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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

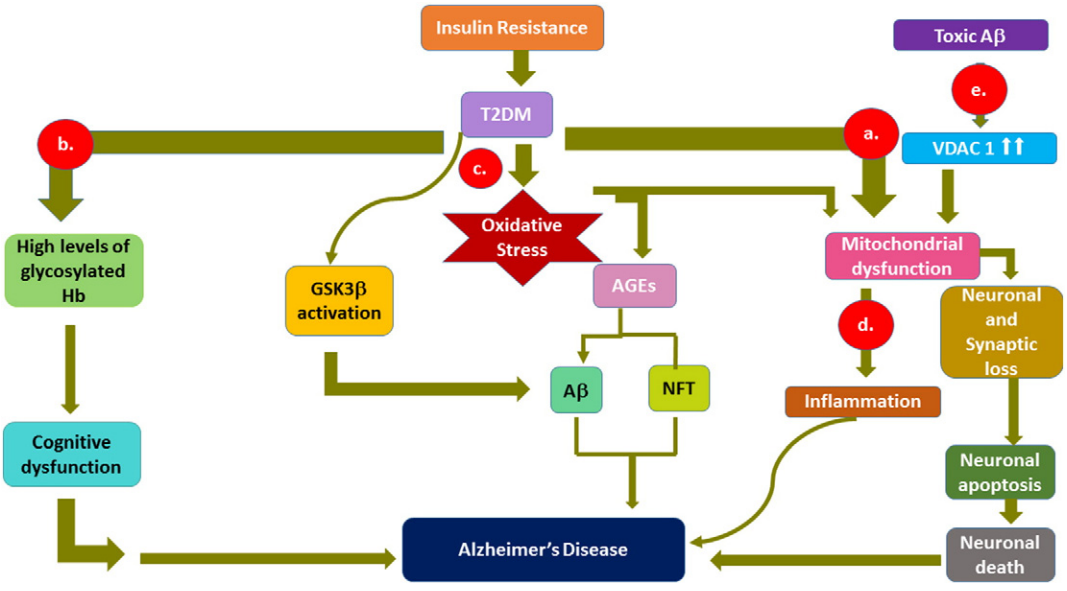

Fig. 1. Schematic representation of T2DM/insulin resistance in Alzheimer's disease through a) mitochondrial dysfunction, which in turn causes synaptic damage, and neuronal death, b) glycosylated hemoglobin in impaired cognitive function by failure in the transport of glucose for neurons, c) oxidative 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.

as important as loss of insulin action. In order to establish the molecular connection between these two conditions, it is important to first establish whether neuronal insulin resistance or neurotoxicity of hyperinsulinemias is responsible for the increased risk of AD type dementia. Intriguingly, studies have shown that in age advances glycemic controls T2DM patients given the fact about insulin receptor (IR) presence in the cerebral cortex and hippocampus not limiting to the skeletal muscle, liver and fat [37].

3. Oxidative stress, mitochondrial dysfunction, advanced glycation end products (AGE) in T2DM and AD

Oxidative reaction is a fundamental process that occurs in aerobic metabolism of every single cell in mammalian species. These reactions are considered "double edged swords" as they are essential for life but can be detrimental if unchecked or uncontrolled as already evidenced in various diseases processes including T2DM, Huntington's disease (HD) and AD [38]. Oxidative stress (OS) occurs when there is an imbalance in reactive oxygen species (ROS) and reactive nitrogen species (RNS) production and inflammatory responses to counteract these free radicals [39]. Both AD and T2DM are prototypical examples of OS induced disease processes and hence AD is rightly proposed as Type 3 Diabetes by Suzanne et al. [40]. Free radicals are constantly produced in the cells as physiological byproducts of metabolism. To maintain homeostasis, antioxidants are produced by the local activation of enzymes, resulting in maintenance of cell integrity and prevention of damage and apoptosis. Free radicals, depending on their oxidative power can be divided into those with a lower reactivity, such as those produced in aerobic metabolism and those with longer reactivity as seen in AD and T2DM. The lower reactive free radicals generally induce minor cell damage and can be repaired relatively efficiently [41]. OS causes cell injury and death by apoptosis by activating various enzymatic cascades at different cell components which include mitochondria, cytoplasm, and cell membranes. Lipid rich membranes in the human brain are particularly vulnerable to oxidative stress. Other modes of cell injury can also be explained by structural alterations in proteins such as amyloid beta and tau. These mechanisms will be discussed briefly in the following sections (Fig. 3).

3.1. Mitochondria and its dysfunction

Cell mitochondria, which are considered powerhouses of cells, are the key structures in the production of ROS and RNS. The mitochondrial membrane is very permeable to these products, which can enter the cell cytoplasm. However, most of these products are produced as a result of metabolism and can easily be converted into water and/or oxygen. This can occur in the mitochondria themselves or after entering into the cytoplasm in the presence of dismutase enzymes, thereby preventing cell damage. Despite this efficient system, oxidative imbalance can occur particularly when the mitochondria are dysfunctional and less efficient in the production of ATP, which results in increased production of ROS as observed in AD and T2DM. The production of ROS by mitochondria can be due to several enzymatic reactions [41]. These enzymes convert molecular oxygen of aerobic respiration to superoxide ion or hydrogen peroxide. The enzymes may be present on the outer or inner membranes of the mitochondria or the mitochondrial matrix itself. It has also been suggested that amyloid beta may play a direct role in the disruption of mitochondrial function (Fig. 3). A recent study reported that mitochondrial localized amyloid beta induces increased production of free radicals and causes mitochondrial dysfunction and neuronal damage in the brains of AD mice [42].

