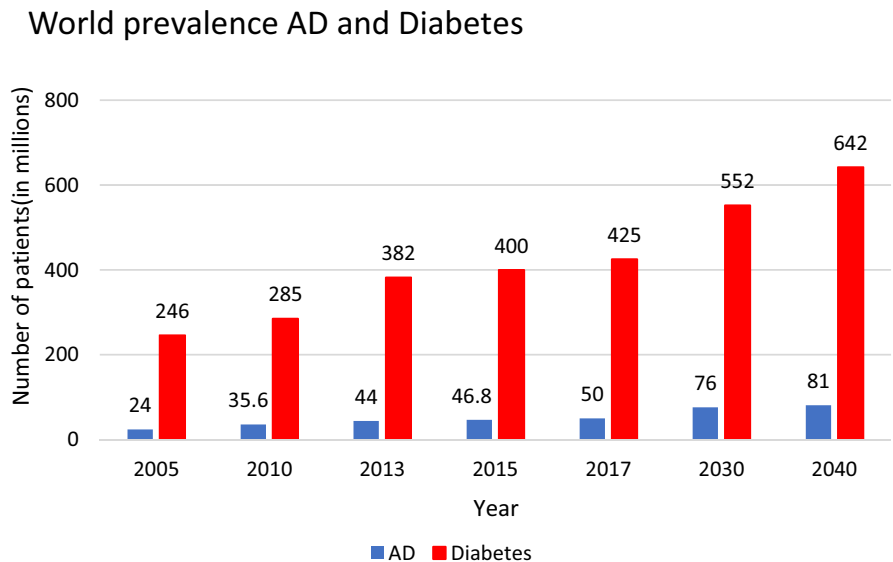
both intracellularly and extracellularly. The main culprit is the hydrophobic beta-amyloid (A $\beta$ ) peptide, secreted in the extracellular space after the proteolytic cleavage of a transmembrane glycoprotein amyloid precursor protein (APP) by beta-secretase followed by gamma-secretase enzymes (O'Brien & Wong, 2011). APP is a transmembrane protein and an integral part of synapses in the brain, while the soluble form of A $\beta$  has a crucial role in neuronal growth and survival in physiological conditions (O'Brien & Wong, 2011; Pearson & Peers, 2006). However, an imbalance in production and/or degradation of insoluble A $\beta$  peptides 40–42 amino acids in length and 4.2 kDa in size leads to its accumulation and polymerization, creating plaques that are detrimental to the cell (O'Brien & Wong, 2011). Another conventional mechanism of neurodegeneration in AD is the neurofibrillary tangles formed by aggregation of tau protein in the cytoplasm due to its misfolding after hyperphosphorylation. The normal physiological function of tau protein is to help stabilize the neuronal cytoskeleton (Mietelska-Porowska, Wasik, Goras, Filipek, & Niewiadomska, 2014). In patients with AD, aggregates of tau protein do not undergo degradation by autophagy, a protein degradation machinery, leading to continuous accumulation of this protein (Iqbal, Liu, Gong, Alonso, & Grundke-Iqbal, 2009). The deposition of tau eventually causes oxidative stress to the cell, and the production of reactive oxygen species (ROS) by the mitochondria results in the activation of apoptotic signals, leading to enhanced neuronal cell death (Iqbal et al., 2009; Liu et al., 2015). Since mature neurons cannot regenerate, degeneration of neurons leads to loss of connections between neurons which are crucial for memory retention. As a result, older adults with AD show various symptoms of dementia, such as confusion, difficulty in thinking, recognizing people, writing, speaking, and reading, as well as other behavioral problems (Ropper, 1979).

Currently, researchers are working on various aspects of the disease to elucidate complete molecular mechanisms, identify drug targets, and design early diagnostic tools and to plan effective AD management methods. Recent clinical studies have demonstrated a dramatic correlation between AD and metabolic diseases such as type 2 diabetes mellitus (ClinicalTrials.gov Identifiers: NCT02501876, NCT02360527, NCT03578991). Hence, AD is now recapturing the attention of neuroscientists as a possible complication of defective glucose metabolism (Bianchi & Manco, 2018).

### 2.2 | Diabetes: A new window to AD pathology

Diabetes mellitus is a lifestyle disease prevalent among people from all over the globe. It is a condition in which the glucose metabolism of the body is dysregulated, resulting in a high level of glucose in the blood. According to a recent report by International Diabetes Federation (IDF), the number of patients with diabetes in the world has increased from 108 million in 1980 to 425 million in 2017, indicating that every 11th person in the world is diabetic (Risk Factor Collaboration, 2016). These numbers probably underestimate the actual number of patients with diabetes, since one out of two people

**FIGURE 1** Graphical representation of the estimated number of AD and Diabetes patients worldwide. It shows a steady increase in the number of AD patients along with the huge increase in diabetic patients every year, indicating a strong correlation between them. The numbers for 2030 and 2040 are extrapolated from the current statistics. (Sources: IDF (International Diabetes Federation), ADI (Alzheimer's Disease International) and WHO (World Health Organization). Data points are the estimates reported in the websites of these organizations, and they are compiled and represented as a histogram for comparison)



remains undiagnosed in most developing countries. According to estimates by the World Health Organization (WHO), by 2030 developing countries like India will contribute five times more than developed countries to the prevalence of diabetes and diabetes-related deaths (Wild, Roglic, Green, Sicree, & King, 2004) (Figure 1). This could also be an indication of the alarming number of patients with AD in developing and underdeveloped countries, where unavailability of modern diagnostic techniques and new treatment strategies for AD are contributing to a major health crisis (Kalaria et al., 2008).

