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RESEARCH ARTICLE
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A COMPREHENSIVE ANALYSIS OF TYPE 3 DIABETES: CONNECTING METABOLIC DYSFUNCTION WITH ALZHEIMER'S DISEASE

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Abstract-

Background-Insulin resistance, which affects neural transmission and energy metabolism, is one metabolic abnormality that is increasingly linked to Alzheimer's disease (AD). Amyloid-beta buildup, tau pathology, and neuroinflammation are all exacerbated by disruption of the insulin pathways in the brain. The idea of "Type 3 Diabetes" (T3D) was born because of these common characteristics. The purpose of this study is to examine the molecular connections between AD and insulin resistance and to highlight new treatment approaches.

Method-

Using PubMed, Scopus, Web of Science, and the Cochrane Library, a systematic review was carried out in compliance with PRISMA standards to find publications that were published between January 2010 and July 2025. "Diabetes Mellitus," "Insulin Resistance," "Alzheimer Disease," "Nerve Degeneration," "Cognitive Dysfunction," and other relevant clinical and biological keywords were among the search terms used. The final analysis contained 213 peer-reviewed articles after duplicates were eliminated and predetermined inclusion and exclusion criteria were applied.

Results-

A major pathogenic factor that has been repeatedly found to affect tau phosphorylation, amyloid-beta clearance, and brain glucose uptake is insulin resistance. Insulin signaling pathway disruption, particularly PI3K/Akt and GLUT4 translocation, has been linked to oxidative stress, neuroinflammation, and cognitive impairment. Transcriptomic evidence also demonstrated how non-coding RNA's, such as MEG3 and MALAT1, regulate insulin sensitivity and glucose homeostasis, connecting metabolic imbalance to neural dysfunction.

Conclusion-The idea of T3D is supported by the fact that insulin resistance and impaired glucose metabolism are key factors in the onset and progression of AD. There is encouraging neuroprotective potential when these pathways are targeted. Validating these therapies in extensive clinical trials should be the main goal of future research.

Keywords: Keywords Diabetes mellitus, Alzheimer disease, Insulin resistance, Nerve degeneration, Glucose metabolism disorders, Oxidative stress, Transcriptome.

INTRODUCTION

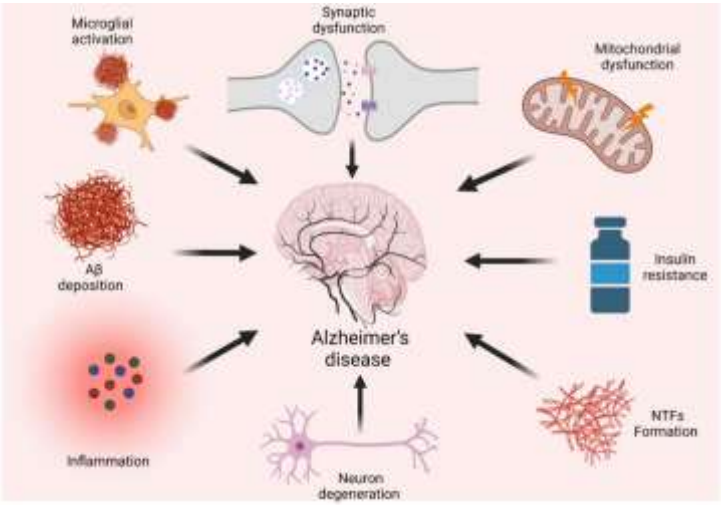
Over 400 million people worldwide suffer from diabetes mellitus (DM), an endocrine condition [1, 2]. The term "Type 3 Diabetes" (T3D) was coined in recent years when researchers discovered a strong connection between metabolic dysregulation and neurodegenerative disorders [3]. This phrase draws attention to a possible link between the onset of Alzheimer's disease (AD), insulin resistance, and poor glucose metabolism [4]. Investigating this connection is essential because it could lead to novel methods for the diagnosis, prevention, and treatment of both illnesses.

The main energy source for the human brain is glucose, and insulin is essential for controlling this process [5, 6]. Amyloid-beta (Aβ) plaques, neurofibrillary tangles, and chronic inflammation are some of the alterations linked to Alzheimer's disease that can occur when insulin transmission in the brain is interfered with [7].

At the same time, the metabolic imbalances seen in diabetes, such as high blood sugar, oxidative stress, and the production of harmful AGE's, or advanced glycation end products, are similar to the processes that lead to brain dysfunction [8,9]. These overlapping pathways raise the possibility that T3D is a distinct type of Alzheimer's disease caused by metabolic abnormalities rather than merely a metaphor. People with diabetes are more likely to acquire AD, and people with AD frequently have symptoms of impaired glucose metabolism, according to population studies [4, 10].