3.2. Mechanism of OS secondary to amyloid and tau protein

Amyloid beta is formed due to proteolytic processing of APP. This is very similar h1APP, which results in islet cell dysfunction leading to T2DM, analogous to AD [9]. Studies indicate that amyloid beta may change the protective mechanisms that cells have against mitochondrial oxidative damage. Uncoupling proteins (UCPs) in the mitochondrial inner membrane have been shown to decrease free radical production [43]. This mechanism seems to be ineffective in AD brains, and amyloid beta accumulation may contribute to changes in the cell that lead to oxidative stress. Hyperphosphorylated tau protein causes neurofibrillary tangles, which are one of the hallmarks of AD pathology [41]. The mechanism by which these tau proteins and h1APP lead to oxidative stress is not well understood, but some investigators believe that these are secondary processes. Su et al. reported that these proteins trigger cellular pathways such as MAPK and AKT, leading to OS and cell structure damage [44]. Many of these proteins have been studied and associated with tau phosphorylation (Fig. 2).

3.3. Hyperglycemia and oxidative stress

Hyperglycemia, either due to decreased insulin production by islet cells or due to impaired insulin receptors, can cause accumulation of advanced glycation end (AGE) products leading to ROS generation and cell damage. It has been shown that AGE products produce superoxide and H_2O_2 resulting in lipid peroxidation and cell damage in brains [40]. The link between oxidative stress and hyperglycemia is that the increase in free radicals that occurs in T2DM may be caused by varying levels of antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) [44]. This resulting imbalance in prooxidants and antioxidants which causes oxidative stress is observed in diseases such as AD and T2DM.

3.4. Lipid peroxidation

The human brain is highly susceptible to OS due to the rich abundance of peroxidizable polyunsaturated fatty acids and relative paucity of antioxidants and enzymes. T2DM pathology induces changes in the lipid profile, which causes the cells to be more likely to undergo lipid peroxidation [45]. Similar processes have been observed in the pathology of AD. Lipid peroxidation is a key biomarker of oxidative stress as polyunsaturated fatty acids with multiple bonds in cells are very likely to associate with free radicals [45]. Therefore, lipid peroxidation is associated with increased levels of ROS and RNS in any disease process which advances with oxidative stress, including AD and T2DM.

3.5. Advanced glycation end (AGE) products

AGEs are peptide/protein molecules formed as a result of the Maillard reaction [46]. These molecules accumulate with aging and also found in both the types of diabetes. The formation of these molecules in diabetes due to the hyper glycemia which is generally accepted that many diabetic complications are potentiated or initiated by the accumulation of specific forms of AGE and their interaction with receptors for AGE [47]. These AGEs promote amyloid oligomer aggregation and thus involve the formation AD neurotoxicity [48], in addition glycation of tau may enhance the formation of paired helical filaments [49]. Sato et al. have shown that the addition of AGEs to primary cortical neurons reduces cell viability, confirming that these molecules are neurotoxic [47].

4. Cellular and molecular mechanisms of insulin in AD

The role of insulin in the brain has been discussed very little in comparison with muscle, adipose tissue and liver. Recent studies have shown important functions of insulin in the brain such as metabolism of glucose (and transportation by GLUT4), regulating GSK3β signaling in maintaining neuronal plasticity, neurotrophic and neuroendocrine functions [50]. The key molecule for the neuroprotective function of IGF/insulin signaling is PKB (Akt) which may be mediated by direct

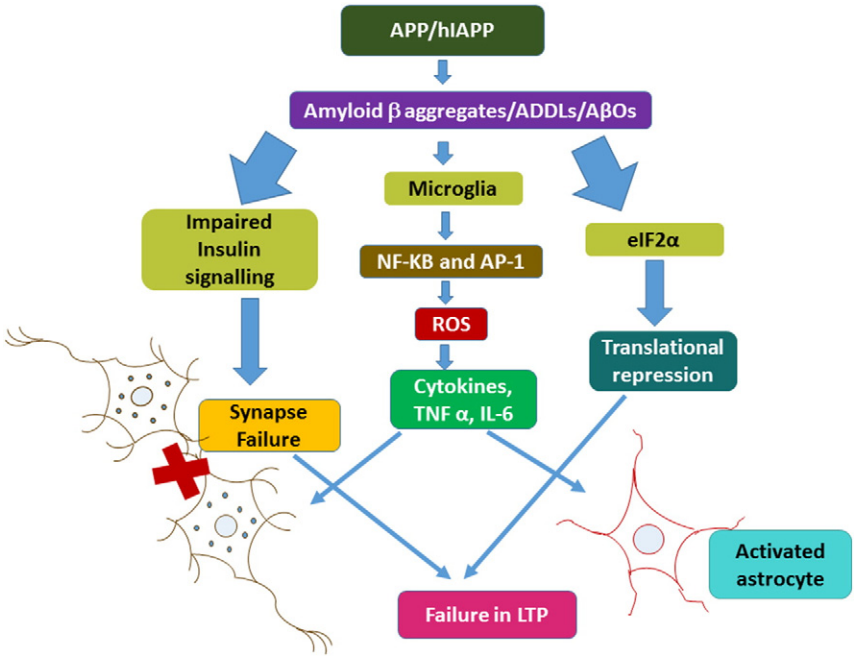

Fig. 2. Insulin resistance in T2DM causes mitochondrial dysfunction, which in turn triggers inflammation response through either APP/hIAPP catabolism. Amyloid beta oligomers activate microglia in the production of cytokines. An orchestrated action triggered by stress kinases promotes both the inhibition of brain insulin signaling and elevated eIF2a-P. While both events act to promote insulin resistance and metabolic deregulation in diabetes, they are likely to contribute to synapse loss and impaired long-term potentiation.

phosphorylation of known regulators of apoptosis, such as the pro-apoptotic mitochondrial protein Bad [51,52] and the transcription factor FOXO [53–55], as well as the pro-survival transcription factors CREB [56] and NF-kB [57,58]. FOXO controls the transcription of the pro-apoptotic Bcl2-family member BIM-1 [59], NF-kB controls transcription of the pro-survival Bcl2-family members Bcl-XL [60], A1 [61], and c-IAP2 [62], and CREB controls the expression of Bcl2 [63] and BDNF [64]. Both IR and insulin are present in the brain, and insulin is actively transported across the blood–brain barrier and might also be produced locally in the brain [65]. IRs regulate neurotransmitter release and receptor recruitment at synapse and thus responsible for synaptic/neuronal plasticity [66–69]. IRs are abundant in cerebral cortex and hippocampus and thus responsible for learning and memory processing which in turn responsible for cognitive functions [70–73]. Intracerebroventricular (i.c.v.) streptozotocin (STZ) studies have shown cognitive impairment in rats when IRs were disrupted [74] and in contrast, i.c.v. injection of insulin improves memory function in rats [75]. Based on these studies it concluded the role of insulin on the cellular and molecular events that underlie in AD pathology. In diabetes, insulin regulates the metabolism of amyloid beta and tau, in the formation AD pathology through three signaling cascades such as phospholipase C, PI3K and MAP kinases.