The cause for increased blood glucose levels in a patients with diabetes can vary based on which diabetes is classified into two major types: type 1 and 2 diabetes. Type 2 diabetes is the more common type. Type 2 diabetes mellitus (T2DM) can be due to insufficient insulin production by the pancreatic beta cells, or due to insulin resistance in the body. Insulin resistance is the inability of a cell to respond adequately to insulin signaling, resulting in decreased glucose uptake by the cell (Saini, 2010). Consequently, insulin-resistant cells die leading to severe complications and inefficient functioning of multiple organs. Diabetic stroke, hypertension, cardiovascular disease, kidney failure, and liver damage are some of them. Neurodegeneration has been recently added to this list (Harding, Pavkov, Magliano, Shaw, & Gregg, 2019). Notably, there are numerous studies on the association between neurodegenerative disease AD and T2DM (Jayaraman & Pike, 2014). Although such studies repeatedly emphasize the relation between AD and T2DM, it is important to note that diabetes-related risk factors are not sufficient to cause AD. However, they indeed promote AD pathology by triggering neurodegeneration by various mechanisms (Moroz, Tong, Longato, Xu, & De La Monte, 2008). In severe cases of T2DM, glucose toxicity in the brain is mainly due to oxidative stress triggered by amplified free radical formation and decreased free radical scavenging mechanisms (Tomlinson & Gardiner, 2008). Excessive glucose levels in the neuronal niche can cause lipid peroxidation, carbonylation of proteins, and DNA damage which causes irreparable harm to neurons (Ito, Sono, & Ito, 2019). High amounts of free radical

production are associated with inflammation. As a consequence of inflammatory pathway activation, metalloproteinases may damage blood-brain barrier (BBB) integrity and cause brain edema (Kamada, Yu, Nito, & Chan, 2007). Hyperglycemic conditions in the brain promote accumulation of lactic acid, which leads to intracellular acidosis and sequentially incites mitochondrial dysfunction and energy failure (Anderson, Tan, Martin, & Meyer, 1999).

Correlations between the pathology of AD and T2DM have been observed. Various studies using AD animal models have shown that diet-induced insulin resistance/chemically induced insulin signaling impairment increases AD pathology (Hascup et al., 2019; Mehla et al., 2014). This implies that insulin resistance in a patients with diabetes may lead to problems related to memory and cognition. There is also evidence to support the idea that patients with diabetes are more susceptible to develop AD (Cheng, Huang, Deng, & Wang, 2012). Researchers have postulated that diabetes could be a novel mechanism of neurodegeneration wherein the classical AD pathophysiology can be explained from the perspective of unregulated insulin/IGF (insulin-like growth factor) signaling and improper glucose metabolism. The diabetic brain starves because of insufficient expression of glucose transporters (mainly GLUT4) on the membrane of neurons without which glucose cannot be transported into the cells (Blázquez, Velázquez, Hurtado-Carneiro, & Ruiz-Albusac, 2014). This can result in oxidative stress in the mitochondria, causing neurons to degenerate by induction of apoptosis (Sripetchwandee, Chattipakorn, & Chattipakorn, 2018). On the other hand, impaired insulin/IGF signaling in the brain is also implied in hyperphosphorylation of tau protein by one of the many kinases (PI3K/Akt/MAPK) in the downstream of insulin signaling pathways. Disrupted regulation of any of these kinases in the diabetic brain can lead to tau hyperphosphorylation and accumulation, one of the hallmarks of AD (de la Monte, 2014; Plum, Schubert, & Brüning, 2005). After several clinical studies, the association between T2DM and AD has finally become well-established, although the molecular mechanism remains to be unveiled (Plum et al., 2005). A point to be noted regarding studies

using AD animal models is that patients with AD present with metabolic disorders and many symptoms of diabetes, which may not be fully represented by animal models (Chakrabarti et al., 2015). Close analysis and further studies are necessary to understand the possible bidirectional mechanism involved in mutually promoting AD and T2DM pathologies (Shinohara & Sato, 2017).

