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From Blood Sugar To Brain Health: Understanding Type 3 Diabetes and Alzheimer's

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ABSTRACT

Alzheimer's Disease (AD), a progressive neurodegenerative disorder, has prominently been recognized as a metabolic disorder with striking similarities to Type 2 Diabetes Mellitus (T2DM), giving rise to the term "Type 3 Diabetes Mellitus" (T3DM). This designation stems from an ever-escalating repository of evidence concerning insulin resistance, impaired glucose metabolism, and mitochondrial dysfunction of the brain cells to the pathogenesis of AD. Insulin mediates a crucial role in synaptic plasticity, memory formation, alongside thrival of neurons. In both AD and T2DM, insulin signalling is disrupted, leading to neuroinflammation, oxidative stress, and accumulation of β-amyloid and hyperphosphorylated tau—core pathological hallmarks of AD. Studies have also shown that peripheral insulin resistance may exacerbate central insulin dysfunction, further implicating metabolic dysfunction in AD progression. The detection of advanced glycation end products (AGEs) and islet amyloid polypeptide (IAPP) in the AD brain, typically seen in diabetic patients, reinforces this association. Moreover, antidiabetic medications such as metformin, GLP-1 receptor agonists, and intranasal insulin have demonstrated potential in improving cognitive outcomes, indicating a therapeutic overlap. Recognizing AD as T3DM provides a novel perspective that bridges endocrinology and neurology, potentially improving diagnostic approaches and enabling more targeted treatment strategies.

Keyword: Type 3 Diabetes Mellitus; Alzheimer's Disease; pathophysiology; Insulin resistance; Intranasal Insulin; Advanced Glycation End products; Beta amyloid; Tauopathy

INTRODUCTION

Diabetes Mellitus is a profound, chronic ailment, distinguished by hyperglycaemia resulting from inadequacies in the secretion and activity of insulin.[1,2] Diabetes is resultant of a number of pathogenic processes, ranging from immunological annihilation of the beta cells of islets of Langerhans, which results in insulin insufficiency, to anomalies which result in insulin action resistance. Defects in insulin activity and impaired insulin secretion often coexist in the same patient, thus which abnormality is mainly responsible for hyperglycaemia is often uncertain.[2]

The clinical manifestations of ushered in hyperglycaemia encompass polyuria, polydipsia, decreased body weight, frequently with polyphagia, along with vision impairment. Persistent hyperglycaemia may also be associated with growth impairment and increased vulnerability to certain illnesses. Diabetic ketoacidosis and Hyperosmolar Hyperglycaemic State are the acute and potentially fatal outcomes of untreated diabetes.[2]

According to the World Health Organization, 20 crores individuals were dwelling with diabetes in 1990; by 2022, that figure had increased to 83 crores. An estimated 16 lac deaths had been directly caused by DM in the year 2021. Nearly half of the fatalities inevitably caused by diabetes occurred in individuals under the age of 70, highlighting the disease's significant impact on younger populations. Approximately 11% of all cardiac deaths globally were caused by hyperglycaemia, and 5.3 lacs of fatalities from diabetic nephropathy. Prevalence happens to be escalating rapidly in low- and middle-income countries than in high-income ones.[3]

In India, 7.7 crores adults are suffering from T2DM which, by 2045, is anticipated to go past over 13.4 crores.[4,5] It is estimated that over 2.5 crores are prediabetic (have an unformidable likelihood of advancing to T2DM).[4] Risk of developing diabetes is substantially impacted by ethnic background, chronological age, overweight and obesity, and stagnant lifestyle poor dietary habits and behavioral patterns, in addition to genetics and family history.[5]

A multitude of people are aware of type 1 or type 2 diabetes nonetheless, a new kind of diabetes, known as type 3 diabetes, has just recently surfaced. This lesser-known kind shows up as insulin resistance in the brain, and it has an undeniable influence on neurocognition, therefore augmenting the likelihood of developing Alzheimer's disease (AD). Within America, it has now become the sixth foremost source, leading to death. Unfortunately, diabetes ranks seventh in the same category, just after Alzheimer's disease.[1] Although these illnesses are typically thought of as separate disorders, but several studies imply that they are interrelated. T2DM and AD share certain pathogenic factors including oxidative stress, mitochondrial impairment, adiponectin deficiency, chronic inflammation, varying expression of plasma cholinesterase activity, and damage to blood vessels.[6] These factors may be the reason why many patients exhibit both conditions contemporaneously illustrated in Fig 1.[1]