Tau is a neuronal cytoskeletal protein and responsible for microtubulin polymerization and stabilization. GSK-3β is responsible for binding the tau protein to microtubules. This process is regulated by protein kinases through phosphorylation. GSK-3β (Figs. 1, 3, 5) activity is downregulated by either insulin or insulin growth factor 1(IGF-1) because it is downstream event of the insulin-signaling pathway. Both IGF-1 and IGF-1 its receptors are homologous and trigger similar intracellular signaling events [65,76]. Hong et al. (1997) demonstrated a decrease in tau phosphorylation by insulin and IGF-1 and promotes binding of tau to microtubules by inhibition of GSK-3β through phosphoinositide 3-kinase pathway in human neuronal cultures [77]. Normally Akt signaling involves phosphorylating the GSK-3β and inactivates glycogen synthase. Insulin resistance leads to dephosphorylation and activation of GSK-3β [9]. Other than tau phosphorylation activity, insulin may also regulate the metabolism of APP and balances Aβ anabolism and catabolism. Qiu et al. [78] and Vekrellis et al. [79] have proposed that insulin influences insulin-degrading enzyme (IDE) in the clearance of Aβ in the brains of AD patients. IDE is the major metalloprotease involved in the degradation of extracellular Aβ along with insulin itself and other peptides [78,79]. Interestingly, insulin was shown to increase extracellular levels Aβ1–40 and Aβ1–42 along with soluble APPα in primary cultures of rat cortical neurons and in mouse neuroblastoma cells that overexpress wild-type APP [80,81]. Insulin alters the extracellular concentration of Aβ by inhibiting the extracellular degradation of Aβ by IDE, and by insulin stimulating Aβ secretion which significantly reduces the intracellular concentrations of Aβ1–40 and Aβ1–42 [80]. (See Fig. 4.)

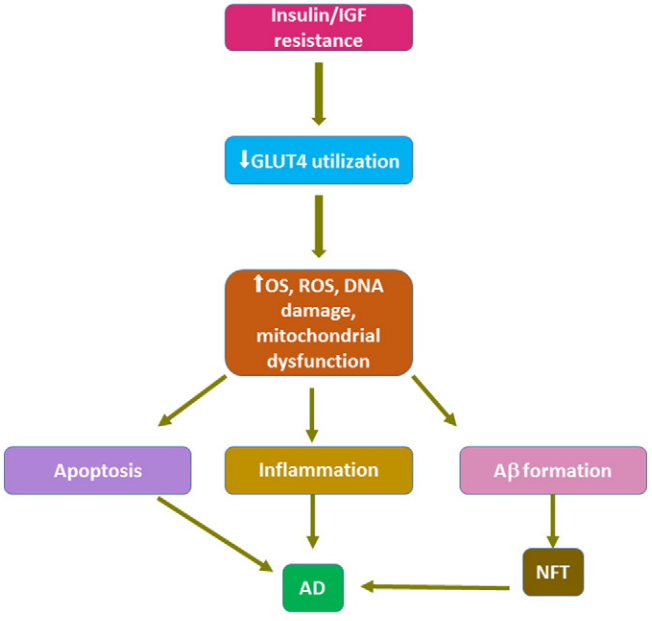

Fig. 3. Insulin resistance decreases glucose metabolism and plays a pivotal role in mitochondrial damage, DNA damage and ROS formation. This triplet action is involved in the formation of plaques.

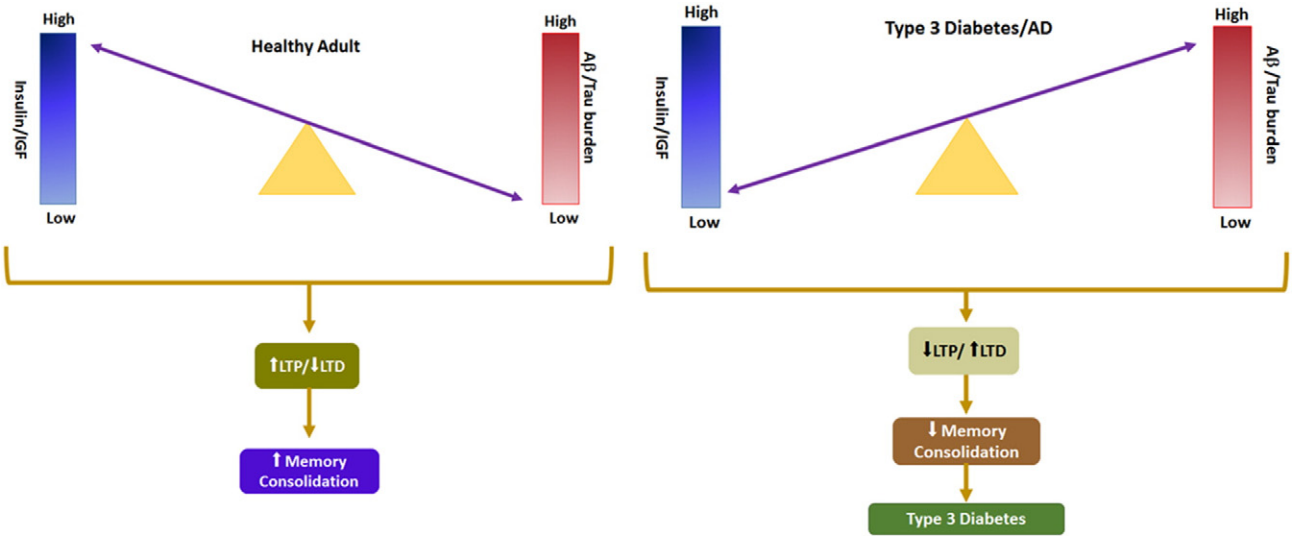

Fig. 4. Brief illustration of insulin signaling pathway in a) healthy brain and b) AD brain.
(Figure concept adapted from "Trends Neurosci. 2016 Jun 17. pii: S0166-2236(16)30037-6." [145])

