



## The Molecular Mechanism of Insulin Resistant and Glycogen Synthase Kinase 3β In the Progression of Alzheimer's disease In Type 2 Diabetes Mellitus Patients

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**Abstract:** Type 2 Diabetes mellitus (T2DM) is characterized by high blood sugar caused by a lack of insulin, insulin resistance, or both. It's linked to the onset of secondary problems, which can lead to a variety of co-morbidities. Recent research has found that diabetics are more likely to acquire cognitive impairment or dementia. Diabetes is linked to a number of neurological illnesses, including Alzheimer's disease (AD). Evidence of a relationship between diabetes and AD is growing. Insulin signalling disruption in the brain has been discovered, resulting in increased tau protein phosphorylation (hyperphosphorylation), a hallmark and diagnostic of AD pathology, and the buildup of neurofibrillary tangles (NFT). Insulin malfunction in the brain has been shown to modify glycogen synthase kinase-3β (GSK-3β) activity, resulting in increased β amyloid and tau phosphorylation in diabetics. GSK-3β signalling has been implicated in the physiological and pathological processes of diabetes and AD, respectively. This could explain why diabetic individuals have a higher chance of developing AD as their diabetes progresses and they get older. Interestingly, several in vivo investigations with oral antidiabetic medications and insulin treatment in diabetic patients showed improved cognitive function and lower tau hyperphosphorylation. The relationship between T2DM and AD as it relates to amyloid and tau pathology will be discussed in this article. A better knowledge of the relationship between T2DM and AD could transform how researchers and doctors handle both diseases in the future, potentially leading to new therapies and prevention techniques.

**Keywords:** Diabetes mellitus; Alzheimer's disease; Insulin resistance; GSK-3β; β amyloid; Tau protein.

### 1. INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is characterized by high blood sugar caused by a lack of insulin, insulin resistance, or both. It's linked to the onset of secondary problems, which can lead to a variety of co-morbidities. Recent research has found that diabetics are more likely to acquire cognitive impairment or dementia. Diabetes is linked to a number of neurological illnesses, including Alzheimer's disease (AD) (Talbot *et al.*, 2012; Chen *et al.*, 2014; Yaffe *et al.*, 2004; Mushtag *et al.*, 2014; Willette *et al.*, 2015). The most prevalent cause of dementia in the elderly is AD. Extracellular β amyloid (Aβ) containing senile plaques, intracellular hyperphosphorylated Tau containing neurofibrillary tangles (NFT), neuroinflammation, synapse loss, and neuronal death are all symptoms of AD. Aging and the allele of the apolipoprotein E 4 are both

known risk factors. T2DM has recently been identified as an additional risk factor for AD. T2DM and AD have comparable pathophysiologies, such as insulin resistance, altered glucose and lipid metabolism, inflammation, and oxidative stress, according to mounting data (Talbot *et al.*, 2012; Chen *et al.*, 2014; Yaffe *et al.*, 2004; Mushtag *et al.*, 2014; Willette *et al.*, 2015).

Once upon a time, the brain was supposed to be an insulin-insensitive organ. Insulin, on the other hand, is now universally acknowledged to play a significant role in neuronal survival and brain function. Insulin is essential for brain synaptic plasticity, which aids learning and memory (Chiu *et al.*, 2008). Insulin also promotes the production of dendritic spines and synapse, neural stem cell activation, neurite growth and repair, and neuroprotection (Apostolatos *et al.*, 2012). As a result, changes in insulin metabolism and signalling in the Central Nervous System (CNS) can play a role in the development of a variety of mental illnesses.