A prominent comorbidity of diabetes mellitus is cognitive impairment, which is becoming more well acknowledged. There are many phases of diabetes-related cognitive impairment, each with unique cognitive traits, affected age groups, prognoses, and perhaps the underlying processes. All age groups experience relatively mild cognitive declines that grow gradually. Geriatric populations are more likely to develop more severe phases, including moderate cognitive impairment and dementia which have progressive deficiencies. Substantial indications about processes are provided by developing understandings from research on neuropathology, risk factors, and brain imaging.[6]

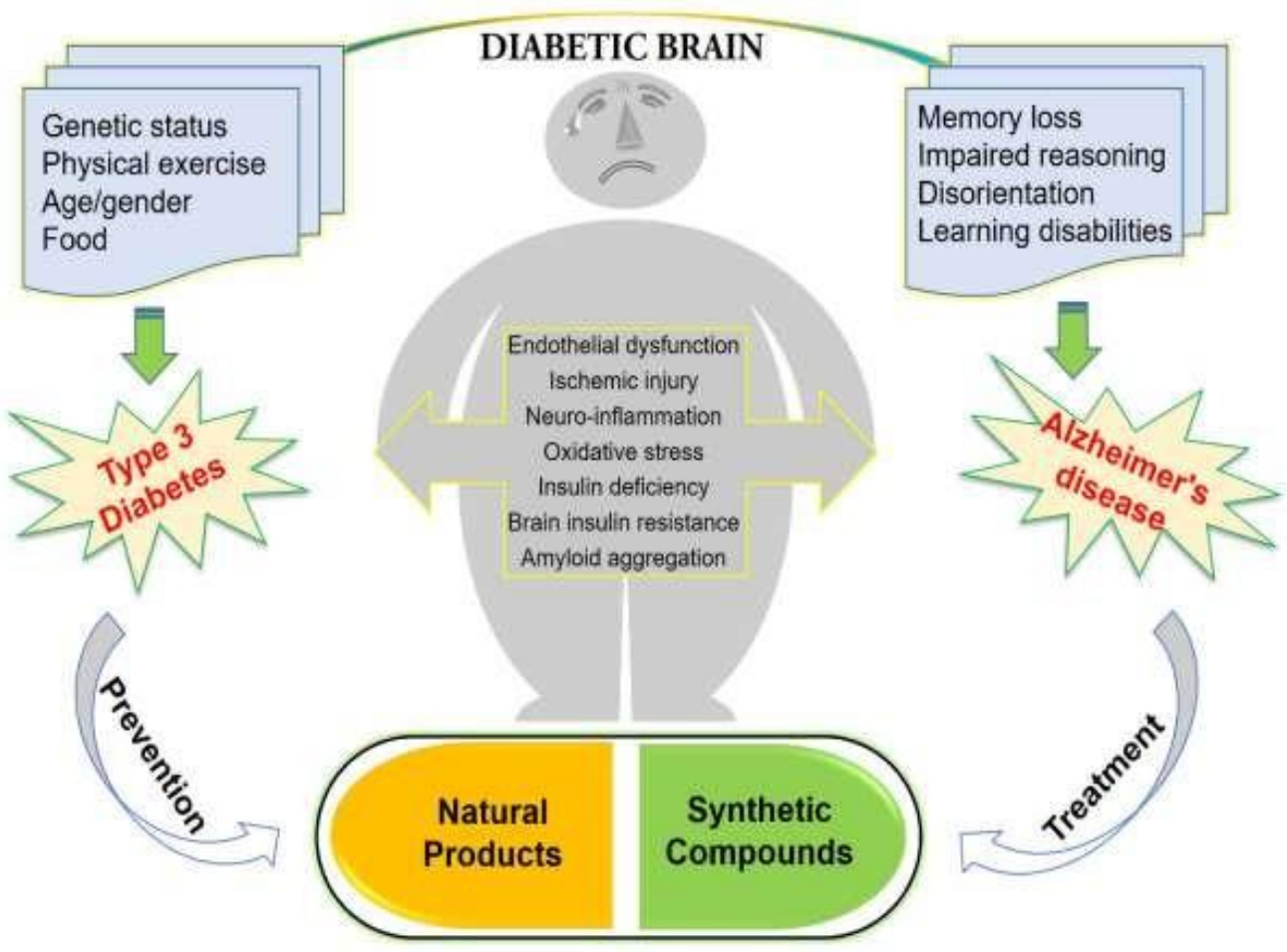

Fig 1. Illustration depicts the shared pathogenic factors of diabetes & AD, the interrelation of AD and diabetes of how one influences the other, and the approaches to treatment and prevention.

Research has been challenging in determining whether type 2 diabetes has a particular association to the biological characteristics of AD or various other dementia causes. T2DM and cognitive dysfunction are often linked, and a substantial amount of research on both humans and animals suggests that T2DM has biological causes that may be treatable.[6] Insulin

resistance and an insulin secretary malfunction evolve together to cause type 2 diabetes. Insulin resistance is characterized by the target tissues' inability to react appropriately to insulin. Usually, insulin resistance occurs years before T2DM manifests. According to certain epidemiological research, insulin resistance raises the incidence of dementia and AD.[1]

Researchers have proposed the name type 3 diabetic mellitus (T3DM) to describe a newly identified variant. These researchers made an effort to outline it as a metabolic syndrome which may result in anomalies associated with progressive insulin resistance in the tissues of the brain, that then may impair central insulin signalling processes, cause neurotoxins to accumulate, induce neuronal stress, and subsequently initiating a course of neurodegeneration. Studies conducted on animals and in vitro have shown that insulin resistance can intrigue pathophysiology of AD by several mechanisms.[1] Chronic exposure to hyperglycaemia can impair mental health, including cognitive function. There may be a cause-and-effect link between hyperglycaemia and dementia since it is closely linked to the onset of cognitive impairment and dementia. Glucotoxicity can cause cerebral blood vessel bleeding, increased amyloid beta buildup, and structural and functional damage to brain cells and neurones. These might be the processes behind dementia brought on by diabetes.[6]

