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Overlapped Metabolic and Therapeutic Links between Alzheimer and Diabetes

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Abstract Alzheimer's disease (AD) and diabetes are among the most common diseases associated with ageing. The pathology of AD is strongly associated with accumulated misfolding proteins that results in neuronal dysfunction within the brain. Diabetes, on the contrary, is characterised by altered insulin signaling that results in reduced glucose uptake, metabolic suppression of energy consuming cells and conversion of glucose to fat in the liver. Despite distinguishing features, these diseases share common elements and may in fact be viewed as fundamentally similar disorders that differ in magnitude of specific traits, primarily affected tissues and time of onset. In this review, we outline the fundamental basis of each of the two diseases and highlight similarities in their pathophysiology. Further ahead we will discuss these features in relation to the development of drugs to treat these two diseases, particularly AD, for which the development of therapeutic chemicals has proven to be particularly difficult. We conclude with comments on efforts to develop a simple organism, *Caenorhabditis elegans*, as a genetic model to be used to study the systems biology of diabetes and AD.

Keywords Alzheimer's disease · Diabetes · Pathophysiology · Impaired metabolism · Therapies · *C. elegans*

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Introduction

Alzheimer's disease (AD) and diabetes are both age-associated diseases. AD is the most common form of dementia in the elderly and is clinically categorized by a progressive loss of cognitive and memory functions. Post-mortem examination of brains of AD sufferers reveals accumulation of extracellular plaques of amyloid beta (Aβ) peptides and intracellular neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau protein. In addition, there is a decrease in synapse density and a corresponding decrease in brain volume due to neurodegeneration [1–3]. On the other hand, diabetes mellitus is associated with decreased body insulin production than required (type 1) and impaired insulin signaling (type 2/T2DM). Another hallmark of diabetes is the formation of Human islet amyloid polypeptide (hIAPP, amylin) that leads to pancreatic β-cells dysfunction. The resulting metabolic disturbance leads to chronic hyperglycemia, which is the immediate cause of many of the symptoms of diabetes [4–6].

Even though the pathologies of these two diseases appear superficially unrelated, diabetes sufferers have an increased risk of development of age-associated neurodegenerative diseases, including AD. In 2005, Suzanne de la Monte [7] introduced the term "type 3 diabetes" in reference to AD. Her team observed insulin impairment associated with AD patient during post-mortem. They observed an inverse correlation between insulin receptor abundance and the Braak score of AD brains, with 80 % reduced IRS levels in the most extreme cases. They observed reduced mRNA levels of IGF-1, polypeptides and increased tau protein levels regulated by these receptors [7, 8]. Further studies on model organisms confirmed the impaired insulin signaling and oxidative insult of rat/mice brains leading to reduced brain size and neurodegeneration when treated with streptozotocin (STZ), a chemical which causes diminution of insulin, and induces an insulin-

resistant brain state [9, 10]. Moreover, the success of diabetic drugs to reduce AD complexities also opens new doors for researchers to understand their mechanisms in depth. In the following discussion, we review the common pathways linking AD and diabetes, and recent advancements in these fields.

Common Features in Alzheimer's Disease and Diabetes

As described earlier, formation of Aβ and NFTs in AD, while hIAPP and insulin resistance in diabetes are characteristic hallmarks for these diseases. Both AD and diabetes are degenerative diseases involving neuronal loss and β-cells destruction, respectively [11–14]. The main systematic link between these diseases is impaired insulin signaling leading to neurodegeneration and cognitive damages [15]. Ott and colleagues in 1999 [16] first observed the association of diabetes with dementia and further studies found 2-fold higher risk of AD in diabetic patients. Diabetes was also found to accelerate the onset of AD rather than only a risk factor in prospective and cross-sectional study [17]. Moreover, in diabetic patients with ApoE4 allele (that is genetically associated with AD), chances of AD were 2-fold higher than in non-diabetic patients with ApoE4 allele. ApoE4 is associated with APP trafficking, inhibition of Aβ clearance and lipid (mainly cholesterol) transportation. Insulin regulates cholesterol biosynthesis and high cholesterol levels were found not only to be a risk factor for diabetes but also for AD [18, 19]. Recent studies also elaborate the role of impaired insulin signaling in tau hyperphosphorylation, revealing another association between AD and diabetes [20].

AD and diabetes not only shares common pathways but also several enzymes (glutamic acid decarboxylase, dopadecarboxylase), growth factor receptors (p75 receptors, neuronal growth factor receptors and thyrotrophin-releasing hormone) and second messenger abnormalities such as dysregulated protein phosphorylation and glycogen synthase kinase 3 (GSK3) overactivity [15, 21–23]. Furthermore, mitochondrial dysfunctions resulting in increased oxidative stress and induced glyceraldehyde-derived advanced glycation end products (AGEs) are also associated with AD and diabetes [10, 24]. This review contains a brief outline about these common features and recent advancements in these fields.