Overall, these results indicate that insulin could play an important role in regulating tau protein, and Aβ and APP metabolism in neurons. Thus, dysfunction of insulin signaling might be involved in the pathological events that lead to the development plaques in AD brains.

5. Inflammation and AD

Insulin resistance in T2DM causes mitochondrial dysfunction, which in turn triggers inflammation response [82,83]. In these conditions, insulin resistance increases the levels of cytokines such as IL-6, IL-1β and IL-18, tumor necrosis factor-alpha (TNF-α), alpha-1-antichymotrypsin and C-reactive protein [84–86]. Likewise, the same inflammatory mechanism triggers in AD as well [87–89]. It has also been reported that T2DM increased the neurodegeneration of the diabetic AD mouse model by promoting Aβ aggregation and cerebrovascular inflammation by up-regulating the receptors for AGEs [90], on the other hand there is elevated immunoreactivity to IL-6 which was found in senile plaques and cerebrospinal fluid in patients with AD [87]. AGEs are expressed in neuronal cells, microglia astrocytes and in brain endothelial cells, and levels are increased in both AD and T2DM. AGEs and Aβ together induce the expression of the pro-inflammatory cytokines IL-6 and TNF-α. The Aβ-mediated activation of glial cells due to inflammation results in nerve cell death by promoting in the formation of NFTs and the progression to AD (Fig. 2). Interestingly, it has been found that inflammation leads to elevation in the AGE, tau and Aβ levels. To strengthen the role of diabetic inflammation in AD, recent reports have shown that incidence of AD is decreased in patients who consumed nonsteroidal anti-inflammatory drugs for pain or antidiabetic drugs peroxisome proliferator-activated receptor-G (PPARG) agonists [38,39p1,91,92]. AGE also causes the stimulation of TNF-α which in turn accelerates β-secretase (BACE) expression further causing APP processing for the formation of Aβ in astrocytes of diabetic models of AD [93,94].

Recently, Lourenco et al. [95] described inflammation and cellular stress, which are known to activate stress-sensitive kinases, some of which target eukaryotic initiation factor 2 alpha (eIF2a) [kinases namely PKR, PERK and GCN2] [95]. This is a mechanism initially conceived to avoid further cellular stress and to provide cells with response options to restore homeostasis. Nevertheless, prolonged brain metabolic stress and eIF2a kinase activity may lead to persistently increased eIF2a-P and exacerbated neuronal damage, in parallel to what has been described for peripheral cells in diabetes [96]. Increased eIF2a-P levels lead to upregulated activating transcription factor 4 expression, recently described as a propagator of neurotoxic signals in AD [97], as well as to Aβ generation [98] and translational attenuation [99] (Fig. 2). All these factors may contribute to neurological outcomes observed in AD. Furthermore, enhanced Aβ oligomerization, in conjunction with genetic and environmental factors (lifestyle, metabolic disease and/or cumulative infections), might instigate a feed-forward cycle that contributes to disease progression.

Aβ oligomers (AβOs) or ADDLs trigger diabetes-related toxic mechanisms in AD brains. AβO accumulation in AD brains leads to removal of neuronal insulin receptor from cell surface [100–102] Aβ further increases microglial release of TNF-a in the brain, which in turn activates neuronal TNF-α receptors and instigates cytosolic stress-sensitive kinases (e.g. JNK, PKR, IKK) [103–105]. An orchestrated action triggered by stress kinases promotes both the inhibition of brain insulin signaling and elevated eIF2a-P [103,106]. While both events act to promote insulin resistance and metabolic deregulation in diabetes, they are likely to contribute to synapse loss and impaired long-term potentiation in AD, resulting in memory impairment and behavioral outcomes (Fig. 2).

All these findings suggest that T2DM insulin resistance generates oxidative stress which in turn causes mitochondrial dysfunction and activation inflammatory response. In one direction, it is responsible for the formation Aβ pathology and in another direction through abnormal expression of dynamin related protein causes the formation of NFTs in brain.

6. Insulin and IGF link to acetyl choline (ACh) in AD

Acetylcholine is a neurotransmitter associated with neuronal signal transmission and synaptic plasticity. Reduced levels of ACh are associated with the progression of AD, and a study done by Rivera et al. [107] demonstrated the relationship between lower ChAT expression and IGF expression [107]. Using Real-time RT-PCR analysis, these authors showed that with increasing clinical AD Braak stage, the mRNA associated with IGF-I, IGF-II, and their receptors as well as tau protein regulated by IGF-I and Hu D neuronal protein are reduced. On the contrary, with increased Braak stage, progressively increased levels of amyloid beta, glial fibrilary acidic protein (GFAP) and microglial transcripts were observed. In a subsequent study, a year later, de la Monte et al. further supported the above findings using intracerebral streptozotocin (ic-STZ) treated rat models [108]. In this study, STZ treated rats produced brain specific insulin depletion and resistance leading to progressive neurodegeneration simulating AD. Hence these authors propose "Type

3 DM" for AD and suggest possible early intervention and treatment using PPAR agonists (rosiglitazone and piloglitazone).