Furthermore, regardless of genotype, insulin resistance and hyperinsulinemia impairment of insulin signalling are the key elements that make it logical to maintain insulin at the forefront of pathologies of these two diseases. According to several recent research, memory and other executive functions are negatively impacted by poor hippocampal insulin signalling due to insulin signalling degradation and insulin resistance development simultaneously. This discussion supports a close connection between insulin resistance and hyperinsulinemia, and the ensuing diseases such as AD and T3D. Reduced insulin signalling in the central nervous system (CNS) due to peripheral insulin resistance causes changes in brain metabolism. Central insulin resistance is linked to increased beta amyloidosis, Tau phosphorylation, oxidative damage, and neuroinflammation, all of which contribute to neurodegeneration.[1]

Mechanisms of pathophysiology of T3DM and Alzheimer's

1. Insulin and brain functioning

It had originally been experimentally demonstrated within mice that there was a spike in the insulin quantities in CSF.[7] Pancreatic peripheral neural insulin accounts for the largest proportion of insulin within brain.[8] Insulin reaches into brain primarily by selective transport along the blood-brain barrier's capillary endothelial cells, a process that is impacted by diabetes mellitus, inflammation, and plasma-lipid. In the brain, insulin has a variety of crucial roles in controlling consumption of food, appetite, and energy equilibrium.[9] It seems to have an impact on neurotransmitters and specifically the density of their receptors.[10] It was always thought that the brain's primary supply of insulin came from the peripheral source, however there are now a number of theories on whether the brain makes its own insulin.[11] It has been shown that some regions of the mouse brain express insulin mRNA, and that cultured neurons, but not glial cells from the mouse brain, produce insulin peptide.[12]

2. Insulin resistance and β-Amyloidosis

Amyloidosis in several tissues is a clinical characteristic of both AD and T2DM.[13] As beta-amyloid molecules build up, they are capable of producing a variety of pliable, soluble oligomers. In addition to being hazardous to neurons, misfolded oligomers can spread incorrect information to the other neurons, playing crucial role as prions.[14] Amyloid peptide's aggregation into oligomers or fibrils sets the fate of AD advancement.[12]