Epidemiological/Environmental Risk Factors

Aging is associated with an increased risk of AD and diabetes. While aging, the decrease in mitochondrial function and oxidative capacity is observed and such is the case in AD and diabetic patients [25, 26]. In the USA, approximately one in eight persons aged 65 and older (13 %), and more than 45 % of people >85 years have AD. Meanwhile 42 % of the population over 65 are afflicted with diabetes [27–29]. The aging process is frequently associated with environmental factors especially the diet of the person. Dietary restriction or caloric restriction (CR) is linked to increased lifespan and numerous model systems showing longer life spans in CR studies. Moreover, CR has also shown to delay several age associated diseases such as neurodegeneration, diabetes, cancer and heart disease [30–33]. The reverse of CR is obesity, which is mainly associated with excess body fat (adiposity) and excessive energy intake.

Obesity is the most highlighted risk factor linked with diabetes and AD. Obesity usually refers to higher amounts of fat in the body than normal, although the normal threshold of adiposity is not clear and is associated with body height. Whereas, increased risk of insulin resistance, diabetes, dyslipidemia, hypertension, heart diseases cancer, and respiratory disease are associated with adiposity [34, 35]. Body mass index and waist circumference are two methods to measure adiposity. Several studies have reported higher risk of diabetes and AD with obesity and individuals with midlife body mass index >30 have greater chances of AD [36, 37]. Increased cognitive impairment has also been reported in patients as well as in experimental models with obesity and/or dyslipidemia [38]. Furthermore, elevated waist circumference than cut off value (cut-off value is 102 cm for men and 88 cm for women) is also associated with diabetes as well AD [39].

Several epidemiological studies performed in different countries have shown the positive correlation of diabetes with AD, where diabetic patients exhibit an increased risk of AD development when compared to non-diabetic individuals. Recent population based studies showed 2–5 times higher incidence of AD in patients suffering from diabetes and a lot of literature is available on AD and diabetic association [40–43]. Furthermore, recent studies reported AD as a form of diabetes and termed as "type 3 diabetes" due to overlapping of molecular and biochemical features that are discussed in detail later on in this review. [44, 45].

Misfolding of Processed Amyloid Peptides to Form Plaques

One of the characteristic features of AD is amyloidogenesis (changing of soluble protein into insoluble fibrillar protein aggregates to form Aβ plaques) in various brain regions that also pathologically represent AD [46]. Extensive study of Aβ formation and its after affects has led to the formulation of Aβ cascade hypothesis, which places Aβ as the primary cause of AD pathogenesis [47]. This process begins with the proteolytic processing of the precursor protein into peptides

predominantly of 40 or 42 amino acids ($A\beta_{1-40}$ and $A\beta_{1-42}$) [48]. These Aβ oligomers can directly inhibit the hippocampal long-term potentiating (LPT) component of memory by impairment of synaptic plasticity [49]. Ultimately the peptides aggregate to form extracellular protein plaques (also called senile plaques) that are cytotoxic resulting in neurological dysfunction [48]. Aβ may undergo conditional conformational changes (from native random coil structure to alpha-helical or beta-pleated strands) under slight alterations in pH, peptide concentration, metal ion concentration and environmental composition. These changes may result in diverse Aβ aggregation; however as to which confirmation is neurotoxicity directly linked to is still unknown. The neurotoxicity of Aβ is discussed later in detail with relation to other mechanisms [50, 51].

A related protein, hIAPP (human amylin), is produced in β-islet cells of the pancreas [52]. It is a 37 residues protein synergistically acting with insulin to control glycemia [53] and regulates food intake by slowing gastric emptying, signaling the brain to decrease meal size thus reducing blood glucose levels [54]. Additionally, it is also involved in the regulation of calcium homeostasis, vasodilation and renal filtration [22]. Damage of β-cells is early onset dysfunction in diabetes with deposition of misfolded hIAPP as amyloid fibrils. As hIAPP is co-secreted with insulin, insulin resistance leads to overproduction of hIAPP that accumulates as amyloid fibrils on β-cells [53, 55]. Reduced β-cells masses with the presence of β-sheet amyloid fibres of hIAPP are the characteristic of T2DM. In isolated islets these amyloids were associated with increased apoptosis with decreased area and viability of β-cells [56].