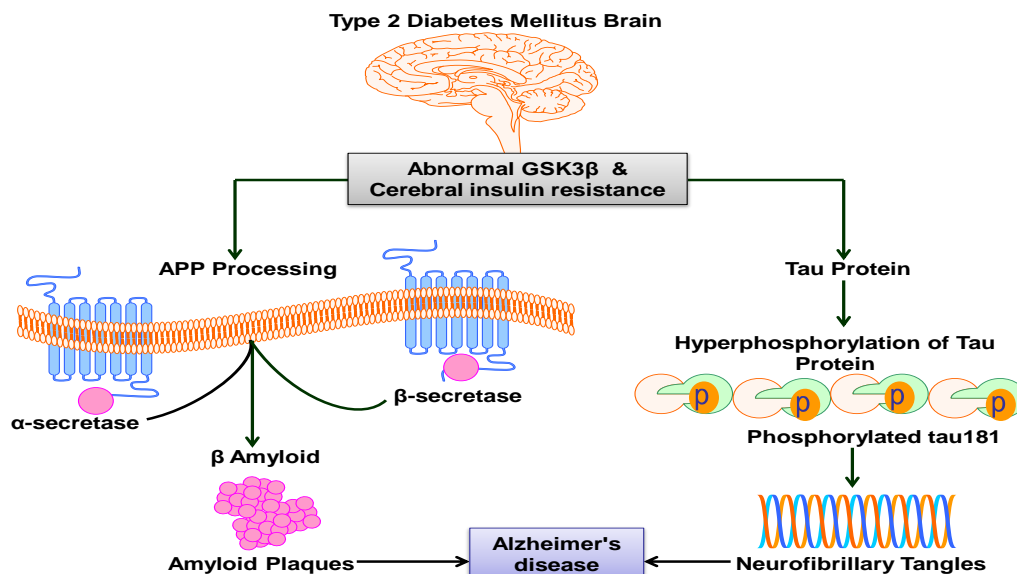
Many animal and clinical investigations have demonstrated a link between neurodegenerative illnesses like AD and altered insulin signalling in the central nervous system over the last 25 years (Kleinridders *et al.*, 2014; Biessels *et al.*, 2014), demonstrating that insulin resistance and decreased insulin activity may play a role in the aetiology of certain brain diseases through several pathways. Following that, we'll go over the primary pathophysiological links between AD and T2DM, emphasising the role of a malfunctioning insulin transduction pathway in neurodegenerative determinism. We'll look at how insulin signalling and Glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) play a role in the creation of intracellular neurofibrillary tangles (NFTs) and the deposition of A $\beta$  plaques, two hallmarks of AD pathology.

## 2. Molecular Mechanism of Insulin Resistant in Type 2 Diabetes Mellitus with Alzheimer's disease

Insulin resistance in the brain is becoming better recognised as a component in the development of AD. A robust link between insulin signalling and A $\beta$  metabolism has been discovered in several investigations. A $\beta$  oligomers, such as dimers, trimers, and dodecamers (A $\beta$  \*56), are particularly harmful in AD. GSK3 $\beta$  is activated by cerebral insulin resistance, resulting in an increase in A $\beta$  synthesis and Tau phosphorylation (Felice., 2013; Avrahami *et al.*, 2013; Phiel *et al.*, 2003). Insulin resistance was found to increase extracellular A $\beta$  deposition by increasing the activity of the enzyme  $\gamma$  - secretase, which is involved in A $\beta$  synthesis, and therefore encouraging A $\beta$  secretion from neurons (son *et al.*, 2012). Insulin, on the other hand, inhibits GSK3 $\beta$  activity, preventing the formation of A $\beta$  and hyperphosphorylated Tau (DaRocha-Souto *et al.*, 2012). The transgenic animals displayed hippocampus insulin resistance, according to studies employing transgenic AD mouse models (Bomfim *et*

*al.*, 2012). After being fed a high fat diet, leptin deficient mice, a T2DM model, showed altered brain insulin signaling and cognitive deficits (Gao *et al.*, 2015; Ramos-Rodriguez *et al.*, 2013). Insulin receptor substrate-1 (IRS-1) phosphorylation at serine residues, a hallmark of insulin resistance, was shown to be significantly increased in postmortem AD brains. Insulin resistance is also linked to a reduction in synaptic plasticity (Grillo *et al.*, 2015). In an AD animal model, insulin treatment reduced chronic neuroinflammation and microglia activation while also improving synapse formation (Adzovic *et al.*, 2015; Chen *et al.*, 2014). These investigations demonstrated links between AD, cerebral insulin resistance, and T2DM.