Insulin resistance and decreased concentrations of IGF-1 may lead to decreased absorption of insulin by the brain, which might result in β-amyloid buildup.[15] Elevated β-amyloid amounts inhibits the reception of insulin by IGF-1 receptors, leading to the release of inflammatory mediators and the development of insulin resistance.[16] Furthermore, in a pathogenic feedback loop, oxidative stress and insulin malfunction and inflammation increase the toxic impacts and concentration of β-amyloid.[17] As a result, insulin signalling disruption may impact APP metabolism and function, ultimately resulting in the buildup of Aβ within the cell, a primary cause of AD neurodegeneration.[18] Research indicates that APP is necessary to preserve a normal glycemic control, and metabolic abnormalities have been seen in mice with APP knockdown.[12,19]

Insulin stimulation is essential for β-amyloid removal because it stops extracellular buildup and the eventual aggregation into plaques. Insulin-degrading enzyme (IDE), the primary β-amyloid degeneration enzyme is believed to be a mediator between insulin resistance and AD because of its potency to break down insulin, amylin, and β-amyloid.[12] Researchers discovered IDE in extrinsic spaces using antibodies and demonstrated that the IDE is redirected to insulin degradation in insulin resistance situations with elevated insulin levels, which lowers β-amyloid breakdown and its detrimental buildup.[20] It has been demonstrated that in mice, elevated γ-secretase activity brought on by insulin resistance augments amyloidosis in brain and IDE to become less responsive. Furthermore, high-dose insulin administered mice showed a decline in β-amyloid elimination, while mice lacking both alleles of the gene for IDE showed a significant reduction in β-amyloid degradation of up to 50%, leading to an abnormal concentration of the protein in the brain.[21,22]

3. Insulin resistance and Tauopathy

Insulin resistance in the brain tissues has a relationship with tau as well as phospho-tau buildup, cholinergic function suppression, and energy utilization abnormalities.[23] According to the tau protein hypothesis, the development of AD is brought on by tau protein hyperphosphorylation, which changes regular tau polypeptide producing paired helical fibers (PHF) as well as neurofibrillary tangles (NFTs).[24]

Phosphorylation of tau protein is critical for the progression of tau protein aggregation. Glycogen synthase kinase 3 is the most significant kinase and phosphatase, and its overactivity can cause hyperphosphorylation and reduced tau protein expression when insulin and IGF signalling are impaired.[23] It has also been demonstrated that insulin activity suppress the action of GSK-3.[25] Furthermore, pancreas of mice suffering from AD as well as T2DM have also been shown to have tau protein hyperphosphorylation.[12]

Thus, it is experimentally verified that insulin resistance and tauopathy is interrelated with each other.

4. Neuroinflammation

The development of AD is significantly influenced by neuroinflammatory reactions. Glial cells' defensive reaction to pathological situations represents neuroinflammation. It is a key participant in autoimmune and neurodegenerative diseases as it is the most relevant component and a possible target for therapeutic interventions. The early phases of AD are marked by neuroinflammation, which manifests as an increase in pro-inflammatory mediators along with infiltration of microglial cells in the plaque-laden amyloid region.[26]

Neuroinflammation contributes to AD progression by generating cholinergic system failure, oxidative stress, tauopathy via hyperphosphorylation, and β-amyloid clumping. The significant contribution of inflammatory response in the pathophysiology of AD has been demonstrated by the elevated amounts interleukins, and interferon-gamma, around amyloid plaques and macrophages.[12]

Several investigations suggest neuroinflammation to be a prominent cause of the insulin resistance observed in the brains of AD patients.[15] High quantities of cytotoxic lipids are produced as a result of peripheral insulin resistance brought on by type 2 diabetes. These lipids then penetrate the BBB and promote insulin resistance and neuroinflammation in the brain.[27]

Despite being a crucial component of AD pathogenesis, neuroinflammation's influence on both AD as well as T2DM is still unclear. As of right now, there is no scientific proof that anti-inflammatory medications may effectively treat AD.[15,12]

