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Review

Is Alzheimer's disease a Type 3 Diabetes? A critical appraisal☆

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ABSTRACT

Recently researchers proposed the term 'Type-3-Diabetes' for Alzheimer's disease (ad) because of the shared molecular and cellular features among Type-1-Diabetes, Type-2-Diabetes and insulin resistance associated with memory deficits and cognitive decline in elderly individuals. Recent clinical and basic studies on patients with diabetes and AD revealed previously unreported cellular and pathological among diabetes, insulin resistance and AD. These studies are also strengthened by various basic biological studies that decipher the effects of insulin in the pathology of AD through cellular and molecular mechanisms. For instance, insulin is involved in the activation of glycogen synthase kinase 3β, which in turn causes phosphorylation of tau, which involved in the formation of neurofibrillary tangles. Interestingly, insulin also plays a crucial role in the formation amyloid plaques. In this review, we discussed significant shared mechanisms between AD and diabetes and we also provided therapeutic avenues for diabetes and AD. This article is part of a Special Issue entitled: Oxidative Stress and Mitochondrial Quality in Diabetes/Obesity and Critical Illness Spectrum of Diseases - edited by P. Hemachandra Reddy.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the progressive decline of memory, cognitive functions, and changes in behavior and personality. AD is the 6th leading cause of death in the United States and the 5th leading cause of death for those aged 65 and older. Currently, 5.4 million Americans suffer from AD, including an estimated 200,000 under the age of 65 and these numbers are expected to increase up to 16 million by 2015. Nearly two-thirds of those with AD are women (3.3 million). AD-related dementia has had a huge economic impact on medical resources, with the total estimated healthcare cost at about $818 billion in 2015, which is estimated to increase to 2 trillion by 2015 [1–3].

Histopathological examination of AD postmortem brains revealed that the presence of extracellular neuritic plaques, intracellular neurofibrillary tangles and neuronal loss. AD is also associated with the loss of synapses, oxidative stress & mitochondrial structural and functional abnormalities, inflammatory responses, changes in cholinergic neurotransmission, hormonal changes and cell cycle abnormalities [3–7].

AD is multifactorial, with both genetic and environmental factors implicated in its pathogenesis. A small proportion of AD cases show an autosomal dominant transmission of the disease, and currently mutations in the genes encoding APP, presenilin 1 and presenilin 2 have been characterized in early-onset familial AD cases. The best described risk factors for AD are age and a positive family history of dementia, since more than one third of AD patients have one or more affected

Abbreviations: AD, Alzheimer's disease; BBB, blood brain barrier; RAGE, Receptor for Advanced Glycation End products; AGE, advanced glycation end products; IL1β, interleukin 1 beta; Aβ, amyloid beta; TNF∝, tumor necrosis factor alpha; TGFβ, transforming growth factor beta; ApoE4, apolipoprotein E4 genotype; APP, amyloid precursor protein; Aβ, β-amyloid; T2DM, type 2 diabetes mellitus; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B; GSK3β, Glucose synthase kinase 3 beta; NMDAR, N-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Bax, Bcl2 associated X protein; Bak, Bcl2 associated K protein; Bcl2, B-cell leukemia/lymphoma2; Drp1, dynamin-related protein1; ADDLs, amyloid-beta-derived diffusible ligands; AβOs, β-amyloid oligomers; hIAPP, human islet amyloid polypeptide; IR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5 bisphosphate; PIP3, phosphatidylinositol 3,4,5 trisphosphate; PKB, protein kinase B; LTD, long term depression; GABA, gamma amino butyric acid; PSD-95, post synaptic density 95; HD, Huntington's disease; ROS, reactive oxygen species; RNS, reactive nitrogen species; MAPK, mitogen activated protein kinase; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; CAT, catalase; Bad, Bcl2 associated death promoter; FOXO, Forkhead box protein; ATF4, activating transcription factor 4; eIF2a, eukaryotic translation initiation factor 2a; Icv, intra cerebro ventricular; IGF-1, insulin-like growth factor 1; JNK, c-Jun N-terminal kinase; LTP, long term potentiation; PERK, PKR-like endoplasmic reticulum kinase; PKR, double-stranded RNA-dependent protein kinase; CREB, cAMP-response element-binding protein; PS1, presenilins 1; PS2, presenilins 2; BIM, Bcl like protein; BDNF, brain-derived neurotrophic factor; IDE, insulin degrading enzyme; STZ, streptozotocin; PPAR, peroxisome proliferator-activated receptors; VDAC1, voltage dependent anion channel.