Therefore, insulin resistance and IGF1/II deficiency may impair in the establishment of synaptic/neuronal plasticity by altering neuronal structure and effect the production of acetylcholine thus establishes a cellular link between T2DM and AD by impairing the cognitive function.

7. Role of ADDLS/AβOs in AD pathogenesis through IR

Klein and colleagues demonstrated the existence of soluble and diffusible Aβ oligomers (AβOs) and can able trigger neurotoxic signaling [109]. These AβOs also called Aβ-derived diffusible ligands (ADDLs), the terminology originally proposed by Klein [109]. Various studies found are found at increased levels ADDLs/AβOs in the brains and cerebrospinal fluid AD patients [110–115]. However these oligomers also target excitatory synapses [113], promote toxic signaling and eventually cause failure in establishment of synaptic plasticity [116–118]. These events likely to underlie rapid memory decline in AD (Fig. 5) [102].

The AβOs when they bind with IR cause synapse toxic effects such as abnormal neurotransmitter release, receptor internalization and removal synapse across the neurons. These cascades ultimately cause oxidative stress, mitochondrial fragmentation, increased cytosolic Ca^{2+} levels which affects PI3K-MAPK-GSK3 signaling mechanisms, inhibition of axonal transport and mitochondria, and hyper phosphorylation tau. Furthermore, AβOs play a role in the impairment of long term potentiation (LTP), to induce cognitive deficits in mice [102,143,144].

8. Is T2DM and late-onset dementia a Type 3 Diabetes: based on available evidences?

Recent concept suggests that AD represents a metabolic disease and the studies have shown that deficits in utilization of glucose by the brain in the early course of disease [119–122] eventually lead to the cognitive dysfunction [123,124]. Hoyer et al. have shown deficits in cerebral glucose utilization worsening in with progression of cognitive impairment [125]. In addition to the deficits in glucose metabolism, human postmortem studies showed insulin and IGF resistance and impairments in signal transduction [107,126]. Insulin resistance in brain is manifested by reduced levels of insulin and IGF receptors [107,126,127], while insulin and IGF deficiencies are associated with altered expression of insulin and IGF polypeptides in brain and cerebrospinal fluid [107,124,126,128]. These findings support the role of insulin/IGF signaling in the pathogenesis of AD [126]. Moreover, AD could be regarded as a brain disorder that has composite features of T1DM (insulin deficiency) and Type2DM (insulin resistance). To consolidate this concept, de la Monte proposed that AD be referred to as, "Type-3-Diabetes" [107,126,129]. As insulin stimulates cerebral glucose uptake and metabolism [130], cognition and memory [131–135], but failure in insulin signaling causes impairments in glucose metabolism and leads to the cerebral energy balance in turn causes ROS production, DNA damage, and mitochondrial dysfunction, all these cascades lead to pro-apoptosis, pro-inflammatory, and pro-AβPP-Aβ cascades [130,136,142]. Correspondingly, experimental suppression of brain insulin/receptor expression causes cognitive impairment [137–141]. So in T2DM because of insulin resistance the above stringent actions may take place and this would be one of the reason researchers termed this metabolic syndrome as "Type-3-Diabetes".

9. Clinical and preclinical evidence for obesity/diabetes contributing to Type 3 Diabetes

Till date the role of obesity in cognitive impairment is not well understood. Some studies have shown direction association, others indirect association, inverse association or U shaped association of obesity in relation either with low or high BMI as increased risk factor for AD (20, 21, 22). Recently, several studies on T2DM, obesity, IR, and hyperinsulinemia have shown links with cognitive impairment and AD [146–148]. A recent meta-analysis on obesity (BMI > 30 kg/m^2) has reported as obesity an increased risk factor for AD [149]; in another study it has shown that cardiovascular disease is also a risk factor for memory loss [150]. Whitmer [151] has shown 'mid-life obesity' strong and independent association with an increased risk of dementia and AD [151]. In this study the author has shown that both obesity and overweight, as measured by body mass index and skinfold thickness, in middle-age are strongly associated with an increased risk of all cause dementia, AD & vascular dementia (VaD), independent of the development of diabetes and cardiovascular-related morbidities. There is also a value in assessing regional body shape distributions of adiposity, particular the role of abdominal obesity. Mechanistic pathways such as adipocyte secreted proteins and hormones, and inflammatory cytokines could explain the association between obesity and increased risk of dementia [151].

Whereas "midlife and late-life obesity and the risk of dementia: cardiovascular health study" has shown that an increased risk of dementia was found for obese (BMI > 30) vs normal-weight (BMI 20–25) persons,

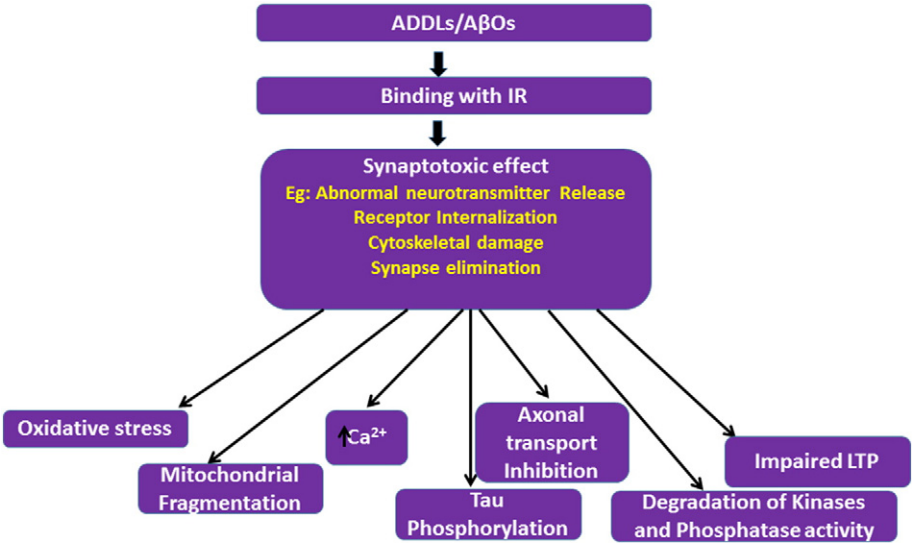

Fig. 5. Role of amyloid beta oligomers on toxic effects of synapses, including synaptic degeneration, abnormal neurotransmitter release and cytoskeletal damage. Synaptotoxic effects cause defective axonal transport, mitochondrial fragmentation, degradation of kinases activity, oxidative stress, impaired LTP, increase in intracellular calcium levels.