### 3 | MECHANISMS OF T2DM-DERIVED NEURODEGENERATION IN AD

#### 3.1 | Neurodegenerative role of Amylin

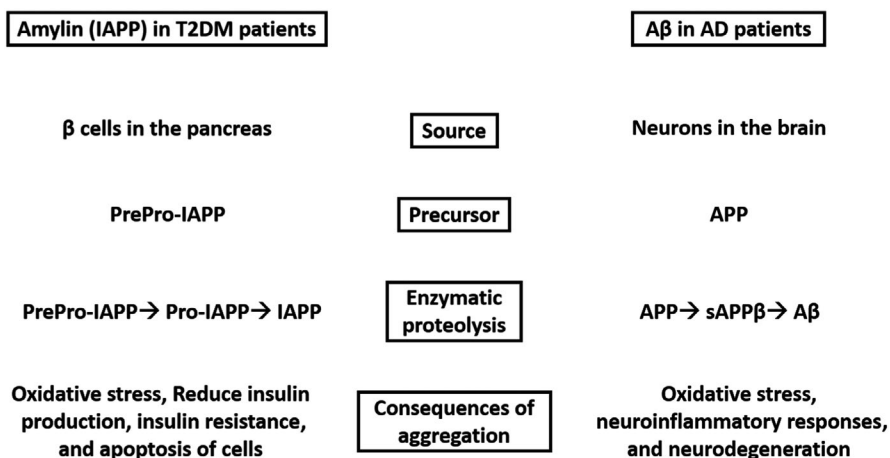
"Islet amyloid polypeptide" (IAPP) or "amylin" is a less understood peptide hormone synthesized and cosecreted along with insulin by the pancreatic  $\beta$  cells (Despa & DeCarli, 2013). It is produced in minute quantities when compared to insulin, but functions similar to insulin. Amylin has recently become a topic of focus in current AD research (Mietlicki-Baase, 2016). Amylin is structurally very similar to beta-amyloid (Lim et al., 2010). Like  $A\beta$ , amylin is also processed through multiple steps by proteolytic enzymes to finally form amylin or islet amyloid polypeptide (IAPP) (Akter et al., 2016; Nagamatsu, Nishi, & Steiner, 1991; Sanke, Bell, Sample, Rubenstein, & Steiner, 1988). Importantly, amylin aggregates have been noticed in the pancreatic islets of patients with T2DM (Mietlicki-Baase, 2016; Mitsukawa et al., 1990). It leads to apoptosis of  $\beta$  cells and thus a reduction in insulin production (Lutz & Meyer, 2015). Amylin deposition also contributes to insulin resistance and oxidative stress responses observed in these cells (Lutz & Meyer, 2015). Interestingly, amylin can also cross the BBB and amylin receptors are distributed in some parts of the CNS, as observed in the case of insulin and its receptors (Mietlicki-Baase & Hayes, 2014) (Figure 2). However, amylin accumulates in several peripheral organs of patients with T2DM as well, which explains the hyperamylinic condition in the diabetic brain (Jackson et al., 2013). Hyperamylinemia eventually leads to deleterious effects in the brain and enhances the symptoms of AD pathology (Lim, Ittner, Lim, & Götz, 2008). Thus, amylin is considered a pancreas-derived neuropeptide playing a crucial role in the

development of AD pathology in patients with T2DM (Jackson et al., 2013). Although the actual mechanism of amylin-mediated neurodegeneration is not completely known, attempts have been made to develop our understanding. One such study involves AD patients with T2DM and diabetic HIP (human islet amyloid polypeptide) rats (a new model for T2DM in which rats express human amylin in pancreatic islets). The study revealed that the accumulation of amylin- $A\beta$  complex in the brain of AD patients with T2DM activates the production of cytokines such as IL-1 $\beta$ , which in turn enhances neuroinflammatory immune responses leading to gradual degeneration of neurons (Verma et al., 2016). Amylin and its analogs are shown to interact and activate different downstream molecules in the insulin signaling pathway (Moon, Chamberland, & Mantzoros, 2012; Nassar, Badae, & Issa, 2018).

Parallel research exploiting the structural and biophysical similarities between amylin and beta-amyloid peptide has unearthed another fascinating finding that patients with AD significantly overexpress amylin receptors (Jhamandas et al., 2011). It is already known that  $A\beta$  and amylin can bind to the same receptor, which indicates a probable amylin receptor-mediated  $A\beta$  action in patients with AD (Nassar et al., 2018). In vitro studies have shown that blocking amylin receptors could mitigate the electrophysiological effects of  $A\beta$  and confer neuroprotection (Jhamandas et al., 2011). These studies provide the rationale for considering amylin receptors as a reliable novel therapeutic target for the treatment of AD.

#### 3.2 | Impaired insulin signaling in beta-Amyloid plaque formation and tau hyperphosphorylation

Insulin signaling is vital for several functions of the brain. Some of these include synaptogenesis, plasticity, neuroregeneration, learning, memory, neuritogenesis, and repair (Tumminia, Vinciguerra, Parisi, & Frittitta, 2018). Insulin also regulates APP metabolism in neurons (Plum et al., 2005; Tumminia et al., 2018). Hence, an imbalance in insulin signaling can reflect on the metabolism and processing of APP, which eventually leads to the accumulation of  $A\beta$  in the cell—a major cause for neurodegeneration in AD. As evidence for the



