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ALZHEIMER'S DISEASE

AND TREATMENT

Exploring and Exploiting a Common Pathophysiology of Type 2 Diabetes and Alzheimer's Disease

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Abstract

In the aging population, Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD) are two of the most prevalent diseases worldwide. It is evident from epidemiological studies that people with T2DM are at a higher risk of developing AD. On the other hand, in AD brains are less capable of glucose uptake from the surroundings resembling a condition of brain insulin resistance. Pathologically AD is characterized by extracellular plaques of Amyloid β (Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau. T2DM is a metabolic disorder characterized by hyperglycemia and insulin resistance. Insulin resistance in T2DM directly exacerbates Aβ and tau pathologies, brought about synaptic dysfunction, inflammation, and autophagic impairments that are common to both diseases and indirectly impact Aβ and tau functions in the neurons. Understanding the pathways that connect these two diseases will be immensely valuable for designing novel drug targets for Alzheimer's disease.

Introduction

Diabetes Mellitus Type 2 (T2DM), though expanding its age related demographic base with rapid urbanization, is traditionally known as disease of the middle aged and elderly population, and its prevalence increases with age. Alzheimer's Disease (AD) is also a disease of the old people. T2DM is associated with higher rate of morbidity and mortality from its macrovascular complications like stroke, Transient ischaemic attack, ischemic heart disease and peripheral vascular disease as well microvascular complications like diabetic neuropathy, retinopathy, nephropathy.

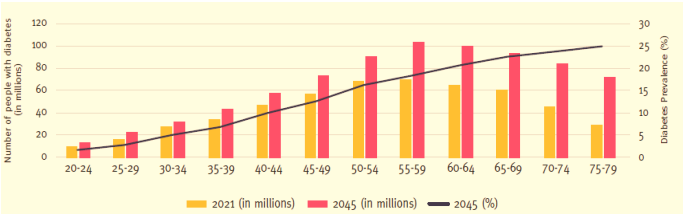

Figure 1: Number of people with diabetes in adults (20-79 years) by age group in 2021 (columns) and estimated Prevalence (standardised to each national population) across age groups in 2045 (black line). Source: IDF Atlas 10th ed. 2021.

On the other hand, AD, typified by the cognitive impairment it causes, renders the last few years of person's life dependent on others putting a significant stress on the family and burden on the national economy when assessed collectively.

Both T2DM and AD significantly contribute to the burden of morbidity and disability of human population. Recent studies have revealed this two disease to share many elements of their pathophysiology. Commonness of their pathophysiology provides a tool to exploit in development of therapeutic modalities and management strategies. While T2DM has very effective ways to control and prevent its complication, the treatment of AD is less effective.

Therefore, it is obvious that early diagnosis and treatment of T2DM prevent or delay development of AD. On the other hand, longevity resulting from good control of diabetes may take the patients into an advanced age which is associated with AD.

Alzheimer 's disease

Alzheimer's Disease (AD), diagnosed by the German psychiatrist and neuropathologist Prof. Alois Alzheimer in 1906, is the

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most prevalent form of dementia in the aging population [1] Patients affected with AD, the sixth major cause of death in the world, suffer a gradual decline of cognitive abilities and memory functions till the disease renders them incapable of performing daily functions [2]. Statistical data reveals that over 30 million people are suffering from AD worldwide and this number is estimated to double every 20 years to reach 66 million in 2030 and about 115 million by 2050 [3].

AD has two clinical subtypes, about 95% of AD patients are aged 65 years or older, and are diagnosed with “late-onset” or “Sporadic AD” (sAD) while 5% of AD patients reveal genetic mutations associated with “early-onset” or “familial AD” (fAD) that causes the onset of symptoms in their thirties, forties, or fifties [4].