This two-way link indicates to deeper, common biology between the two conditions. However, the fundamental mechanisms remain poorly understood. Whether diabetes directly contributes to the pathophysiology of AD or if both conditions are caused by similar molecular and metabolic pathways is still unknown. Although earlier studies have made strides in identifying possible connections, the results are frequently dispersed, and there isn't a thorough synthesis that combines transcriptomic, clinical, and genetic information from many investigations. This draws attention to a significant gap in the literature. Consequently, a comprehensive review is necessary to compile existing knowledge, elucidate mechanistic overlaps, and evaluate emerging therapeutic strategies targeting this intersection.

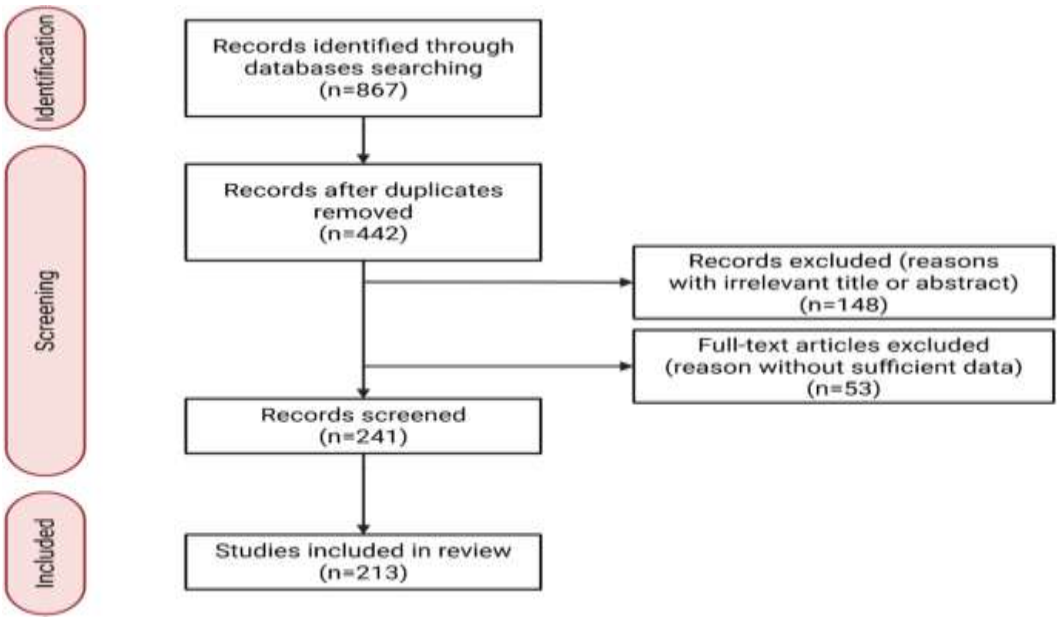
In order to address the concept of T3D, this systematic review synthesizes the available data on the molecular and metabolic connections between insulin resistance and AD. In particular, it looks at the roles that neuroinflammation, oxidative stress, and neuronal energy deficits play in AD pathogenesis, as well as how impaired insulin signaling, disrupted glucose metabolism, and regulatory non-coding RNAs contribute to this process. Additionally, it assesses the therapeutic potential of agents that target these shared mechanisms. Finally, this article aims to provide an integrated understanding of T3D as a bridge between metabolic dysfunction and neurodegeneration, as well as to direct future research directions and clinical interventions.



Scheme 1 A schematic illustration of multiple pathological mechanisms contributing to Alzheimer's complaint progression is shown in Scheme 1(as a graphical epitome). Multiple pathological mechanisms contribute to Alzheimer's complaint progression. The figure illustrates the major pathological processes involved in announcement, including microglial activation, synaptic dysfunction, mitochondrial dysfunction, insulin resistance, neurofibrillary distraction(NFTs) conformation, neuronal degeneration, inflammation, and amyloid- β(Aβ) deposit

Study selection process

867 potentially material studies were set up in the database after a primary hunt. The remaining 442 titles and objectifications were examined in agreement with destined eligibility criteria after 425 indistinguishable papers were excluded. The studies were chosen because they examined the molecular mechanisms that connect Alzheimer's complaint(also known as type 3 diabetes) to insulin resistance and metabolic dysfunction, with an emphasis on cellular relations, molecular pathways, and their neurobiological counteraccusations . We barred case reports, conference objectifications,non-peer-reviewed papers,non-English studies, those that only concentrated on clinical issues without mechanistic disquisition, and papers with inadequate data. Eventually, we included only original exploration, reviews, meta- analyses, cohort, cross-sectional, and clinical trial papers published in peer- reviewed journals, written in English, with clear methodological details, and conducted on humans or beast models(Fig. 1).