Figure 1 depicts a model that links between T2DM, cerebral insulin resistance, and AD pathogenesis. Through GSK3 $\beta$ , hyperinsulinemia, oxidative stress, and advanced glycation end products (AGEs), T2DM and the metabolic syndrome may exacerbate AD pathogenesis (Eldar-Finkelman *et al.*, 1997) Hyperinsulinemia in T2DM may impair A clearance through competitive inhibition of the insulin degrading enzyme (IDE), which is a key regulator of A $\beta$  levels in neural cells. Through a number of shared or contemporaneous pathways involving predisposing genes and environmental variables, brain insulin resistance may develop in tandem with T2DM. T2DM related hyperinsulinemia may cause brain insulin resistance by reducing insulin receptor expression and receptor kinase activity (Kim *et al.*, 2011) and, as a result, increasing A $\beta$  and tau pathology. Inversely, or even reciprocally, abnormal oligomeric or fibrillar A $\beta$  can cause brain insulin resistance. A $\beta$  has a similar sequence to insulin and can attach to the insulin receptor directly, causing insulin resistance (Xie *et al.*, 2002).



**Figure: 1**

### 3. Molecular Mechanism of GSK3β in Type 2 Diabetes Mellitus with Alzheimer's disease

GSK3β is a key regulatory kinase that plays a role in a variety of processes including glycogen metabolism, apoptosis, protein synthesis, cell signalling, cell transport, gene transcription, proliferation, and intracellular communication. Many substances linked to AD have been discovered to interact with it, including the microtubule-associated protein tau, presenilin 1, the Aβ peptide, amyloid precursor protein (APP), and acetylcholine. GSK3β may also have a role in brain ageing and lifespan (Vinothkumar *et al.*, 2021).

T2DM is caused by a lack of insulin secretion caused by islet β cell failure, which can be congenital or acquired. Although the specific mechanism is unknown, it could be linked to glucose toxicity, lipid toxicity, inflammatory response, oxidative stress, and other variables (Nolan 2014; Donath *et al.*, 2003; Robertson *et al.*, 2007). GSK3β is one of the primary mediators of islet β cell apoptosis, and it's linked to insulin insufficiency (Robertson *et al.*, 2004). Excessive activation of GSK3β resulted in a reduction in islet β cell proliferation in DM model mice (Liu *et al.*, 2008). Islet β cells are endocrine cells in the body that release insulin, which helps to regulate blood sugar levels. Endogenous GSK3β inhibits the PI3K/Akt signaling pathway, which controls islet β cell development, and therefore plays a key role in blood glucose regulation.

Insulin modulates the equilibrium between Aβ anabolism and catabolism via regulating peripheral Aβ and tau metabolism, which controls Aβ release in the brain through modulating APP metabolism (Suzanne, 2012). T2DM and AD may be linked by changes in Aβ production and degradation caused by insulin deficiency or action. Deficiencies in insulin dependent pathways may increase GSK3β activation, which has been linked to an increased risk of AD. In the context of Aβ toxicity, T2DM alters mitochondrial antioxidant mechanisms and supports brain weakening (Suzanne, 2012).

A previous clinical study found that hyperglycemia induced islet β cell loss is associated with increased oxidative stress, and that some enzymatic markers of oxidative stress are similar in mild cognitive impairment (MCI) and AD patients, implying that oxidative damage could be a key factor in the development of severe cognitive impairment (Padurariu *et al.*, 2010). According to studies, elevated oxidative stress causes APP cleavage and Aβ generation, and increased Aβ causes LPO levels (Butterfield., 1997; Tabner *et al.*, 2005). According to Grimes and Jope (2001), oxidative stress activates GSK3β in neuronal cells, while GSK3β inhibition regulates oxidative stress in neuronal hippocampus cell lines (Lee *et al.*, 2007). GSK3β and oxidative stress are linked, according to this discovery.