Early onset fAD is caused by mutation in three known genes namely, Amyloid Precursor Protein (APP), Presenilin-1 (PS-1), and Presenilin-2 (PS-2). PS-1 mutations cause most of the fAD. There are undiscovered mutations outside these three genes. The genetics of sAD is more complex [5]. Other than aging, the strongest risk factor for sAD, GWAS studies reveal that the epsilon four allele of the Ppolipoprotein E (ApoE4) gene is a significant risk factor for the development of this disease. Two copies of ApoE4 gene increases risk of AD by 12-fold, while one copy of this allele enhances the risk by 4-fold [6]. However, only 50–60% individuals are carriers of this gene suggesting that other factors also confer risk. Studies suggest that these include factors such as cerebrovascular infarction, family history of diabetes, hypertension and obesity [7].

At a cellular level, AD is characterized by a progressive loss of pyramidal cells in the entorhinal cortex and CA1 region of the hippocampus that are responsible for maintenance of higher cognitive functions [8]. Early symptoms of AD are also marked by synaptic dysfunction that disrupts connectivity between neural circuits, thereby initiating the gradual loss of memory.

Neuropathologically, AD is characterized by extracellular plaques of insoluble amyloid-b protein, and intracellular neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein [8,9]. In AD, abnormal cleavage of APP results in the formation of insoluble amyloid-b protein, densely packed with beta sheets, which form the core of the senile plaques [10]. Tau protein, in a physiological state serves as a microtubule binding protein and plays an important role in axonal and vesicular transport [11].

Conversely, in the disease state tau protein is hyperphosphorylated and detached from the microtubules. In animal models this phospho-tau-mediated disruption of cytoskeletal

Integrity manifests in synaptic and behavioral impairments [12]. Although a large body of in vitro studies have investigated tau-microtubule binding interactions, most of these studies have been conducted in silico or in non-neural cellular models [13].

In a series of elegant experiments involving single-molecule tracking of tau in axonal processes, Niewidok et al. and Janning et al. have shown that the interaction of tau with the microtubules follows a “kiss-andhop” mechanism. Their studies show that a single tau molecule resides only 40 ms on a particular microtubule and then hops longitudinally and transversely on adjacent microtubules. This novel mechanism has been particularly effective in resolving the paradoxical observation that despite regulating microtubule dynamics, alterations in tau levels may not interfere with axonal transport [14]. Using pseudo-hyperphosphorylated tau constructs, they observed a considerable weakening of the tau-microtubule interactions that corroborated with previous in vitro studies.

A large body of evidence supports the idea that the formation of Ab plaques occurs 15-20 years earlier before the cognitive functions decline, whereas the spatial and temporal spread of tau pathology correlates more strongly with the severity with disease progression [8]. Although Ab and tau are the pathological hallmarks that characterize sAD, it is not yet clear whether these two factors trigger AD or if they are manifested as the effect of the disease. The drug therapy of AD is still at a nascent stage providing symptomatic relief but not slowing down disease progression. Such treatments include FDA-approved choline esterase inhibitors and NMDA (glutamate) receptor agonists. Thus, from a public health perspective AD exerts a significant healthcare burden that is expected to escalate 5-fold in the coming decades. Hence, the need for early detection and effective treatment is an urgent priority [15]. In recent times, it has been hypothesized that various risk factors promote Ab and tau-related pathological changes before the onset of clinical symptoms in AD. One of the formidable challenges of the twenty-first century is to identify these risk factors and enable early detection of pathophysiological alterations at the cellular and biochemical level so that effective treatments can be designed against this devastating disease. A significant risk factor associated with sAD that has received a considerable attention in recent times is Type 2 Diabetes (T2D) [7].

Type 2 Diabetes

Diabetes mellitus is a chronic metabolic disorder that is increasing worldwide at an alarming rate. It is estimated that 387 million people are affected by Type1 and T2DM and this number is expected to reach 552 million by 2030 [16]. The financial costs for the treatment of diabetes and support for the patients presents a significant healthcare challenge for any country across the world. The most prevalent subtype of diabetes is the Type 2 Diabetes Mellitus (T2DM) that comprises 95% of this disease. The salient features of T2DM are high levels of blood glucose (hyperglycaemia), hyper-insulinemia, and insulin resistance [17]. Insulin resistance arises due to decreased insulin sensitivity of muscle, liver, and fat cells to insulin. Another prominent feature of T2DM is the formation of human islet amyloid polypeptide that causes pancreatic b-cell dysfunction [18]. Both these features ultimately result in a reduced uptake of circulating blood glucose for glycogenesis eventually leading to chronic hyperglycemia as one of the pathological hallmarks of T2DM.