adjusted for demographics (hazard ratio [HR], 1.39; 95% confidence interval [CI], 1.03–1.87) and for cardiovascular risk factors (1.36; 0.94–1.95). The risk estimates were reversed in assessments of late-life BMI. Underweight persons (BMI < 20) had an increased risk of dementia (1.62; 1.02–2.64), whereas being overweight (BMI > 25–30) was not associated (0.92; 0.72–1.18) and being obese reduced the risk of dementia (0.63; 0.44–0.91) compared with those with normal BMI [152].

Luchsinger et al. [153] results have little contradiction with the above studies' results and shown decreased risk of dementia with increasing BMI, but the subjects are ≥76 years of age, but a U-shaped association in subjects < 76 years of age [153]. These results suggested that changes in body size and composition with age make BMI a poor measure of obesity in older subjects and also weight loss could be the preclinical condition of AD [151,154,157].

Till now the literature says that the pathology of AD may develop in the advanced stage of AD so the current risk factors such as obesity and IR in mid-life may be far more important than they are in later life to treat mild cognitive loss. In the later life, it is also possible that insulin sensitivity may mediate the effects of obesity on dementia, VaD and AD risk. Interestingly, numerous studies shown increase in insulin concentrations in AD patients compared to controls [146,147,155–157].

All these clinical and preclinical studies have shown that obesity, and insulin resistance/hyperinsulinemia would be the risk factors for AD, but whether adiposity and peripheral insulin sensitivity mediate incidence of AD remains unknown. However Baker et al. [158] have shown little evidence on the role of peripheral insulin sensitivity on cognition [158]. In detail, greater IR was associated with an AD-like pattern of reduced cerebral glucose metabolic rate (CMRglu) in frontal, parietotemporal, and cingulate regions in adults with PD/T2D. The relationship between CMRglu and homeostasis model assessment insulin resistance (HOMA-IR) was independent of age, 2-hour OGTT glucose concentration, or apolipoprotein E ε4 allele carriage. During the memory encoding task, healthy adults showed activation in right anterior and inferior prefrontal cortices, right inferior temporal cortex, and medial and posterior cingulate regions. Adults with PD/T2D showed a qualitatively different pattern during the memory encoding task, characterized by more diffuse and extensive activation, and recalled fewer items on the delayed memory test [158]. All these changes suggest that IR may be a marker of AD risk that is associated with reduced CMRglu and subtle cognitive impairments at the earliest stage of disease, even before the onset of mild cognitive impairment [158]. Another study has shown that higher levels of HOMA-IR along with hyperinsulinemia have also been linked to an increased burden of amyloid plaques over 10 years later in autopsy samples [159].

Overall, obesity/diabetes and Type 3 Diabetes are directly and indirectly associated with AD. Further research is still needed to better understand the precise molecular links among obesity/diabetes, Type 3 Diabetes and AD.

10. Effects of diabetes and obesity on the brain independent of Type 3 Diabetes

Central obesity and diabetes are the key components of metabolic syndrome (MS) [160]. Several studies have shown the deleterious effects of MS on the brain both structurally and functionally, leading to neurodegeneration and dementia [161].

The co-occurrence of metabolic risk factors for T2DM and cardiovascular disease (CVD) which includes central obesity, hyperglycemia, dyslipidemia, and hypertension suggests the existence of a "metabolic syndrome" [160]. Other names for MS include syndrome X, the insulin resistance syndrome, and the obesity dyslipidemia syndrome. Genetic predisposition, lack of exercise, and body fat distribution all affect the likelihood that a given obese subject will become overtly diabetic. The mechanism by which obesity induces insulin resistance is poorly understood. Several studies have focused on the role of inflammation as a mediator linking obesity to both the pathogenesis and vascular changes in several organs including the brain [162]. The incidence of T2DM has been correlated with increased levels of markers of inflammation or so called "metaflammation" including C-reactive protein (C-RP), IL-6, plasminogen activator inhibitor 1 (PAI-1), and TNF [3]. Evidence from various studies strongly favors that morbid obesity/MS causes a low grade inflammation inducing tissue and vascular damage [160].

Recent studies have demonstrated that the hypothalamus in the brain plays a crucial role in energy homeostasis by regulating two opposing neuronal axes, namely orexigenic axis and anorexigenic axis [163] (Fig. 6). When the balance in this homeostasis mechanism is disturbed, it results in disturbances in appetite with changes in insulin secretion pattern, leading to T2DM. In addition, insulin resistance in the brain plays a significant role as described in Sections '2, 8, and 9' in this review article including promotion of amyloid beta protein and tau protein.

As described elsewhere in this review, this met inflammation releases cytokines inducing cellular damage by way of free radicals or oxidative stress and autophagic effect. In addition, insulin resistance in the brain parenchyma causes microglial and astrocytic cellular abnormalities with resultant accumulation of amyloid beta protein and tau protein characteristic of AD.

Based on these it can be concluded that disturbances in hypothalamic function (a brain component) cause MS which in turn induces cellular damage in the rest of the brain causing AD. However, the cause and effect relationship is poorly understood and needs further research.