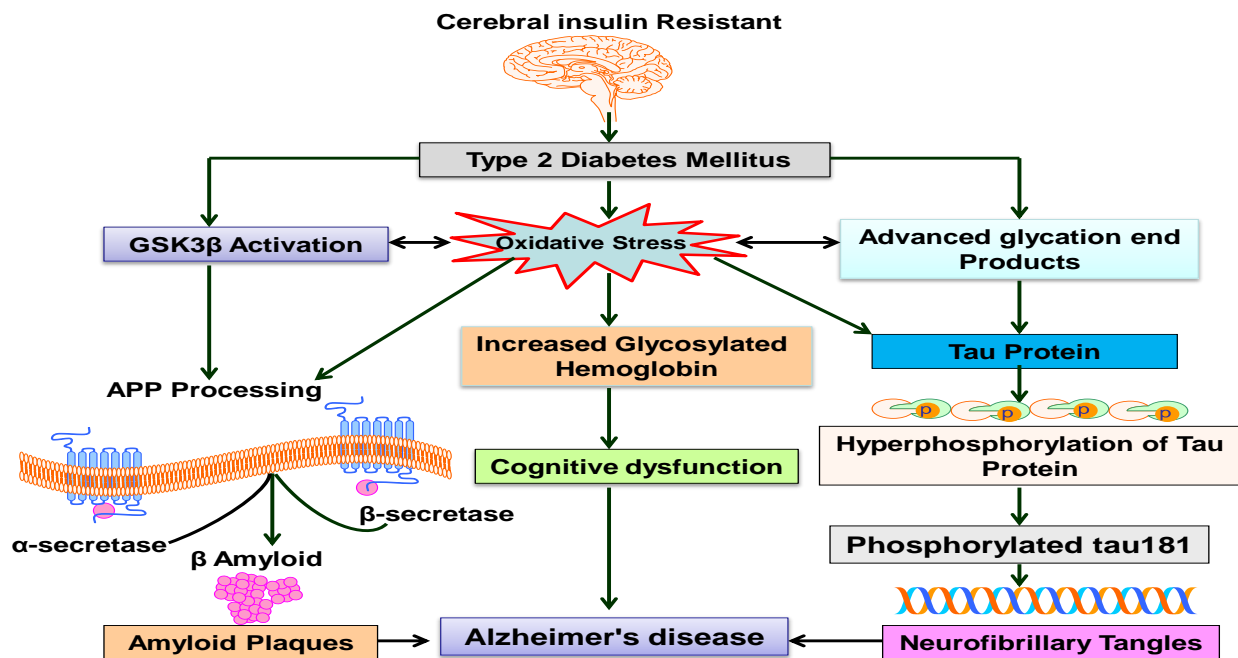


Figure: 2

### 4. CONCLUSION

We endeavoured to highlight the rising body of literature that portrays the shared pathophysiology of T2DM and AD, as well as expound on the underlying molecular pathways at the crossroads of these two diseases, in this review. GSK3β is the main rate limiting

enzyme for glycogen production suppression in T2DM. More significantly, it is one of the leading causes of insulin insufficiency and resistance, and insulin resistance is a hallmark of T2DM development and progression. GSK3β is involved in both hyperphosphorylation (NFT creation) and APP

metabolism (A $\beta$  generation) in AD. While insulin resistance in T2DM can generate A $\beta$  deposition, which is removed by tau, excessive tau phosphorylation can exacerbate A $\beta$  neurotoxicity, damage the brain, and impair cognitive function. GSK3 $\beta$  may not only be a promising therapeutic target, but also a key hint to overcoming the AD Mountain. T2DM with AD has the potential to deliver a multitude of preventative and therapeutic techniques to existing patients, despite the fact that the specific mechanisms connecting T2DM and AD remain convoluted and ambiguous, which may have disastrous socioeconomic repercussions on public health and healthcare systems. For the time being, it appears that more anti T2DM medications with positive benefits against cognitive impairment will be investigated.

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#### CRedit authorship contribution statement

**Balaji Vijayam:** Visualization, Investigation, Supervision.

**Taarika Balaji:** Data curation, Writing-original draft preparation.

**Madhuri S Balaji:** Methodology, Software and Validation.

**Seshiah Veerasamy:** Writing and Reviewing.

**Vinothkumar Ganesan:** Conceptualization, Writing-original draft preparation.

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