Evidence from previous studies

Epidemiological studies show that T2DM increases the risk of AD by at least 2-fold [19]. In a study cohort recruited from Manhattan in 1992-1994 and then in 1999-2001 Cheng et al. demonstrated that T2DMis associated strongly with Late-Onset AD (LOAD) after adjustment of sex and age.

Their findings also suggested that the link between T2DM and LOAD is partly mediated by cerebrovascular pathology [20]. Recent studies from Li et al. report that T2DM in an elderly Chinese population with mild cognitive impairment (MCI) influences the progression to AD, while no change is observed in age-matched control [21]. These data are supported by longitudinal studies in which patients with adult onset diabetes exhibited a significantly higher risk of developing AD than age-matched

subjects without T2DM [22,23] Epidemiological studies have also examined the association between ApoE4 genotype and diabetes or insulin resistance, although the reports are controversial. For instance, a longitudinal study in Japanese-American men demonstrated that ApoE4 increases the risk of LOAD in individuals with T2DM [24] In contrast, population-based studies conducted by Marseglia et al. show an association between T2DM and risk of dementia only in ApoE4 non-carriers [25].

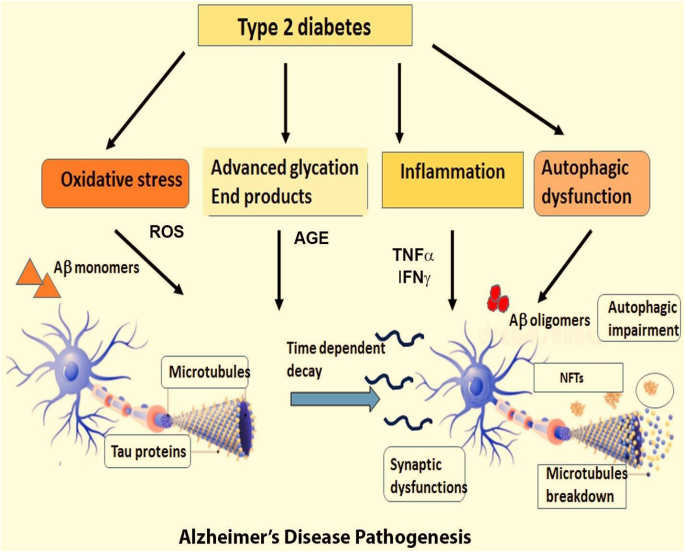

Figure 2: Overview of the diverse mechanisms by which Type 2 Diabetes can cause AD pathogenesis. Type 2 Diabetes accompanied by insulin resistance and hyperglycemia gives rise to metabolic problems in the brain and other target tissues that sets off a cascade of pathogenic processes such as oxidative stress, inflammatory responses, advanced glycation products and autophagic dysfunction. The reactive oxygen species generated by these pathways expedite the process of neuronal death. At the same time, the insulin resistance impairs the downstream signaling pathways and exacerbates the formation of Aβ oligomers and aggregates of hyperphosphorylated tau. The cumulative effect of all these factors expose the neurons to a range of assaults and gradually result in the loss of synapses and neuronal death.

The data from the neuroimaging (PET and MRI) studies reveals a considerable overlap between the vulnerable brain regions in AD and T2DM patient groups. AD is generally associated with widespread brain atrophy that initiates in the transentorhinal and entorhinal cortex in the early stages and then spreads to the remaining neocortical areas [26]. Neuroimaging studies show that the widespread pattern of neurodegeneration caused by AD in the limbic and neocortical regions correlates closely with cognitive deficits and behavioral patterns that AD patient's exhibit.