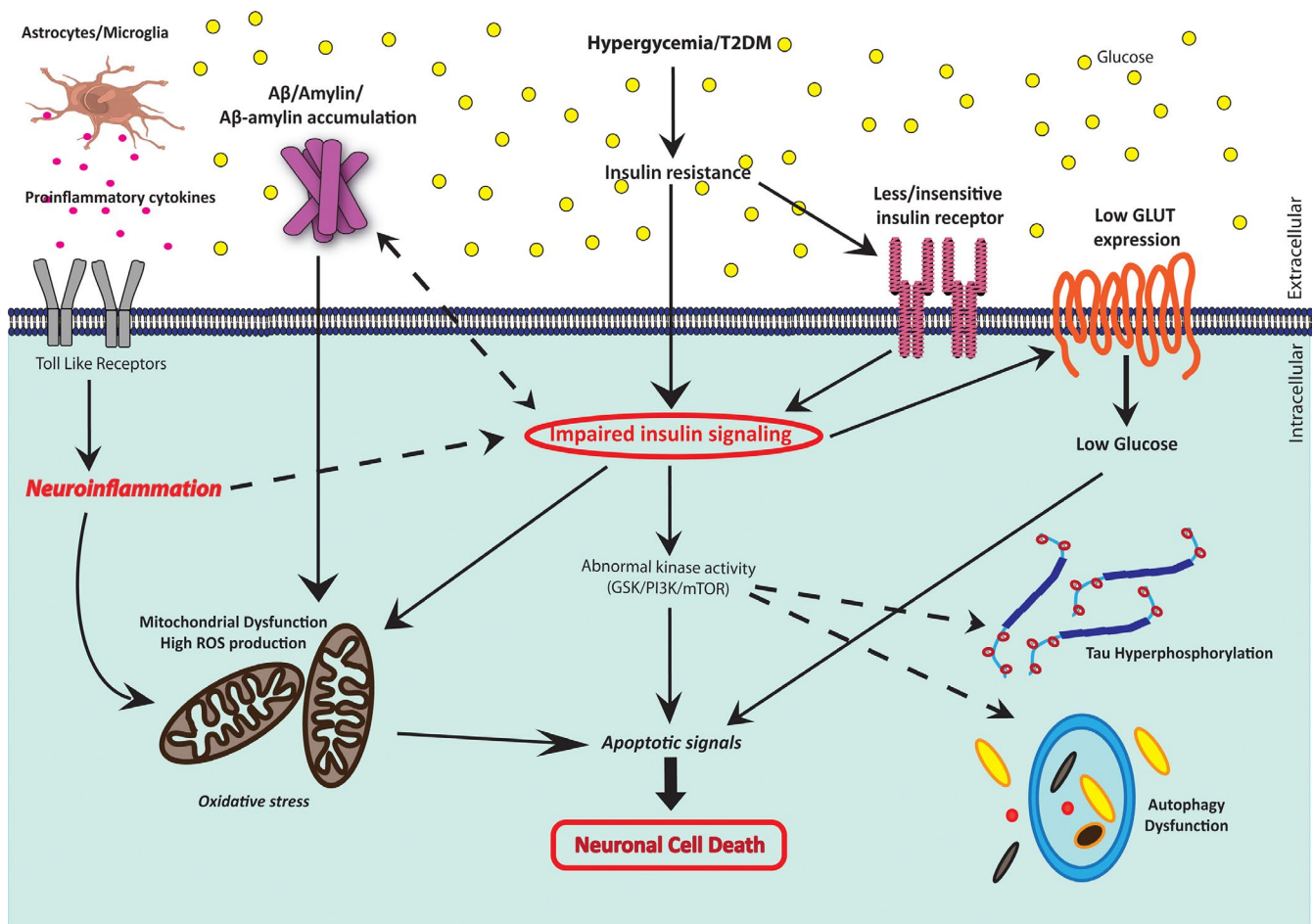
**FIGURE 2** Comparison between the role of amylin (IAPP) in T2DM patients and  $A\beta$  (beta-amyloid) in AD patients. It supports the fact that the dysfunction and accumulation of Amyloidogenic peptides are common causes for both the pathologies. Amylin is now considered as one of the prominent links in the molecular mechanism of glucose-mediated neurodegeneration

potential role of insulin signaling in neurodegeneration in AD, significantly reduced expression of insulin receptor (IR) has been observed in the brains of patients with AD (Frazier et al., 2019). Decreasing the intracellular accumulation of A $\beta$  by modulating insulin signaling is another strong indication of the vital role of insulin signaling in AD pathology (Craft, 2006). Interestingly, APP appears to be essential for maintaining healthy glycemic regulation. Studies using APP knockdown mice demonstrate that these mice develop metabolic disorders as well (Kulas et al., 2018).

Furthermore, hyperphosphorylation of the tau protein, one of the critical features of AD pathology is also increased due to impaired insulin signaling in the brain of patients with T2DM (Plum et al., 2005; Tumminia et al., 2018). Glycogen synthase kinase-3 (GSK-3) is an enzyme downstream to IR in the insulin signaling cascade, and its GS phosphorylating activity is downregulated by insulin. GSK-3 has been recently demonstrated to phosphorylate tau proteins. Thus, altered insulin signaling may modulate GSK-3 $\beta$  activity, leading to the hyperphosphorylated state of tau proteins observed in the brains of patients with T2DM (Frazier et al., 2019). The hyperphosphorylated tau proteins eventually get converted into neurofibrillary tangles, which is one of the key indications of neurodegeneration in AD.