5. Oxidative stress and Mitochondrial hypothesis

Insulin resistance in T2DM is considered be a contributing element to the oxidative stress that causes AD neurodegeneration.[28] Oxidative damage is caused by a disparity with regard to the exceptionally reactive species of nitrogen as well as oxygen, that equate to the reactive forms of oxygen. It oxidizes several DNA, lipids, and proteins, damaging mitochondria and inducing genetic mutations in DNA/RNA. Reactive oxygen increases cytokine mediation and accelerates cellular lysis.[29]

T2DM pathology is significantly influenced by impaired mitochondria and a surplus of ROS.[30] Insulin resistance augments oxidative reaction products in blood, visceral and cerebral tissue, and the liver.[31] It has also been demonstrated that T2DM inhibits neural outgrowth and deregulation of mitochondrial function in mice was also observed via modulating mitochondrial bioenergetics through JAK/STAT3.[32]

Despite making up only 2 percent of the body weight, human brain utilizes more than 20% of the oxygen inhaled, increasing oxidative damage susceptibility.[33] Other characteristics that amplifies brain injury include low antioxidant levels, high concentrations of oxidizing metal ions (Fe^{2+}, Cu^{2+}), and the ease with which polyunsaturated fatty acids of the cellular membrane can undergo hyper-oxidation.[12,31,33]

Oxidative stress generates active forms of oxygen, and the damage is most noticeable in AD where ATP synthesis is suppressed, neurons degrade, and oxidative stress byproducts become apparent in neurofibrillary tangles.[34] It is demonstrated that the primary constituent of amyloidosis (beta amyloids) in AD, may generate reactive forms of oxygen when metal ions like Fe^{2+} and Cu^{2+} catalyzes the reaction.[35,36] It has been shown that tau and β-amyloid protein buildup can be caused independently by insulin resistance and oxidative stress, suggesting a close relationship with AD pathophysiology.[12]

6. Toxic Advanced Glycation End products (AGE)

AD is significantly influenced by advanced glycation end products (AGEs) - peptides or protein molecules that undergo the Maillard process, which causes them to become glycated when exposed to sugars.[37] As byproducts of normal ageing, AGEs build up in different cells, but the pace at which they do so is higher in DM patients.[38] Complications result from their interaction with the receptors (RAGE) and the activation of many signalling pathways that raise oxidative stress and harm organs.[39]

AGEs contribute to the neurotoxic consequences seen in AD by encouraging the aggregation of amyloid oligomers.[40] Moreover, tau protein glycation seems to encourage the development of paired helical fibres.[41] Additionally, it has been proposed that the APOE4 gene and AGEs coexist in the amyloid plaques of dementia affected individuals, particularly those who are suffering from AD.[42] Since Sato et al. (2006) demonstrated that these compounds decreased cell viability when given to cortical neurons, they are unquestionably neurotoxic chemicals.[39] Furthermore, it has been demonstrated that AGEs can generate free radicals by triggering NADPH oxidase action, the primary generator of reactive oxygen species in neurons and glial cells.[43]

Conclusively, AGEs induce neurodegeneration, particularly when hyperglycaemia is present.[43]

7. Islet Amyloid Polypeptide (IAPP) or Amylin

β-cells of the pancreatic islets emit a hormone called islet amyloid polypeptide (IAPP), also known as amylin.[44] It plays a critical role in inducing satiety which in turn assists in managing blood glucose, suppress glucagon production, alongside postponing gastric emptying.[45]

Similar to insulin, people with obesity or insulin resistance have elevated amylin levels, and it is typical for hyperinsulinemia and hyperamylinemia to coexist. Immunofluorescence is used to detect amylin receptors and amylin deposits in AD patients' brains. Amylin deposits and mixed amylin-β-amyloid plaques are characteristics of amyloid plaques.[46]

Thus, clarifying our comprehension of the pathogenic feedback between AD and T2DM, as it seems that amylin, which is present in AD patients' brains, may induce amyloid development through heterologous contact.[46]

The figure below bridges the pathophysiology and therapeutic approaches of T2DM and AD.[47]