However, determining the early stages of AD pathophysiology remains a challenge. Recently a comprehensive study based on high-resolution MRI on people with MCI and AD revealed that the earliest signs of AD pathology appeared in the cholinergic cells of the nucleus basalis of Meynert (NbM) in the basal forebrain [27]. Interestingly, neuroimaging studies of brains in individuals with T2DM also show structural alterations that resemble those seen in AD patients. In a study conducted by Moran et al. 350 people with T2DM and 363 control individuals were assessed for cognitive functions with an MRI scan to identify the regional distribution of brain atrophy to identify the causes of cognitive impairment in T2DM patients [28,29]. The investigators found that T2DM was associated with more cerebral infarcts and reduced volumes of gray matter, white matter, and hippocampus compared to non-diabetic individuals. It was further observed that in people with T2DM, gray matter loss was most prominent in medial temporal, anterior, cingulate, and medial frontal lobes-the regions maximally vulnerable to AD. Moreover, cognitive functions, and in particular visuo-spatial skills, were markedly affected in the T2DM group. Another study by Roberts et al. examined the associations of T2DM with imaging biomarkers and cognitive abilities in 1,437 elderly individuals without dementia [30]. They found that midlife T2DM was associated with reduced hippocampal and whole brain volumes strongly indicating decline of cognitive functions later in life.

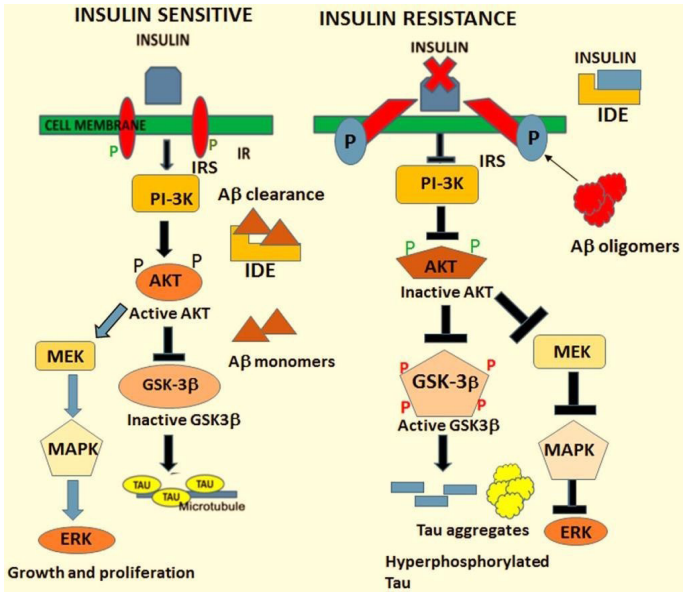

Figure 3: Neuronal signaling mechanisms in a state of insulin sensitivity and insulin resistance. In the insulin sensitive state insulin binds to the receptor and activates the insulin receptor tyrosine kinase that initiates a cascade of phosphorylation events at the IRS/PI3K/AKT and Ras/Raf/ERK pathways. AKT phosphorylates GSK-3β at the inhibitory serine 9 residue and allows tau to maintain its physiological function of binding to microtubules and facilitates normal axonal transport of neuronal vesicles. In a state of insulin resistance, GSK-3β is activated by phosphorylation at Tyrosine 216 residue and hyperphosphorylates tau at pathological epitopes.

Hyperphosphorylated tau then detaches from the microtubules and aggregates to form neurofibrillary tangles. Likewise, in the presence of excess insulin, the Insulin Degrading Enzyme (IDE) is unable to degrade and facilitate clearance of Aβ oligomers that act as a competitive substrate for insulin. Thus, insulin resistance facilitates the formation of both Ab and tau oligomers.

Wennberg et al. conducted a study on 233 cognitively normal individuals who were assessed for fasting blood glucose and cortical thickness measurements by MRI [31]. This study showed that higher blood glucose was associated with reduced average thickness in the AD vulnerable regions. Based on these observations, the authors conclude that the brain atrophy in T2DM, evident from imaging studies, bears striking resemblance to that seen in preclinical AD.