### 3.3 | Neuroinflammation and defective insulin signaling

It is well-known that neuroinflammatory pathways can cause deleterious effects on neuronal cells. In the hyperglycemic condition, neuroinflammatory pathways can be induced in numerous ways (Refer to Figure 3). First, increased mitochondrial activity creates a stressful environment within the cell, thus enhancing ROS production which leads to the activation of inflammatory pathways. One of the other key features of T2DM is the overproduction of proinflammatory cytokines such as TNF- $\alpha$  and IL-6, in part due to hyperactivation of microglia and astrocytes, the immune cells of the brain (Bahniwal, Little, & Klegeris, 2017; Nasoohi, Parveen, & Ishrat, 2018). Persisting inflammation and abnormal levels of circulating cytokines that may even breach the BBB can be observed in patients with T2DM (Nasoohi et al., 2018). TNF- $\alpha$  promotes various stress-sensitive kinases which induce serine phosphorylation of IRS-1, an essential molecule in the insulin signaling cascade which is usually activated by phosphorylation at a tyrosine residue to propagate the insulin signal (Nasoohi et al., 2018). Thus, increased cytokine levels in the brain can lead to defective insulin signaling, which is one of the mechanisms through which



**FIGURE 3** Schematic representation of the different mechanisms involved in glucose-mediated neurodegeneration. Impaired insulin signaling is at the center in T2DM patients, which leads to various AD symptoms and then ultimately to the neuronal cell death

T2DM affects brain functions (Ferreira, Clarke, Bomfim, & Felice, 2014). It is clear that T2DM-induced chronic inflammation has a significant impact on the brain and is one of the important causal mechanisms of many neurological disorders such as AD and multiple sclerosis (MS) (Van Dyken & Lacoste, 2018). High levels of TNF- $\alpha$  in the cerebrospinal fluid (CSF) of patients with AD indicate that inflammation-induced impaired brain insulin signaling may be a major cause of insulin resistance observed in these patients. This implies that in patients with AD, impaired cerebral insulin signaling due to neuroinflammation may be a possible link between cerebral dysfunction and T2DM (Ferreira et al., 2014; Mehla et al., 2014; Nasoohi et al., 2018). Another mechanism by which hyperglycemia-induced neuroinflammatory pathways may affect the brain is through Toll-like receptor 4 (TLR4). TLR4 is highly expressed in all parts of the CNS and may be one more link between T2DM and AD (Huang, Jin, Zhou, Shi, & Jin, 2017). TLR4 signaling pathways are continuously active in diabetes, leading to insulin resistance. Although activation of TLR4 in the initial stages of AD helps remove A $\beta$  depositions, long-term activation appears to be detrimental to the brain. Chronic TLR4 activation causes chronic inflammation, which leads to diabetic neuropathy and AD (Huang et al., 2017).

### 3.4 | Cognitive impairment in T2DM

The CNS is one of the most important targets of insulin. Insulin receptors (IRs) are widely expressed in different parts of the brain, especially in the hippocampus. Insulin mediates metabolic homeostasis and regulates neurotrophic processes and synaptic plasticity of the brain (Calvo-Ochoa & Arias, 2015; Gudala, Bansal, Schifano, & Bhansali, 2013; Nguyen et al., 2018; Zhao, Chen, Quon, & Alkon, 2004). Earlier, *in vitro* studies using hippocampal cell cultures established a neuroprotective role for insulin (Duarte, Proença, Oliveira, Santos, & Rego, 2006; Stockhorst, Fries, Steingrueber, & Scherbaum, 2004). As mentioned before, insulin can activate PI3-K/Akt and S6K/mTOR kinase pathways which apart from regulating glucose metabolism also have a pivotal role in neuronal growth and synaptic plasticity (Calvo-Ochoa & Arias, 2015; Stockhorst et al., 2004; Zhao et al., 2004). Importantly, it has been observed that insulin can mediate the expression and recruitment of AMPA, NMDA, and GABA receptors in the postsynaptic cluster and control release of neurotransmitters such as acetylcholine and norepinephrine, all of which are directly related to the generation of long-term potentiation (LTP) needed for long-term memory in the hippocampus (Boyd, Clarke, Muther, & Raizada, 1985; Skeberdis, Lan, Zheng, Zukin, & Bennett, 2002; Van Der Heide, Kamal, Artola, Gispen, & Ramakers, 2005; Wan et al., 1997). Several transgenic and genetic T2DM models reported significant reduction in LTP, synaptic damage, decreased expression of neurotrophic factors, compromised BBB integrity, and neuroinflammation. These processes are associated with hippocampus-based cognitive impairment and memory deficit (Calvo-Ochoa & Arias, 2015).

Clinical findings and numerous epidemiological studies also support the beneficial role of insulin on cognition, and now, it is well-established that the insulin resistance associated with T2DM can also lead to vascular dementia (Skeberdis et al., 2002). Vascular dementia is a general term for the cognitive impairment associated with any metabolic disorder; in particular, diabetes-induced cognitive impairment is known as diabetic encephalopathy (DE). Furthermore, all these symptoms may eventually lead to the onset of AD. Evidently, all AD pathophysiology are well linked to insulin signaling and T2DM (Johnson, Torres, Impey, Stevens, & Raber, 2017). These studies indeed indicate the importance of insulin in cognitive functions, learning, and memory formation. Hence, when compared to nondiabetic individuals, patients with diabetes are at approximately 70% higher risk for the development of vascular dementia or AD (Gudala et al., 2013).