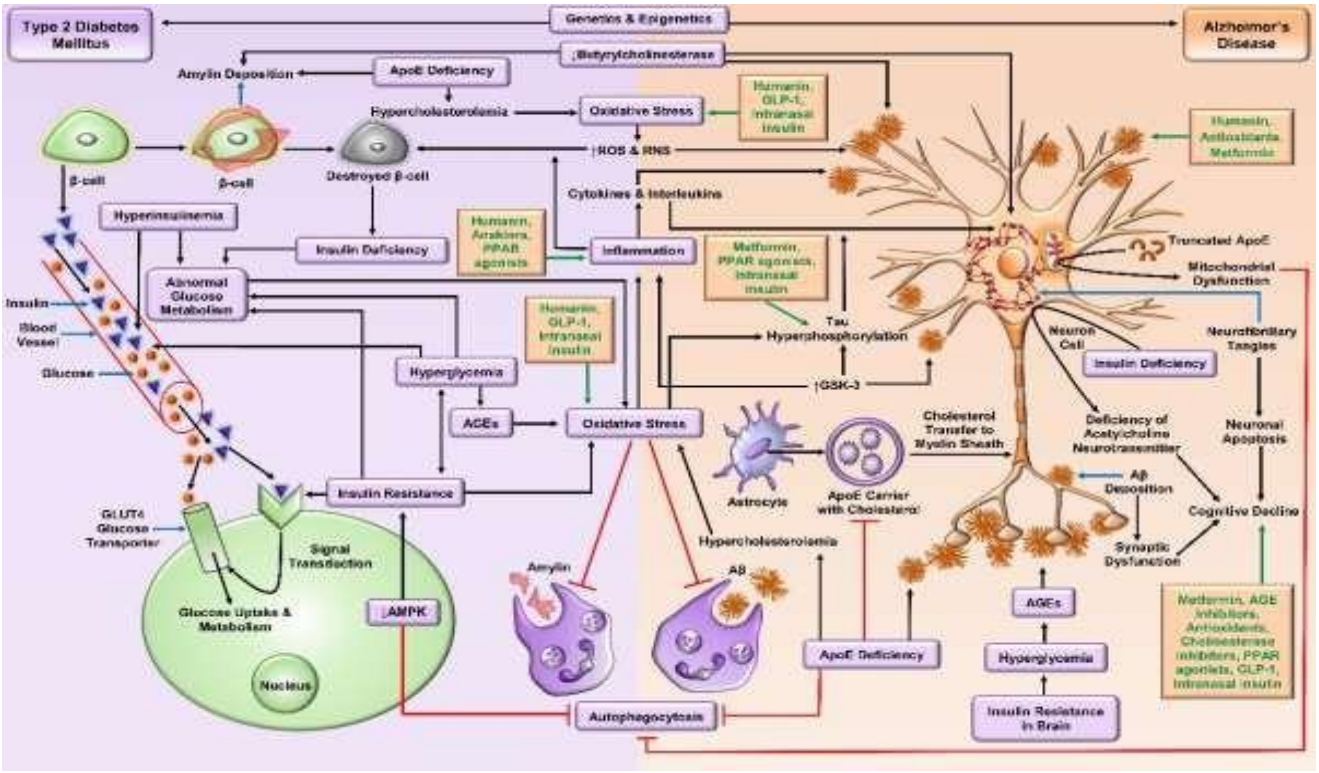

Fig 2. Linking the pathophysiology and therapeutic approaches of T2DM and AD.

Management of T3DM in Alzheimer's Disease

Since insulin resistance is widely recognized as a crucial aspect of type 3 diabetes, therapeutic approaches for the disease are especially those which concentrate on enhancing the responsiveness to insulin.[48] Because type 2 diabetes, insulin resistance, and cognitive decline all share similar but different pathological characteristics, multitargeted medicinal products and lifestyle modifications are also being investigated.[49] Utilization, advantage and mechanisms of such agents are discussed below.