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first degree relatives. Other risk factors that may be associated with the development of AD include severe head trauma, low levels of education, female gender, previous depression, and vascular factors [3,4].

The increase incidence in AD would be due to one of the emerging complication of type 2 diabetes mellitus (T2DM). In the United States alone there are more than 23 million T2DM patients present. Currently, 366 million people have diabetes mellitus world-wide, and this number is expected to reach 552 million by 2030 (IDF, Diabetes atlas) [8]. T2DM is characterized by high blood sugar (hyperglycaemia), insulin resistance, and relative lack of insulin. This arises due to a reduced sensitivity of muscle, liver and fat cells to insulin (also called insulin resistance). In general, immediately after the meal there is increase in production of insulin by pancreas. The targeted organ for the insulin is adipose tissue, skeletal muscle, liver, and fat and induces the uptake of glucose from the blood and promotes glycogenesis by inhibiting glucose production. Another hallmark of diabetes is the formation of human islet amyloid polypeptide (hIAPP, amylin) that leads to pancreatic β-cell dysfunction. The resulting metabolic disturbance leads to chronic hyperglycemia, which is the immediate cause of many of the symptoms of diabetes such as retinopathy, peripheral neuropathy and nephropathy [2,9].

Substantial epidemiological evidence suggests that T2DM are strongly associated with cognitive impairment [10–14] due to failure in the action of glucose absorption in the neurons for energy production. The association between T2DM and AD is complex; both are interlinked with insulin resistance, insulin growth factor (IGF) signaling, inflammatory response, oxidative stress, glycogen synthase kinase 3β (GSK3β) signaling mechanism, amyloid beta (Aβ) formation from amyloid precursor protein (APP), neurofibrillary tangle formation, and acetylcholine esterase activity regulation. Because of shared mechanisms among Type-1-Diabetes (T1DM), T2DM and AD; researchers termed "Type-3-Diabetes". The purpose of the review article is to discuss the shared cellular and molecular connections between diabetes and AD for terming Type-3-Diabetes.

2. Impaired insulin and IGF actions in the brain

The insulin receptor (IR) is expressed both in neurons and glia of the brain and especially it is seen with highest in the hippocampus, hypothalamus, cerebral cortex and olfactory bulb [15,16]. In the brain, insulin and IGF signaling mechanisms are important in establishing synaptic plasticity for cognitive function. Once insulin binds with IR there is the activation of various several tyrosine residues by auto phosphorylation (Fig. 1). These phospho-tyrosine residues are important for insulin receptor substrate (IRS) 1 and 2 for initiating several signaling cascades such as phosphatidylinositol 3-kinase (PI3K), GSK3β signaling, mitochondrial regulation for energy production and Wnt signaling cascades. PI3K is associated with almost all of the metabolic actions of insulin [17–19]. PI3K converts phosphatidylinositol 4,5 bisphosphate (PIP2) to phosphatidylinositol 3,4,5 trisphosphate (PIP3). Then, PIP3 recruits protein kinase B (PKB, also known as Akt) to the plasma membrane, where it is phosphorylated and activated by specific protein kinases [20]. PKB has many important cellular targets including GSK3β phosphorylation. This pathway connects IR at the cell surface with enzymes of glycogen metabolism within the cell. Several potent and selective inhibitors of GSK3 have been developed that mimic the action of insulin on glycogen synthesis [21], and these are being evaluated for the treatment of insulin resistance and T2DM.