### 3.5 | Autophagy dysfunction and diabetes-induced AD

Autophagy is the catabolic degradation of misfolded or nonfunctional proteins and parts of damaged organelles (Calvo-Ochoa & Arias, 2015; Chen et al., 2019). Autophagy dysfunction is known to contribute to several neurodegenerative diseases, including AD (Calvo-Ochoa & Arias, 2015; Kiriya & Nochi, 2015; Komatsu et al., 2006). A $\beta$  accumulation and neurofibrillary tangle formation may be caused by the downregulation of autophagy in neuronal cells. Recently, it has been demonstrated that downregulation of autophagy is also associated with T2DM, which indirectly suggests that autophagy dysfunction could be another important mechanism by which it disrupts the homeostasis of neuronal cells and induces neurodegeneration (Kanamori et al., 2015; Wilson, Magnaudeix, Yardin, & Terro, 2014). The PI3K/mTOR pathway has an essential role in the regulation of autophagy, which is disrupted in conditions such as insulin resistance and/or impaired insulin signaling (Calvo-Ochoa & Arias, 2015). Researchers are also interested in finding new therapeutic targets using knowledge of the shared mechanisms of disease pathology between AD and T2DM. Pharmacological autophagy induction could be a viable therapeutic strategy not only for AD but for many other neurodegenerative diseases (Chen et al., 2019; Friedman, Qureshi, & Yu, 2015).

### 3.6 | Involvement of cell adhesion molecules in glucose transport and AD

Prion protein (PrP<sup>c</sup>) is a neuronal membrane protein involved in cell-cell adhesion and intercellular communication. Prion has been shown to interact with beta-amyloid and is thus suspected to have a significant role in AD-related pathologies (Jarosz-Griffiths, Noble, Rushworth, & Hooper, 2016). Interestingly, prion antagonists are currently being used effectively to reduce the neurotoxic effects of the prion- $\beta$ -amyloid interaction and cognitive deficit in

AD models (Sagare, Sweeney, Nelson, Zhao, & Zlokovic, 2019). Recently, correlations have been observed between prion protein (PrPc) and its modulatory effect on intracellular iron levels in various cell types including neuronal cells. Intracellular iron overload is considered a risk factor for diabetes. Imbalance in iron homeostasis in diabetes results in beta cell failure and insulin resistance, which are the hallmarks of T2DM (Simcox & McClain, 2013). The underlying molecular mechanism is not clear, but it has been observed that iron overload in diabetes induces hypoxia and ROS production, which leads to beta cell damage and decreased insulin gene expression (Kaneto, Katakami, Matsuhisa, & Matsuoka, 2010; Walter et al., 2002). Also, hypoxia-inducible factors (HIF) may downregulate GLUT1 and GLUT2 expression, thus enhancing hypoglycemic conditions in the cell. In brief, apart from oxidative stress due to HIF and ROS, iron overload may induce glucose-mediated neurodegeneration (Merelli et al., 2018). A role for prion in glucose uptake of the cell by altering the GLUT2 expression has also been reported, which indicates that prion can indirectly affect glucose metabolism (Ashok & Singh, 2018).

## 4 | CURRENT RESEARCH ADVANCES AND AD MANAGEMENT

Both AD and T2DM are called amyloidoses because of the overlapping mechanisms noted between them, as discussed above. Currently, very few FDA approved drugs are available for the treatment of AD, and these are only partially effective in preventing further deterioration of the condition. Therefore, at present, the main goals of AD researchers are to find new drugs for designing better treatment strategies and to investigate newer therapeutic targets to reverse AD pathology. Brain insulin resistance and reduced glucose uptake by neuronal cells due to ineffective insulin signaling are some of the common pathophysiological mechanisms observed in all neurodegenerative processes, and hence, novel research advances in this direction will be widely appreciated (Griffith, Eid, Rose, & Patrylo, 2018; Kim & Feldman, 2015).

### 4.1 | Insulin sensitizers for AD treatment

Soon after the association between neurodegeneration and T2DM was established, the idea of using insulin as a therapy for neurodegenerative diseases emerged (Kim & Feldman, 2015). Thus, insulin therapy was developed to improve cognition and delay the onset of memory loss and confusion in patients with AD (Chapman, Schiöth, Grillo, & Benedict, 2018). In most cases of patients with T2DM, insulin signaling is impaired or the cell is insensitive to insulin (insulin resistance). To treat this, insulin sensitizers are used (Ye, Luo, Xiao, Yu, & Yi, 2016). Some of the commercially available, famous insulin sensitizers are Metformin and Thiazolidinediones (TZDs). Interestingly, these insulin sensitizers have shown therapeutic potential against AD, which soon