Shared pathophysiology between AD and T2DM

PET and MRI studies show marked impairment of glucose and energy metabolism in both T2DM and AD [32]. In addition, amyloidogenesis remains a salient feature in both these diseases. Extracellular β-amyloid plaques form one of the characteris-

tic features of AD. Likewise, deposits of Amyloidogenic Peptide (IAPP) are detected in the pancreatic islets of Langerhans of T2DM patients [33]. Interestingly, diabetic mice overexpressing IAPP develop oligomers and fibrils with more severe diabetic trait similar to AD mouse models that APP [34]. Advanced glycation End Products (AGE) and their receptors (RAGE) accumulate in the sites of diabetic complications such as kidney, retina, and atherosclerotic plaques under conditions of ER and oxidative stress [35]. Similarly, glycated products of Ab and tau form in transgenic AD models as well as in post- mortem brains of AD patients under similar stress conditions and form an important component of neurofibrillary tangles [36]. Moreover, additional traits of synaptic dysfunction, activation of the inflammatory response pathways and impairment of autophagy are pathological features common to both AD and T2DM [37,38].

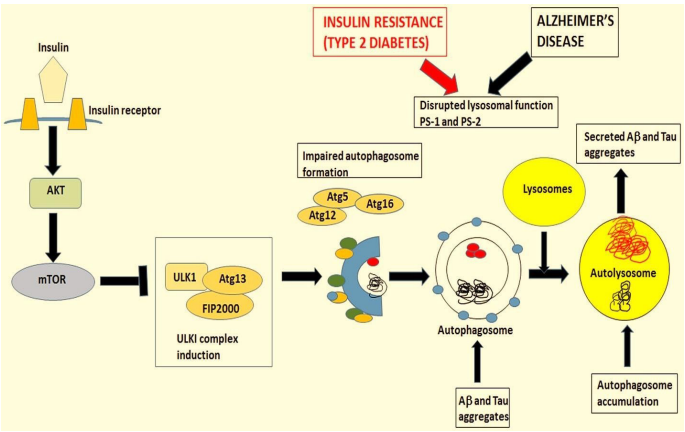

Figure 4: Insulin signaling also controls mTOR pathway that inhibits autophagy. Both insulin resistance in Type 2 Diabetes and Alzheimer's disease impairs the formation of autophagosomes and disrupts lysosomal function.

Autophagosomes fuse with lysosomes to form autolysosomes. These autolysosomes have impaired lysosomal function in AD and T2DM and accumulate Aβ and tau aggregates. Undigested toxic aggregates are secreted out of the neurons and propagate toxic oligomers in adjacent neurons.

Brain insulin resistance evident in T2DM on the two hallmarks of AD, Aβ and tau, and describe the possible mechanisms that interconnect AD and T2DM in the areas of synaptic dysfunction, inflammation, and autophagic impairment. Disrupted lysosomal function and autophagosome formation result in Aβ and tau aggregates.

Conclusion

More and more evidences suggest that the structural and functional integrity of the CNS is compromised in T2DM by excess insulin in a state of insulin resistance. In addition, T2DM impairs glucose metabolism and generates oxidative stress in vital cell organelles. Insulin resistance, which is a prominent feature of T2DM, is capable of increasing the production and secretion of Aβ by decreasing proteolysis by IDE. Also, insulin resistance dysregulates the PI3K/AKT/GSK-3b signaling cascade and generates hyperphosphorylated tau. Insulin resistance leads to loss of synapses, impaired autophagy and increased neuronal apoptosis. These alterations might trigger a cascade of events leading to abnormal Aβ and tau accumulation culminating in Alzheimer's disease pathology. Hence, targeting brain insulin signaling with pharmacological therapies used for treating T2DM is a novel and compelling approach to treat AD. This has given way to "drug repositioning" strategies in which pre-existing anti-diabetic drugs are subjected to clinical trials to test their efficacy in AD therapeutics.

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