PRISMA flow diagram for the selection of included studies

Type 3 diabetes frequence in populations worldwide

Type 3 diabetes epidemiological substantiation According to a recent meta- analysis, people with Type 2 diabetes(T2D) are 59 more likely than people without diabetes to develop madness(10). 81 cases, or 24.4, had cognitive impairment in across-sectional descriptive study of 332 diabetes cases at Holy Family Hospital in Pakistan[11]. In a analogous tone, Mexican cases with type 2 diabetes were doubly as likely to witness madness as those without the complaint[12]. About 68 of diabetes individualities in Lebanon displayed symptoms of implicit cognitive impairment[13](Table 1).

Region	Sample Size	Percentage with Cognitive Impairment	Study Duration	Ref.
United States	14,988 (4,192 diabetic patients)	19.9%	22 years	[14]
Sacramento Area Latino	1,617 patients	9.8% (159)	10 years	[15]
Mexico	1,193 patients	Twice the risk compared to non-diabetics	3 years	[16]
Chile	358 patients	2.8 times higher risk in older T2DM	Oct. 2017 to Sep. 2019	[17]
Pakistan	332 patients	24.4% (81 patients)	6 months	[11]
Lebanon	318 patients	68.2% (217 patients)	5 months	[13]
South India	108 patients	41.70% (45 patients)	1 month	[18]

Disparities in age and gender

Dementia is largely caused by aging, and diabetes significantly exacerbates nerve damage, raising the chance of dementia [10]. The mental Compared to men, women with diabetes are more likely to experience disability [19]. However, compared to males, diabetic women demonstrated a considerably lower frequency of cognitive impairment and outperformed men on tests of cognitive function, especially memory [20]. In terms of age, dementia affects up to 24% of people over 75 and 16% of people with diabetes over 65 [21].

Ethnic and genetic influences on prevalence

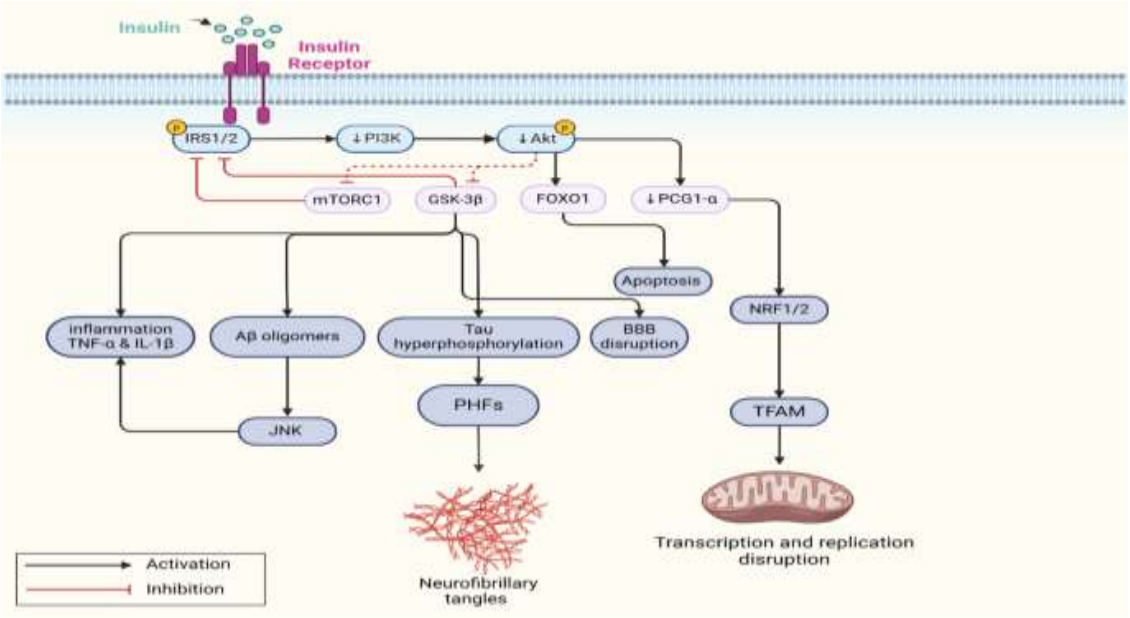
In an ADVANCE trial of 11,140 individuals with T2D from 20 countries, Participants of Asian ethnicity had greater chances of dementia or cognitive deterioration than non-Asians [22]. Similarly, ethnic-specific R192H polymorphism in PAX4 has been associated with attention-specific cognitive impairment in Chinese individuals with diabetes [23].

Table 2 provides an overview of the pathophysiology and molecular processes of type 3 diabetes.