1. Humanin (HN)

Mitochondria produce a peptide known as HN. HN seems to ameliorate cognitive deterioration in animal studies.[50] Nonetheless, HN has been found to have neuroprotective activity against stressors associated with Alzheimer's.[51] HN has proved to prevent neural apoptosis in Alzheimer's by amending intrinsic cytotoxic processes and hindering neural toxicity produced by Amyloid β.[52] By inhibiting the development of Amyloid β fibrils and their aggregation, HN also has beneficial cytoprotective action.[53] HN can suppress Aβ-mediated apoptosis of human cerebrovascular smooth muscles and arrest cell death in the CNS.[54] HN seems to counteract the effect of inflammation progression by reducing pro-inflammatory cytokines.[55]

2. Anticholinesterases

Anticholinesterases comprise an available symptomatic relief option for AD, as it has been established that AD patients benefit from chronic usage of them.[56] These agents aid in delaying the breakdown of acetylcholine available at the synapses, thus enhancing the cholinergic action.[57] The anticholinesterase, Donepezil is remarkably selective. It is anticipated to be advantageous in everyday functioning and cognition in AD patients, despite the fact that minor adverse outcomes are uncovered.[58] Galantamine is another such selectively reversible antagonist of acetylcholinesterase.[59]

3. Advanced Glycation End products (AGE) antagonists

Only recently has aminoguanidine, an AGE inhibitor, garnered attention as an appealing pharmacological agent for AD. However, it is presently undergoing clinical trials for managing complications associated with diabetes. According to reports, Tenilsetam, which has been a part of phase II trials, meticulously improves memory and cognitive functioning during the course of the three-month study period. It is believed that these AGE inhibitors help prevent AD by preventing AGE-Aβ deposition.[60]

4. Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists

The brain's solitary tract nuclei and peripheral intestine L cells both release a hormone termed as incretin also known as glucagon like peptide-1 (GLP-1).[61] The DPP-4 enzyme quickly breaks down GLP-1 once it reaches the bloodstream.[62] Consequently, GLP-1's half-life is typically less than two minutes. GLP-1 lowers pancreatic glucagon secretion, enhances insulin responsiveness and insulin production addressing blood glucose levels.[63] Because GLP1R agonists can activate pathways that circumvent insulin resistance, they can enhance the reduction in insulin signalling, a causal factor for the development of AD. Additionally, GLP-1 has the ability to enhance insulin signalling pathways.[64] According to reports, GLP-1 regulates memory formation and synaptic plasticity. GLP1R agonists like liraglutide have been shown to improve cognition, protect neurons and synapses, rectify impaired insulin signalling, and reduce amyloid buildup in transgenic mice models of AD.[65]

5. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

DPP-4 enzyme is responsible for the degradation of GLP-1 enzyme in the bloodstream, thus, to increase the half-life of GLP-1, DPP-4 inhibitors are administered alongside GLP1R agonists to deactivate the DPP-4 enzyme.[62] DPP-4 inhibitors, sitagliptin and vildagliptin enhanced the mitochondrial and cognitive function of rats' brains.[66] DPP-4 inhibitors are employed alongside GLP-1R agonists to protect GLP-1 from degradation. Thus, DPP-4 inhibitors are administered in combination with GLP-1 receptor agonists to augment its action.

6. Metformin

Metformin reduces gluconeogenesis, thus assisting in lowering insulin resistance as well as reducing blood glucose levels. It also increases fatty acid oxidation and reduces intestinal absorption of glucose.[67] When compared to individuals who were not treated, metformin treatment reduced cognitive impairments in patients with AD and T2DM.[68] This finding implies that anti-diabetic medications activate the brain's neural networks, which helps AD patients by preserving cognitive function. Metformin can lessen the hyperphosphorylation of tau protein in cortical neurons in mice.[69] It has even been demonstrated

that metformin safeguards the brain from oxidative stress triggered by T2DM.[70] Analyzing epidemiological research revealed that people with type 2 diabetes who used metformin for an extended period had a marginally increased risk of acquiring AD in comparison to those individuals who were not using the medication.[71]

7. Anakinra

Hyperglycaemia induces loss of pancreatic beta cells, through augmented production of interleukin-1β (IL-1β). Interleukin-1 receptor antagonist (IL-1Ra) can prevent this hyperglycaemia-induced β-cell apoptosis.[72] In patients with T2DM, Anakinra has been demonstrated to suppress IL-1 activity, which improves β-cell secretory function and glycemic management.[73] Moreover, IL-1β contributes to neurodegeneration by neuroinflammation linked to AD. Anakinra may thus also have therapeutic promise in AD by reducing neuroinflammation caused by IL-1β.[74]