came to be known as type 3 diabetes (De La Monte & Wands, 2008; Moreira, Campos, & Soldera, 2013). In order to analyze the effects of commercially available insulin sensitizers on AD, researchers have used them to restore glucose metabolism in the brain of AD mouse models and demonstrated that these drugs are effective in overcoming AD symptoms by attenuating neuroinflammation and tau hyperphosphorylation (Yu et al., 2015). Metformin is one of the well-known drugs for maintaining glycemic control in patients with T2DM. It was recently reported as a potential therapeutic for AD as it improves cognitive performance and decreases the chances of developing diabetic encephalopathy (Hsu, Wahlqvist, Lee, & Tsai, 2011; Ng et al., 2014; De Oliveira et al., 2016; Pintana, Apaijai, Pratchayasakul, Chattipakorn, & Chattipakorn, 2012). In vitro and in vivo studies using diabetic mouse models have reported that metformin treatment improves autophagic clearance of hyperphosphorylated tau protein in patients with AD (Chen et al., 2019). This is indeed a promising step toward the generation of effective therapeutics targeting neurodegeneration in both AD and T2DM-associated early-AD patients.

### 4.2 | Neuroprotective role of Amylin

Amylin as discussed before is a relative new candidate in AD research. Currently, there are two controversial sides regarding the role of amylin in the brain. Apart from its neurodegenerative and neurotoxic effects, amylin has surprisingly shown some neuroregenerative and neuroprotective effects as well (Adler et al., 2014; Bharadwaj et al., 2017). Interestingly, when scientists investigated correlations between cognitive efficiency in patients with T2DM and amylin concentration, in the initial stages amylin deposition in the brain caused a detrimental effect, while in the later stages when the  $\beta$  cells failed, amylin had a beneficial role. It helped in A $\beta$  autophagic clearance, and an improvement in cognition was also observed (Grizzanti, Corrigan, & Casadesus, 2018; Patrick et al., 2019). In addition, various functions of amylin in the CNS have been discovered; improvement of glucose metabolism (Roth, 2013), relaxation of cerebrovascular structures (Edvinsson, Goadsby, & Uddman, 2005), and enhancement of neural regeneration (Trevaskis et al., 2010). Currently, amylin and amylin analogs are considered as potential therapeutic candidates for diabetes as well as for cognitive improvement in patients with AD (Grizzanti, Lee, Camins, Pallas, & Casadesus, 2016; Wang et al., 2017).

### 4.3 | Antidiabetic drugs and AD management

Although diabetes research is at its peak with several new antidiabetic drugs, advanced patient-specific stem cell transplant/therapy, and insulin therapy, we are yet far from identifying a permanent cure for the "silent killer" (Abdelalim, Bonnefond, Bennaceur-Griscelli, & Froguel, 2014). Patients with diabetes are also under the risk of

**TABLE 1** Antidiabetic drugs in clinical trials for neurodegenerative diseases

| Drug                     | Type  | Status  | Data availability statement   |
|--------------------------|---|---|---|
| Liraglutide              | GLP-1 analog  | FDA approved drug for T2DM and in phase IIb clinical trial (NCT01843075) (Batista et al., 2018; Femminella et al., 2019) for AD   | The data that support the findings of this study are openly available in PubMed at <a href="https://doi.org/10.1002/path.5056">https://doi.org/10.1002/path.5056</a> (Batista et al., 2018)   |
| Pioglitazone             | Peroxisome proliferator-activated receptor gamma (PPAR-gamma) agonist, thiazolidinedione insulin sensitizer | FDA approved drug for T2DM and in phase II clinical trial for AD (NCT00982202) (Galimberti & Scarpini, 2017; Geldmacher, Fritsch, McClendon, & Landreth, 2011)                        | The data that support the findings of this study are openly available in PubMed at <a href="https://doi:10.1001/archneuro.2010.229">https://doi:10.1001/archneuro.2010.229</a> (Geldmacher et al., 2011)  |
| Exendin-4 (or Exenatide) | GLP-1 agonist   | FDA approved for T2DM and in phase II clinical trial for AD and (NCT02847403) Parkinson's disease (NCT01174810) (Aviles-Olmos et al., 2013)   | The data that support the findings of this study are openly available in PubMed at <a href="https://doi.org/10.1172/JCI68295">https://doi.org/10.1172/JCI68295</a> (Aviles-Olmos et al., 2013)  |
| Lixisenatide/Adlyxin     | GLP-1 receptor agonist  | FDA approved drug for T2DM and in phase II clinical trial for PD (NCT03439943)  | The data that support the findings of this study are openly available in Clinical Trials at <a href="https://clinicaltrials.gov/ct2/show/NCT03439943">https://clinicaltrials.gov/ct2/show/NCT03439943</a> (Study to Evaluate the Effect of Lixisenatide in Patient With Parkinson's Disease n.d.) |
| Metformin                | Biguanide-Insulin sensitizer  | FDA approved drug for T2DM and in phase II clinical trial for AD (NCT00620191)  | The data that support the findings of this study are openly available in PubMed at <a href="https://10.1212/01.wnl.0000140292.04932.87">https://10.1212/01.wnl.0000140292.04932.87</a> (Luchsinger, Tang, Shea, & Mayeux, 2004)   |
| Telmisartan              | Telmisartan is an Angiotensin 2 receptor blocker  | FDA approved drug for hypertension and in phase III clinical trial (NCT00274118) for T2DM and in phase III clinical trial for AD (NCT00274118) (Cummings, Lee, Ritter, & Zhong, 2018) | The data that support the findings of this study are openly available in PubMed at <a href="https://doi.org/10.1016/j.trci.2018.03.009">https://doi.org/10.1016/j.trci.2018.03.009</a> (Cummings et al., 2018)  |