Author	Molecular Mechanism/Pathway	Key Findings	Ref.
Pan et al.	PI3K/Akt Signaling Pathway	Impaired PI3K/Akt pathway leads to decreased neuronal survival, tau hyperphosphorylation, and amyloid plaques	[24]
Albaik et al.	GLUT4 Dysfunction	Impaired GLUT4 translocation leads to decreased glucose uptake, disrupting synaptic transmission	[25]
Pivovarova et al.	IDE Dysfunction	Insulin resistance lower IDE expression, reducing Aβ clearance and promoting plaque formation	[26]
Jitendra Joshi, and Raja Sekhar Reddy	Tau Hyperphosphorylation	GSK-3β hyperactivity results in tau hyperphosphorylation and aggregation into NFTs	[27]
Dash et al.	Oxidative Stress and ROS Production	Elevated ROS levels, due to impaired mitochondrial function, contribute to oxidative stress and neurodegeneration	[28]
Marttinen et al.	Aβ Aggregation and Toxicity	Aβ aggregation induced by oxidative stress leads to synaptic dysfunction and neuroinflammation	[29]
Trigo et al.	Mitochondrial Dysfunction and Impaired Energy Homeostasis	Reduced mitochondrial biogenesis and increased oxidative stress hinder neuronal energy supply	[30]
Zhang et al.	Neuroinflammation (Microglial Activation)	Chronic inflammation and microglial activation elevate pro-inflammatory cytokines (e.g., IL-1β, TNF-α)	[31]
Green et al.	Astrocytic Dysfunction and Glutamate Toxicity	Reduced EAAT2 expression in astrocytes leads to glutamate accumulation, overstimulation of NMDA receptors	[32]
Davanzo et al.	Insulin Resistance and BBB Dysfunction	Insulin resistance leads to BBB breakdown, allowing pro-inflammatory monocyte infiltration	[33]

Insulin resistance and glucose metabolism in the brain

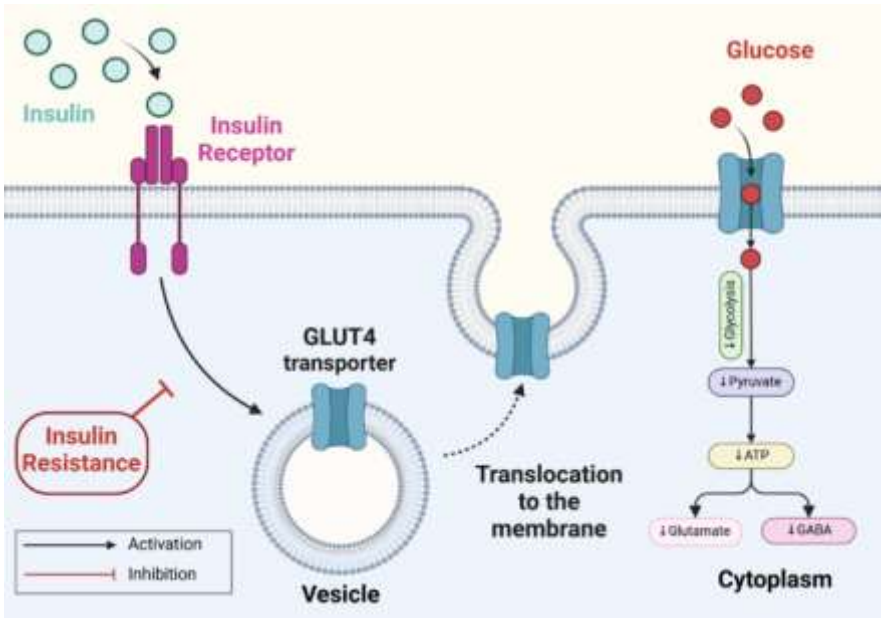
Reduced neuronal survival and PI3K/Akt signalling Reduced insulin receptor (IR) sensitivity in insulin-resistant conditions leads to diminished Akt phosphorylation and decreased PI3K activation [34]. Tau hyperphosphorylation and neurofibrillary tangles (NFTs) are encouraged by this malfunction, which causes glycogen synthase kinase-3 beta (GSK-3β) to be dephosphorylated and activated [35, 36]. Additionally, Akt failure can hinder the suppression of FOXO1 (forkhead box O1), which lowers cell survival and increases apoptosis [37]. (Fig. 2).



Disruption of the insulin signaling pathway is observed in neurodegenerative disorders. Insulin attaches to its receptor, which triggers the activation of insulin receptor substrates (IRS1/2) and the PI3K-Akt pathway. When this pathway is dysregulated, it results in downstream consequences such as the inhibition of mTORC1 and activation of GSK-3β, which contribute to the hyperphosphorylation of tau and the formation of neurofibrillary tangles (NFTs). The dysregulation of FOXO1 leads to apoptosis and compromises the integrity of the blood-brain barrier (BBB), while the dysfunction of PGC1-α disrupts mitochondrial biogenesis due to decreased activity of NRF1/2 and TFAM. Additionally, the presence of inflammatory cytokines (TNF-α, IL-1β), Aβ oligomers, and JNK activation further intensifies neuronal injury, demonstrating a complex mechanism of neurodegeneration. Black arrows illustrate pathways of activation, while red lines denote inhibition.