11. Type 3 Diabetes and astrocytes

Impairment of mitochondrial function is another common link between diabetes, obesity and AD. In the insulin resistance condition in T2DM, oxidative stress triggers mitochondrial injury, which finally leads to not only the activation of inflammatory markers but also the activation of macrophages such as microglia in the brain. So in the T2DM patient's brain microglia plays crucial role for the inflammation. The precise mechanism of microglia in this diabetic inflammation has not been fully investigated even though the microglial activation pathway in the hypothalamus has been widely discussed in T2DM. However, oxidative stress signals induce microglia based inflammation through chemokines and the high mobility group protein in advanced stage of T2DM [2]. On the other hand silent information regulator (SIRT) genes (sirtuins) play crucial role in the inflammation of the brain in obesity

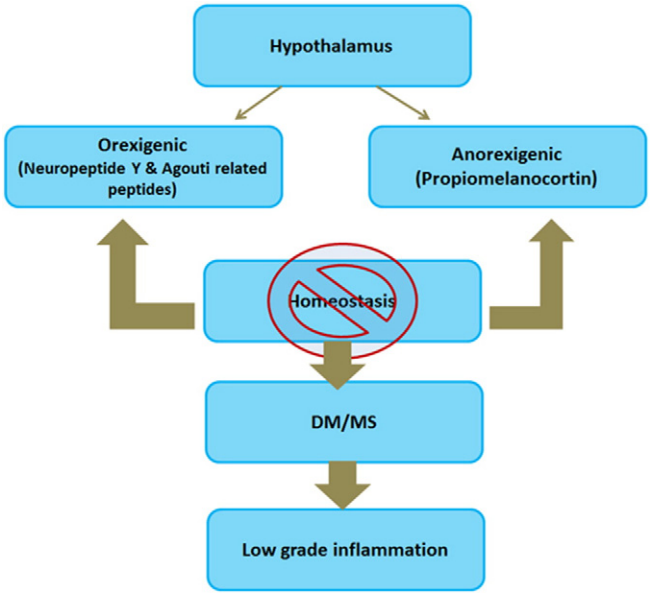

Fig. 6. Illustration of hypothalamus in the brain plays a crucial role in energy homeostasis by regulating two opposing neuronal axes, namely orexigenic axis and anorexigenic axis.

and T2DM via macrophages [2]. Nicotinamide riboside (NAD+) is an activator of SIRT1 and increases neuronal mitochondrial biogenesis such as PGC1α, NRF1, NRF2 and TFAM and anti-inflammatory action in glial cells [2,164–166]. However further research is needed to understand the therapeutic interventions of nicotinamide riboside in the brain.

Insulin resistance in T2DM increases the levels of not only cytokines and chemokines but also astrocytes. Earlier all the researchers were thinking that astrocytes have nutritive role in addition with structural support and a physical scaffold for neurons. Recent studies have shown that astrocytes play a crucial role in glutamatergic neurotransmission and in synaptic transmission by "tripartite" synapse mechanism [astrocytes themselves excite and they communicate with neurons by sensing neurotransmitter release and in turn release their own signaling molecules (glia-transmitters), and intimately associated with synapses physically]. In addition, astrocytes also associate with the cerebrovascular capillaries through "endfeet" processes. These astrocyte 'endfeet' ensheath intraparenchymal blood vessels in the brain and maintenance ionic and osmotic homeostasis and gliovascular signaling [167–169]. Thus astrocytes are in close contact with microglia as well, and there is a strong evidence for bidirectional signaling between the two cell types. Like microglia, astrocytes also activated by various stimuli such as stress, and astrocytic activation are increasingly appreciated event in AD and HD. Astrocytic involvement in the inflammation of brain is characterized by increased cytokine production and the release of signaling molecules. These events either directly or through microglial activation may affect the neuronal function. NF-kB activated astrocyte pathway releases complement protein C3, which can bind neuronal C3aR and induce neuron damage [170]. Another astrocytic signaling molecule CD40 ligand binds to the microglial cell surface receptor which in turn increases the production and release of TNFα. Insulin resistance in diabetes may cause changes such as the inflammatory response of both astrocytes and microglia may be seen in peak during MCI, ultimately causes cortical tissue destruction in AD [171].

12. Cerebral metabolic changes in Type 3 Diabetes

Rich intake of carbohydrates and unsaturated fatty acids (omega 6), low antioxidant intake, and lack of physical activity cause oxidative stress in the brain, ultimately leading to severe cognitive decline in T2DM. Recent research on T2DM strongly suggests a connection between impaired glucose metabolism, and insulin signaling with AD. In T2DM dysregulation between glucose metabolism and insulin signaling causing additional risk factor for developing AD. Clinically, AD patients have decreased cognitive function and lapses in memory that decline progressively and ultimately affect performance of tasks involved in everyday living. Physiological hallmarks of AD such as insoluble extracellular plaques, intracellular NFTs, loss of hippocampal neurons, decrease in acetylcholine production, decrease in glucose consumption in cortex and hippocampus (associated with memory and learning) can be measured by biopsy, positron emission tomography (PET) scan, or autopsy [172–175]. All of these changes in the brain were results from long-term dysregulation of insulin signaling and glucose metabolism [176]. In AD patients there is a significant decrease in the rate of glucose metabolism especially in the regions where the memory processing and learning take place [173,175,177,178]. Interestingly, the PET scans of people who are at high risk for developing AD have shown decrease in the rate of glucose metabolism before the appearance of AD symptoms and can be detected before 2–3 decades [173]. These declines in the rate of glucose metabolism are associated with normal aging, but in people who are at risk for AD, they begin at a younger age and decline more aggressively.

In the CNS, Apo-E is mainly produced by astrocytes, and transports cholesterol to neurons via Apo-E receptors. Cholesterol synthesis is upregulated and absorption downregulated in insulin resistance and in T2DM. ApoE isoform ApoEε4 allele has shown the risk factor AD. The presence of this allele is associated with increased risk of both early-onset AD and late onset AD. Localization studies demonstrate that Apo-E is deposited in the extracellular senile plaques AD patients. Aβ deposition in the form of senile plaques is more abundant in ApoEε4 carriers when compared with ApoEε4 non-carriers. Whereas ApoEε3 expression and microglial phagocytosis, reduce soluble Aβ levels, and improve cognition. The formation of NFTs in the brain is regulated by glycogen synthase kinase 3β (GSK-3β) by hyper phosphorylation tau but insulin inhibits this hyperphosphorylation of tau action. In T2DM/insulin resistance hyper phosphorylation of tau is not inhibited but an interesting feature ties hyper phosphorylated tau back to ApoEε4. Of the three isoforms of ApoE, ε4 is unique in its inability to bind tau. The E3 isoform has been proven to bind to tau (with the same suspected for E2), thus preventing or minimizing its phosphorylation [4,179,180].