Insulin regulates synaptic plasticity by internalization of neurotransmitter receptors. For example, insulin induces long term depression (LTD) by internalization of AMPA receptors, [22–28] and also promotes GABA receptor-mediated synaptic transmission by the recruitment of GABA receptors to postsynaptic membranes [29,30]. Insulin also controls the internalization of β-adrenergic receptors [31] and GluR2 (of AMPA receptor) [25] and induces translation of dendritic synapse scaffolding protein PSD-95 [32]. These observations suggest that insulin not only involved for the glucose metabolism for the neuronal survival but also involved in the regulation of synaptic transmission neurotransmission for the establishment if synaptic plasticity. Other studies also explored neuronal functions of insulin such as neurite outgrowth [33] and enhancement of axonal regeneration in rat sensory neurons [34]. Till date, researchers have shown different types of cognitive defects in T2DM population but there are no studies on the role of insulin on spine density, synapse number and size. It is therefore of great interest to investigate whether T2DM, a disease of reduced insulin action, is associated with abnormal neuronal function. The increasing evidence supports the hypothesis that neuronal as well as peripheral insulin sensitivity is defective in T2DM.

There are many studies that shown neurodegeneration and cognitive decline in insulin-resistant patients who do not show hyperglycaemia (pre-diabetes) [35,36], concluding that hyperglycemia

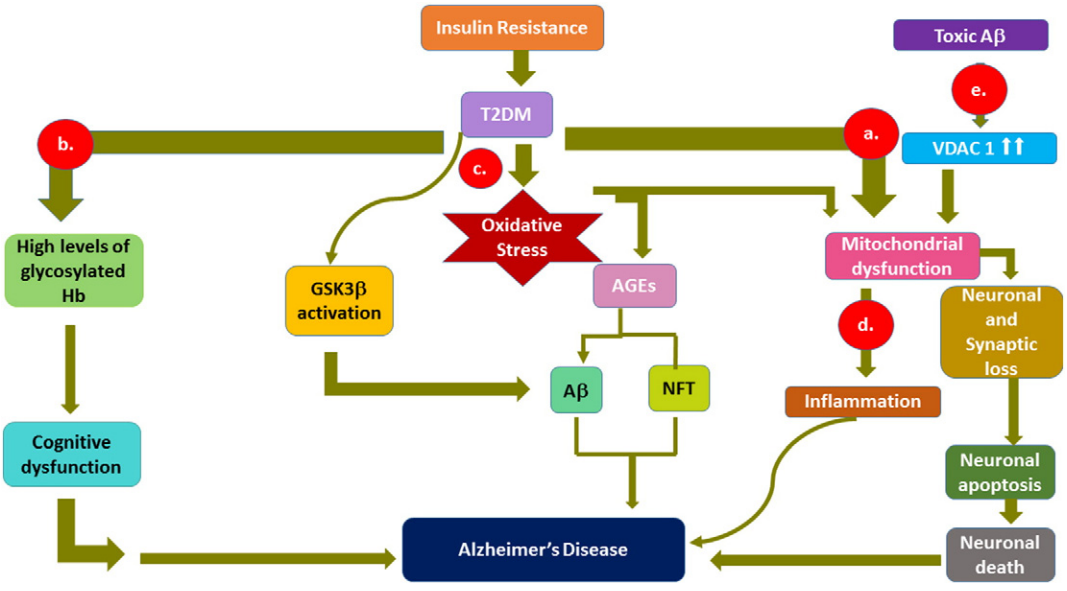

Fig. 1. Schematic representation of T2DM/insulin resistance in Alzheimer's disease through a) mitochondrial dysfunction, which in turn causes synaptic damage, and neuronal death, b) glycosylated hemoglobin in impaired cognitive function by failure in the transport of glucose for neurons, c) oxidative stress-induced amyloid beta and phosphorylated tau formations through advanced glycation end products, d) inflammation by mitochondrial dysfunction and toxicities of amyloid beta and glycation end products, e) activation of voltage-dependent anion channel by amyloid beta-induction in neuronal loss.