Cognitive decline and GLUT4 dysfunction

Disrupted PI3K/Akt signaling impairs glucose transporter type 4 (GLUT4) translocation in insulin r esistance [38]. Neurons experience an energy crisis as a result of this drop in glucose uptake, which lo wers ATP synthesis and ultimately results in a failure to maintain ion gradients and neurotransmitter release [39, 40] (Fig. 3).



Insulin-mediated glucose uptake pathway and its impairment in insulin resistance. Insulin resistance inhibits this process, resulting in reduced GLUT4 membrane translocation and decreased glycolysis, which in turn leads to reduced pyruvate and ATP production. The downstream effects include impaired synthesis of neurotransmitters such as glutamate and GABA, contributing to cellular energy deficits and dysfunction. Black arrows denote activation, while red lines represent inhibition. For a detailed discussion of its implications in AD pathology

Alternative energy substrates for energy shortfalls

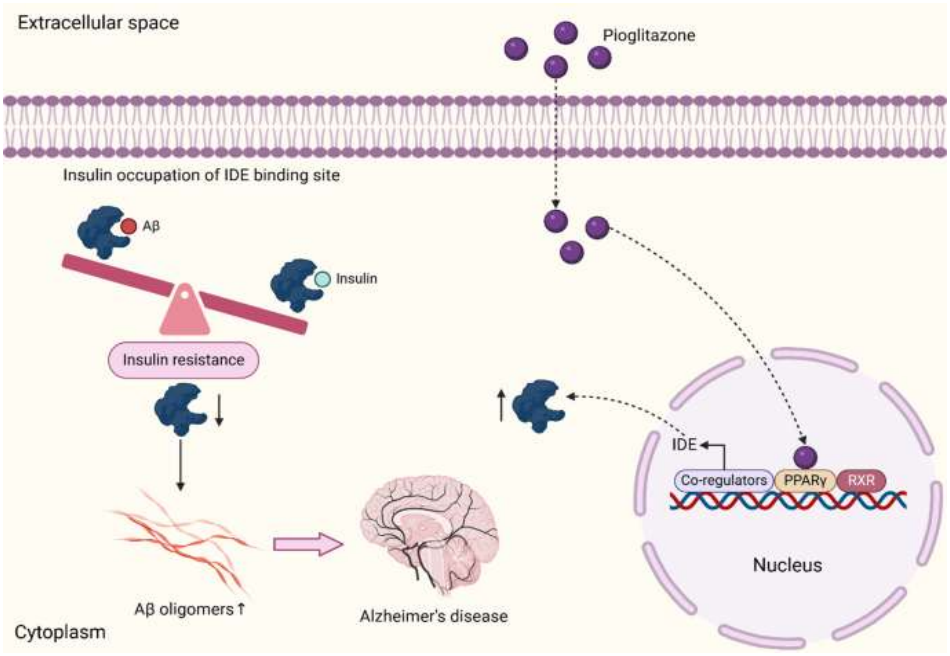
Neurons adjust to glucose shortages by using different energy substrates, like lactate and ketone bod ies [41]. Ketone bodies are metabolized more efficiently by neuron, astrocytes, and oligodendrocytes, ensuring a more optimal energy supply for brain cells [42].

Furthermore, astrocytes provide lactate through the astrocyteneuron lactate shuttle (ANLS), which t urns lactate into a major energy source [43].Astrocytic dysfunction, on the other hand, decreases lact ate availability in insulin resistance, further jeopardizing neuronal energy homeostasis [44].Because la ctate is essential for memory consolidation, decreased lactate transport also impacts synaptic plastici ty [45].

Pathology of amyloid-beta in metabolic-dysfunction

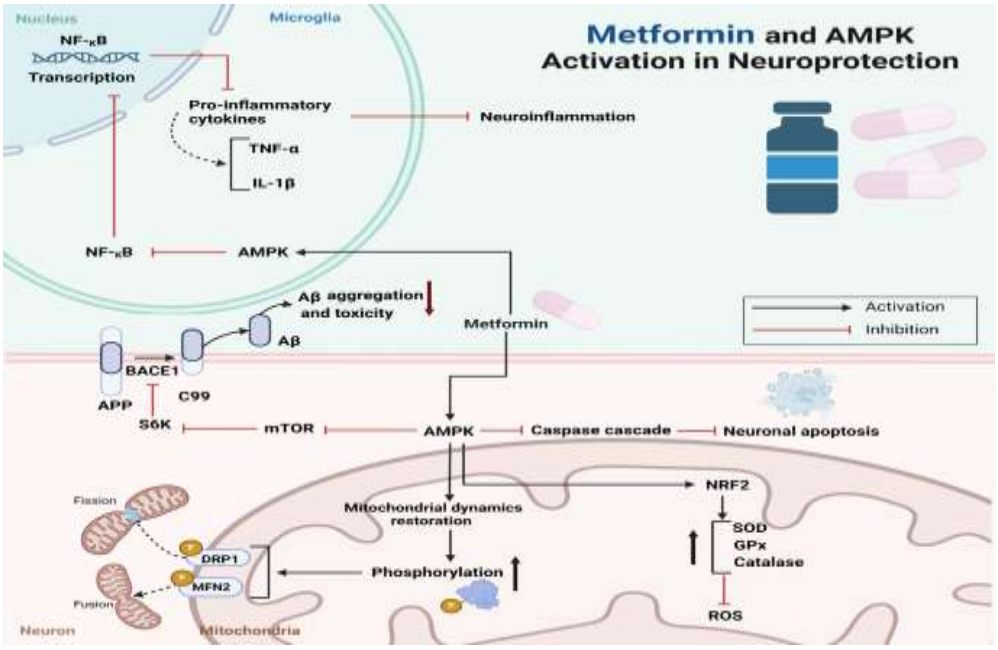
Aβ generation:

Involvement of insulin-degrading enzyme (IDE).IDE is involved in the degradation of both insulin and Aβ. [46]. IDE is sequestered to break down excess insulin in insulin-resistant conditions, which lowers the amount of insulin available for Aβ clearance [47, 48]. As a consequence, Aβ builds up and forms extracellular plaques [49] (Fig. 4). According to Benedict et al., rats given large amounts of insulin showed a substantial decrease in Aβ clearance. This implies that too much insulin has saturated the IR, decreasing its ability to promote Aβ breakdown [50].



Schematic representation of the molecular relations. Molecular relations between insulin singling, amyloid- beta(Aβ) aggregation, and the part of insulin- demeaning enzyme(IDE) in Alzheimer's complaint(announcement) pathogenesis. Insulin binds to IDE, contending with Aβ for its declination point, leading to increased Aβ accumulation. This imbalance contributes to insulin resistance and the conformation of poisonous Aβ oligomers, a hallmark of announcement. Pioglitazone, a PPARγ agonist, modulates IDE expression through nuclear transcriptional regulation involvingco-regulators and RXR, promoting Aβ concurrence and upgrading insulin

resistance.Through modifying β- secretase(BACE1) exertion, the PI3K/ Akt pathway also affects the product of Aβ[51]. Insulin resistance interferes with Akt signalling, which causes BACE1 to come more phosphorylated and Amyloid precursor protein(APP) to stick more readily into Aβ[52](Fig. 5). multitudinous knockout mice models have shown that BACE1 is directly linked to the generation of Aβ and has been considerably delved for its function in brain amyloidogenesis[53].



Metformin-mediated AMPK activation pathway in neuroprotection. These include inhibition of neuroinflammation through NF-κB pathway suppression, reduction of Aβ aggregation and toxicity, restoration of mitochondrial dynamics through DRP1 and MFN2 phosphorylation, and activation of antioxidant responses via NRF2. The pathway also shows metformin's role in inhibiting mTOR signalling and the subsequent caspase cascade, ultimately preventing neuronal apoptosis.

Aggregation of Aβ and its toxicity

Insulin resistance not only increases production but also causes metal ion dysregulation and oxidativ e stress, which encourage Aβ aggregation [54, 55].Aβ oxidation brought on by oxidative stress increase s their propensity to assemble [56].Because iron and copper are catalysts for Aβ oxidation, their dysre gulation in insulinresistant brains makes this process much worse [57–60].

NFT production and tau hyperphosphorylation

GSK-3β's function in Tau pathogenesis

NFTs are created when tau, a microtubule-associated protein, is hyperphosphorylated in AD [61]. Since tau is a key modulator of insulin signaling, it has also been linked to insulin resistance [62]. Insulin signaling tightly regulates the activity of GSK-3β, a crucial kinase that causes tau phosphorylation [63] (Fig. 2).

Hyperphosphorylated Tau aggregation

PHFs, which are subsequently assembled into NFTs, are formed when hyperphosphorylated tau aggregates [64]. By enclosing normal tau and other microtubule-associated proteins, these aggregates impair neuronal function [65] (Fig. 2). Additionally tau aggregates propagate transmitting disease throughout the brain in a prionlike fashion between neurone [66].

Tau disease and oxidative stress

By increasing tau phosphorylation and aggregation, oxidative stress aggravates tau disease [67]. Through oxidative post-translational modifications (PTMs), such carbonylation, reactive oxygen species (ROS) alter tau and encourage its aggregation [67]. Acetylation and phosphorylation are also seen as important PTMs linked to AD [68]. Both phosphorylation and acetylation can decrease tau's affinity for microtubules, which can result in tau aggregation, according to the Kelly et al. article [69].

Oxidative stress and mitochondrial dysfunction: the energy collapse

Insulin resistance and mitochondrial energy deficiencies: Mitochondria are essential for neuronal survival, providing energy through oxidative phosphorylation (OXPHOS) [70]. Insulin resistance leads to a reduction in mitochondrial number.