Sources: [clinicaltrials.gov](http://clinicaltrials.gov) and [druginfo.nlm.nih.gov](http://druginfo.nlm.nih.gov)

early onset of dementia and other age-related diseases such as AD. Recently, there have been many attempts to prevent the AD-like alterations induced by inflammation and oxidative stress in patients with T2DM. While some of them target cognitive improvement of patients with AD using commercially available antidiabetic drugs/insulin sensitizers, others explore the beneficial effects of glucose metabolism-related natural peptides or synthetic mimics/analogs of these natural peptides on neurodegeneration (Moreira et al., 2013). Glucagon-like peptide 1 (GLP-1), also known as incretin, is a hormone produced by enteroendocrine L cells that impacts food ingestion. It acts as a neuropeptide in the brain and also helps in glucose-stimulated insulin secretion from pancreatic islets. GLP-1 may regulate glucose metabolism and improve cognition, thus serving as a future treatment strategy for diabetes-associated AD. GLP-1 is generally considered to be neuroprotective and anti-inflammatory, as it works by attenuating neuroinflammation (Qin, Chong, Rodriguez, & Pugazhenth, 2016). Moreover, it is known to improve insulin sensitivity and promote neurogenesis (Bae & Song, 2017; Tai, Liu, Li, Li, & Hölscher, 2018). Fibroblast growth factor 21 (FGF21) also demonstrated similar effects on improvement of cognitive function after high fat and sugar diet (HFD)-induced cognitive dysfunction in mice, probably due to its anti-inflammatory properties (Wang et al., 2018).

Interestingly, GLP-1 receptor agonists commercially used for the treatment of T2DM, such as *lixisenatide* and *liraglutide*, have been tested on AD mouse models and shown to have neuroprotective effects. These drugs appear to reverse all the classical pathophysiologies of AD including strong LTP in the hippocampus, improving synaptic plasticity (Gault & Hölscher, 2008a), increasing number of synapses, and reduction in the A $\beta$  accumulation and neuroinflammatory responses (McClean & Hölscher, 2014a, 2014b). Along similar lines, extensive studies have been performed using glucose-dependent insulinotropic polypeptide (GIP), another less discussed peptide hormone which targets pancreatic islets enhancing beta cell growth and differentiation, and promoting insulin release (Gault, O'Harte, & Flatt, 2003). It also independently helps regulate blood glucose levels (Irwin et al., 2006) which makes it an attractive target for T2DM drugs. But because GIP is prone to degradation by proteases, it has a very short half-life in the bloodstream (Gault & Hölscher, 2008b; Irwin et al., 2006). Thus, the newer approach is to develop long-lasting GIP agonists to diminish the potential risk of cognitive impairment and neurodegeneration due to T2DM (Gault & Hölscher, 2008b). These recent developments toward designing an effective treatment strategy for neurodegenerative diseases have been summarized in Table 1.



## 5 | CONCLUSION

To date, only a total of five FDA (Food and Drug Administration)-approved drugs for treating AD are available, which indicates the level of complexity in addressing research problems among neurodegenerative diseases. This is partially because AD research in the last decade has mostly focused on conventional AD pathophysiology, which is not easily reversible. Moreover, it is evident that patients with T2DM are at a higher risk of developing AD symptoms, which is why the concept of metabolism-dependent neurodegeneration mechanisms is gaining importance. This concept enables researchers to study neurodegenerative diseases such as AD with an entirely different perspective, through the lens of a metabolic disorder. The overlapping mechanisms of AD and T2DM justify why AD must be considered as “type 3 diabetes.” This fresh perspective takes us toward an entirely different approach, which involves targeting insulin signaling, and glucose metabolism as a novel therapeutic strategy for AD. A greater understanding of the underlying mechanisms of T2DM-associated neurodegeneration will guide researchers to develop advanced AD management strategies. Thus, insulin sensitizers/insulin therapy and antidiabetic drugs are also among the latest focus of AD research.

In short, diabetes-related neurodegeneration is a challenging problem, which needs to be explored further. The progress in AD research in this direction is considerable; however, much needs to be done in the near future. This fresh perspective opens the window to promising new developments in the treatment of several neurodegenerative diseases, especially Alzheimer's disease. These striking parallels are a matter of concern, not only for scientists but also for the public, because of the alarming increase in the number of patients with diabetes all over the world. Thus, by exploring new knowledge about the pathogenesis of diabetes-associated neurodegeneration, we anticipate that scientists will develop more advanced and effective therapeutics in the near future.

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### CONFLICT OF INTEREST

Authors declare no conflicts of interest.

### AUTHOR CONTRIBUTIONS

JM wrote the manuscript and contributed Figures 1 and 2. GS wrote the manuscript and contributed Figure 3. VD wrote the manuscript and had full access to all data in the study.

### DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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