8. Antioxidants

Oxidative stress induced by AD and T2DM counts for a number of cognition-related health hazards. Thus, antioxidant-potent substances can be employed as therapeutic treatments to mitigate the progression of AD and T2DM.[75] Several moieties have proved to be beneficial in reducing the quantities of interleukins and Tumor Necrosis Factor-alpha in individuals. Several such compounds are flavonoids – Rutin[76], Quercetin[77], and Naringenin[78]; phenolic compound – Pterostilbene[79]; polyphenolic phytoalexin – Resveratrol[80]. Several clinical trials have been associated with the reaffirmation of this utilisation. These compounds are employed with several other agents to mitigate the effects inflammatory cytokines and thus proved to prevent neuronal damage in AD patients.[47]

9. Peroxisome Proliferator-Activated Receptor-Gamma (PPARγ) Agonists

Inflammation is one of the causes of plaque development in the AD brain, where PPARγ activators might function as an inhibitor to slow down cognitive loss. Potential PPARγ agonists include anti-diabetic medications, especially rosiglitazone and pioglitazone of the thiazolidinediones family. As insulin sensitizers, these medications can reduce insulin resistance[81] and reduce the inflammatory effects on the brain[82] by blocking TNF-α and IL-6.

10. Intranasal Insulin (INI)

Intranasal Insulin is an easily administrable form of insulin with minimized systemic adverse effects and thus is chosen over subcutaneous and intravenous form of the same. INI is thus currently becoming an emerging therapy strategy for AD management. Intranasal route provides a rapid absorption of the moiety in the systemic circulation and thus has an onset of action way prior to the other routes of administration. Insulin breaks down Aβ as well as their buildups[83], prevents tau hyperphosphorylation,[84] preserves the number of synapses,[85] and reduces the binding of Aβ-derived diffusible ligands, to hippocampal neuronal synapses to prevent the advancement of AD.[86,87]

DISCUSSION

The intricate pathophysiological link between Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD) has led to the emerging term Type 3 Diabetes Mellitus (T3DM), highlighting shared mechanisms such as insulin resistance, amyloidosis, tauopathy, neuroinflammation, oxidative stress, and mitochondrial dysfunction. Insulin plays a critical neuromodulatory role in the brain, and resistance to insulin disrupts neuronal signalling, fosters β-amyloid accumulation, and exacerbates tau hyperphosphorylation. Furthermore, oxidative stress and the accumulation of advanced glycation end products (AGEs) contribute to neurotoxicity and plaque formation. The overlap in pathology offers an opportunity for integrated therapeutic strategies. Agents like GLP-1 receptor agonists, metformin, antioxidants, and intranasal insulin demonstrate neuroprotective benefits by improving insulin sensitivity, reducing inflammation, and minimizing amyloid and tau pathology. Notably, Humanin and anticholinesterases offer promising symptomatic relief and cellular protection. Despite the progress, long-term efficacy and safety of these treatments remain under investigation. A multifaceted therapeutic approach targeting shared molecular pathways may hold the key to managing both T2DM and AD, potentially slowing cognitive decline and improving patient outcomes.

CONCLUSION

The intricate overlap between Alzheimer's Disease (AD) and Type 2 Diabetes Mellitus (T2DM) has led to the apt classification of AD as "Type 3 Diabetes Mellitus" (T3DM). This conclusion arises from the compelling evidence of shared pathological mechanisms such as insulin resistance, β-amyloidosis, tau hyperphosphorylation, oxidative stress, and neuroinflammation. The central nervous system's dependence on insulin for synaptic function, memory processing, and neuronal survival becomes compromised in insulin-resistant states, thereby accelerating AD pathology. Additionally,

molecules like β-amyloid and tau—hallmarks of AD—are shown to interact with insulin signalling pathways, further establishing a mechanistic link. The presence of advanced glycation end products (AGEs) and islet amyloid polypeptide (IAPP) deposits in AD brains—common features in T2DM—further blurs the boundaries between the two diseases. Moreover, therapeutic agents effective in T2DM, such as metformin, GLP-1 receptor agonists, and intranasal insulin, have shown promising neuroprotective effects in AD. Collectively, these findings underscore the neuroendocrine nature of AD and support its redefinition as T3DM, emphasizing the need for integrated metabolic and neurological therapeutic strategies

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