Overproduction of ROS and oxidative stress

An imbalance between the production and removal of ROS leads to oxidative stress [71]. One important ROS that builds up in insulin-resistant conditions is mitochondrial superoxide [72]. A mitochondrial antioxidant enzyme called manganese superoxide dismutase (SOD2) is downregulated in diabetes, which permits superoxide to react with nitric oxide (NO) to produce peroxynitrite [73–75]. According to Olufunmilayo et al., lipoproteins extracted from AD patients can stimulate astrocytes to produce more peroxynitrite [76].

This demonstrates how cellular components of the central nervous system (CNS) are involved in the intricate relationship between oxidative stress and the development of AD pathogenesis [76].

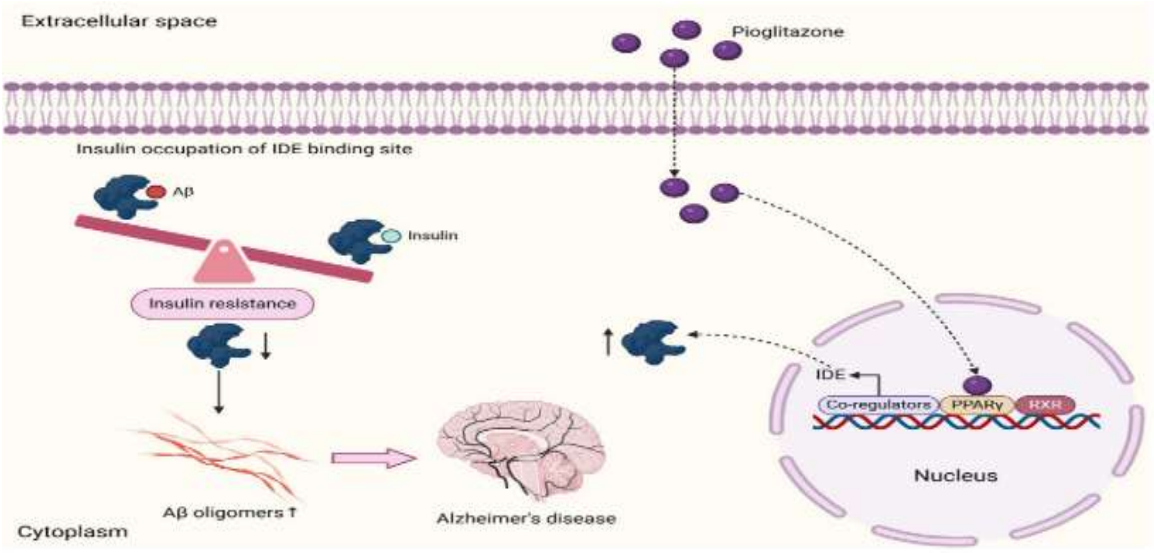


Fig. 4 Schematic representation of the molecular interactions. Molecular interactions between insulin signalling, amyloid-beta (Aβ) aggregation, and the role of insulin-degrading enzyme (IDE) in Alzheimer's disease (AD) pathogenesis. Insulin binds to IDE, competing with Aβ for its degradation site, leading to increased Aβ accumulation. Pioglitazone, a PPARγ agonist, modulates IDE expression through nuclear transcriptional regulation involving co-regulators and RXR, promoting Aβ clearance and ameliorating insulin resistance

Neurodegeneration and compromised mitophagy

The PINK1/Parkin pathway controls mitophagy, which guarantees the elimination of damaged mitochondria [77]. Hepatic lipogenesis, inflammation, and insulin resistance have all been demonstrated to worsen when Parkin- and PTEN-induced putative kinase 1 (PINK1)-mediated mitophagy is inhibited [78]. When mitochondrial depolarisation occurs, PINK1 builds up on damaged mitochondria, undergoes autophosphorylation, and phosphorylates Parkin and ubiquitin. This causes Parkin to be released from its auto inhibited state, enabling it to move to mitochondria, attach to

substrates such as VDAC1 and MFN2 (mitofusin 2), and mediate polyubiquitination of outer mitochondrial membrane proteins to attract the autophagic machinery and promote mitophagy [79–81].

Insulin resistance due to neuroinflammation dysfunction

Glutamate toxicity and astrocyte dysfunction

Through glutamate uptake via excitatory amino acid transporter 2 (EAAT2), astrocytes play a crucial role in preserving glutamate homeostasis [82]. Extracellular glutamate buildup results from decreased EAAT2 expression in insulin resistance, which is caused by compromised Akt signalling [83,84]. Excitotoxicity and calcium overload in neurones are brought on by high glutamate levels overstimulating NMDA receptors, which in turn causes calpain-mediated proteolysis and death [85,86]. Additionally, lactate shuttling to neurone is disrupted by astrocyte insulin resistance. Under metabolic stress, neurone use lactate, which is created by astrocytic glycolysis, as an energy substrate [87]. Decreased lactate availability accelerates neurodegeneration by compromising synapse function and the neural energy supply [88] (Fig. 6).