Increased production of Aβ inside the cell indicates that reduced extracellular clearance and causes Aβ to accumulate as senile plaques. Aβ is cleared primarily by insulin degrading enzyme (IDE). The affinity of IDE for insulin is so high, however, that the presence of even small amounts of insulin completely inhibits the degradation of Aβ [181]. Insulin acts as a competitive inhibitor for IDE and allows Aβ to accumulate. When age advances, the production of IDE declines with age, so there is an increasing amount of substrate combined with lower enzyme activity. Just as insulin can be seen as a competitive inhibitor of IDE for degradation of Aβ, Aβ can be viewed as a competitive inhibitor of insulin for its receptor. This has been proven in human cells in vitro—Aβ reduces the binding of insulin to its receptor in a dose-dependent manner [182].

It had long been believed that glucose uptake in the brain was entirely independent of insulin with GLUT1 and GLUT3 glucose transporters and is non-insulin-sensitive. However, it is now recognized that GLUT4 glucose transporter is an insulin receptor and insulin-sensitive glucose transporter which is present at the blood brain barrier (BBB) and in some types of brain cells. Interestingly these transporters are rich in the regions where memory and learning processing takes place at high rate [183,184]. Entry of insulin and glucose into the brain happens by saturable mechanism i.e. when increased peripheral insulin levels no longer elevate levels in the CNS. In addition, GLUT1 transporters at the BBB are saturated by normal physiological concentrations of glucose [185]. Ultimately, increasing glucose uptake by the brain/CNS would require an increase regulation of GLUT4 or insulin receptors. But in AD when GLUT4 or insulin receptors have been compromised, it could cause dynamics to a functional hypoglycemia in the brain and thus decreases the rate of brain glucose metabolism. On the other hand, if there is deficiency in insulin this could cause increase in glycation (AGE) which can be seen in AD brains even though glucose enters in to the brain interstitial fluid. In one clinical study it has shown that patients with advanced AD have higher plasma insulin levels and lower CSF insulin levels when compared with healthy controls [184]. This indicates that, entered glucose in to the brain could not able to metabolize (insulin resistant) and eventually leads to the formation of AGEs and thus affects key enzymes in cognitive function. Intriguingly, in most biological mechanisms, acute administration of insulin improves performance on tests of memory and cognition, but chronically elevated insulin levels have the opposite effect [147,185–187]. This is due to the pathology of T2DM, in which normal, acute injections of insulin help regulate glucose uptake, but chronically elevated levels lead to insulin resistance, hyperglycemia, and complimented with inflammation and vascular damage. Chronically elevated insulin levels in the periphery, it seems, depress insulin sensitivity at the BBB and therefore increases glucose utilization in the brain. Usually in the absence of an alternative fuel source, brain cells starve and neurons will show decrease in their metabolic activity for other physiological functions. Metabolic fuel is inside the body, but the brain cells are not able to derive energy from it. The parallels to T2DM are striking, making the term "Type 3 Diabetes". However, further

research is needed to better understand cerebral metabolic changes In Type 3 Diabetes in relation to the progression of AD.

13. Conclusion and future directions

Earlier T2DM and AD were earlier considered as two independent metabolic disorders. But the recent literature on clinical and basic research has shown that there are common pathophysiological changes and signaling pathways such as PI3K-GSK3β signaling, neuronal stress signaling and inflammatory pathways which associate a relation between the two pathologies and termed as T3D diabetes. The current notion in AD is that abnormally activated neuronal stress signaling pathways have functional consequences in pathological conditions that affect the brain which raises the possibility that targeting these mechanisms through anti-diabetic agents and/or small molecule inhibitors may constitute an approach to treat defective brain insulin signaling, cognitive impairment and neurodegeneration. Finally, understanding disease modifiable risk factors such as aging, ApoE abnormalities, defective insulin signaling, and metabolism is critical in the development of therapeutic interventions. Several studies have reported diet and exercise in slowing the progression of AD. Exciting new therapies, including immunotherapy and deep brain stimulation (DBS), are in the horizon. The recent discovery of an immune system associated gene coding for the immune signal IL-1 receptor accessory protein (IL-1 RAP) provides another target in the treatment of AD. Abnormalities in this gene were reportedly associated with lower levels of microglial activity, faster cognitive decline, and progression to AD. In the future, targeting the IL-1 RAP pathway may be a viable approach to clearing amyloid from the brain and slowing the progression of AD. Further research is needed to better assess the impact of such exogenous mediators of neurodegeneration, and the spectrum of agents that can produce similar abnormalities leading to AD-type neurodegeneration.

Although, significant research has been done till date in understanding the cellular and molecular pathogenesis of diabetes and AD, still several questions remain unanswered on the shared mechanisms of AD and diabetes termed 'Type-3-Diabetes'. How upstream components (IR and IRS) of brain insulin/IGF signaling successfully involved in AD pathogenesis. Further, investigation of how insulin acts on long term potentiation and long-term depression across synaptic contacts is required in order to understand how stimulators of insulin signaling act to promote neuroprotection in AD brains. The role of ApoEε4 allele on the cerebral insulin signaling in the pathogenesis of AD is not studied. Current research evidence is largely based on a few rodent models and on observational clinical studies. Genetically modified mouse models by 'CRISPR-gene editing' on the brain insulin signaling along with meta-analysis studies on insulin resistance and neurodegeneration may provide important clues in the pathogenesis of AD.

Transparency document

The Transparency document associated with this article can be found, in online version.

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