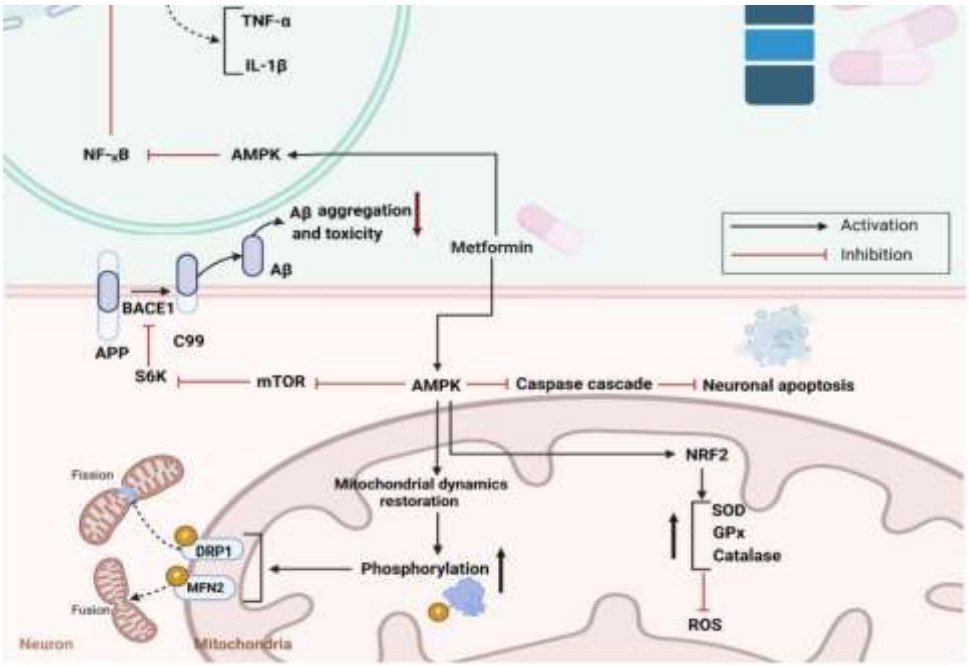


Fig. 5 Metformin- interceded AMPK activation pathway in neuroprotection.

The pathway also shows metformin's part in inhibiting mTOR signalling and the posterior cascade, ultimately preventing neuronal apoptosis. supplemental-central vulnerable crosstalk supplemental inflammation drives neuroinflammation by easing monocyte infiltration into the brain[89]. Insulin resistance reduces the expression of occluding and claudin- 5, which compromises the integrity of the blood- brain barricade and permits pro inflammatory monocytes to enter the central nervous system[90,91]. The inflammatory response and microglial activation are heightened when these overrunning cells develop into macrophages[92]. habitual inflammation accelerates Aβ aggregation, causes tau hyperphosphorylation, and encourages oxidative stress, all of which lead to neurodegeneration and cognitive loss[93](Fig. 7). Transcriptomic understanding of type 3 diabetes Regulatory RNAs in glucose metabolism and insulin resistance Longnon- rendering RNAs(lncRNAs) and microRNAs(miRNAs) are samples of nonsupervisory RNAs that have been linked as pivotal contributors to the emergence of insulin resistance and poor glucose metabolism[94]. Several studies have demonstrated that lncRNAs play a major part in the development of type 2 diabetes mellitus(T2DM) by causing insulin resistance and dysregulated glucose homeostasis, among other mechanisms[95 – 96].

Conclusion

This regular review explores T3D as a possible physiological connection between insulin resistance and Alzheimer's complaint(advertisement). The disturbance of PI3K/ Akt signaling, GLUT4 translocation, and oxidative stress contributes to dysfunctions in synapses and neurone. supplemental insulin resistance exacerbates central inflammation by compromising the blood- brain barricade(BBB) and twiddling microglia. A unique point of this review is the incorporation of transcriptomic data, which underscores the nonsupervisory functions ofnon- rendering RNAs(analogous as MEG3, MALAT1, BACE1- AS, 51 A) in impacting insulin perceptivity and amyloid pathology.The results indicate that RNA- predicated biomarkers and antidotes present new openings. Interventions showing pledge, analogous as intranasal insulin, GLP- 1 receptor agonists, metformin, pioglitazone, and SGLT2 impediments, cortege neuroprotective parcels by restoring insulin signaling and lowering oxidative stress. nonetheless, there are ongoing challenges, including the absence of standardized individual criteria, inconsistent biomarkers, and limited operation in clinical settings. future disquisition should emphasize the development of biomarkers, RNA-predicated mechanisms, and evidence on a large scale. Admitting T3D as a unique clinical condition could revise the opinion and treatment of Alzheimer's complaint.

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