Thus, Aβ and hIAPP both can aggregate to form extracellular plaques, but this occurs in two distinct organs, brain and pancreatic β-cells, respectively [52]. The distinct tissue plaque formation is associated with the unique pathology of each disease, but whether this is a causal relationship is still unknown [50]. Despite the dissimilarity in amino acid homology, these amyloids share structurural similarities. More than 90 %, and are believed to share common mode of toxicity [57]. A recent study by Fu et al. [58] found that Aβ and hIAPP both were involved in triggering multiple cellular pathways such as MAPK, Akt, cFos and signal transduction mediator protein kinase A by increasing cytosolic cAMP and Ca^{+2} levels in HEK293 cell line through amylin receptor-3 (AMY3). This change was blocked using AMY3 antagonist AC253. Meanwhile, in a study by Gazit group small aromatic molecules naphthoquinones termed as NQT_{rp}[23] and Cl-NQT_{rp}[31] were observed as potential inhibitors of Aβ, in vitro as well as in fly and murine model systems of AD. Furthermore, they found that these molecules were also capable to disaggregate amyloid formed by hIAPP with unknown mechanisms [59]. These results not only strengthen the AD–diabetes association but also point out new therapeutic target for AD and diabetes. Moreover, human Ca^{+2} binding protein nucleobindin 1 (NUCB1) was found be useful in inhibiting hIAPP fibril formation as well as disaggregation of pre-existing hIAPP fibrils through unknown mechanism [60]. We purpose that NUCB1 should be checked as potential inhibitor for Aβ plaques formation in AD patients.

Impaired Insulin and Glucose Metabolism in AD and Diabetes

Insulin is a hormone that has an important role in glucose homeostasis in a dynamic relationship with both feeding and fasting as well as in growth and development of body tissues [61, 62]. Insulin is mainly synthesized by pancreatic β-cells and secreted to peripheral circulatory system. Although insulin is transported to brain through the blood–brain barrier (BBB), evidence indicates that the brain can synthesize insulin locally. In the central nervous system, insulin also normalizes and maintains cognitive functions by regulating key processes such as neuronal survival and longevity, learning, and memory. Defective insulin signaling leads to energy deficient neurons resulting in various metabolic insults and impaired synaptic plasticity which is discussed later [63, 64].

Insulin Resistance in Peripheral System and Central Nervous System

Insulin resistance may be defined as a diminished ability of cells or tissues to respond to physiological levels of insulin. Insulin resistance can be associated with defects in insulin receptor function, insulin signal transduction, glucose metabolism, transport, glycogen synthesis, hyperinsulinemia, hyperglycemia, inflammation and lipids metabolism [65]. Increased lipid content induces insulin secretion referred to as hyperinsulinemia for maintaining normoglycemia. Any defects in insulin secretion (low insulin levels, type 1 diabetes) and signaling (insulin resistance at cellular levels, type 2 diabetes) may cause hyperglycemia or high blood sugar levels. In this situation, diabetes is a disease originated from defects in the body's ability to control insulin and glucose homeostasis due to hyperglycemia, insulin resistance and β-cell failure [66, 67]. Insulin resistance also has a pivotal role in the progression of neurodegenerative diseases especially in AD. Many studies have found neuroprotective effects of insulin actions in the brain [9, 68, 69]. Insulin deficiency, resistance and hyperinsulinemia are involved in cognitive impairments observed in patients with diabetes [70]. AD is associated with reduced insulin and insulin mRNA as well as decrease level of insulin receptors [8]. In vitro studies have shown the impaired insulin signaling,

hyperphosphorylated tau proteins, and neural loss in T2DM affected AD animal models [70–73].

Increased cerebrospinal fluid (CSF) insulin levels are correlated with high peripheral insulin in AD patients [13]. Insulin also has effects on Aβ metabolism. Hyperinsulinemia can increase extracellular Aβ concentration by stimulating its trafficking from Aβ generating sites (trans-Golgi network and endoplasmic reticulum) that results in reduced intracellular concentrations of Aβ. Insulin-degrading enzyme (IDE) plays an important role in Aβ degradation. Insulin can competitively inhibit IDE that results in reduced Aβ degradation [74, 75]. Induced activity of IDE in transgenic mice brain results in decreased levels of Aβ thereby preventing cognitive decline [76]. Furthermore, persistent peripheral hyperinsulinemia leads to decreased transportation of insulin to the brain and causes an insulin-resistance brain state resulting in reduced insulin levels in CSF [7]. Brain insulin resistance consequently decreases the IDE levels in AD patients resulting in increased Aβ neurotoxicity [77]. Interestingly, Aβ also has the ability to reduce insulin signaling and receptor autophosphorylation suggesting that Aβ competitively inhibits insulin binding. Moreover, Aβ is also reported to reduce insulin receptors substrates signaling in cultured cells [74, 78]. These findings suggest an important role of insulin dysfunction in neurodegenerative diseases.

Insulin Signaling Mechanism

Insulin implements its actions through insulin signaling pathway by interacting with insulin receptors. A brief outline is presented here. Preproinsulin an inactive single chain precursor with a signal sequence is the primary form of insulin secreted by pancreatic β-cells. After removal of signal sequence by proteolysis, preproinsulin changed to proinsulin that is further converted to insulin by special proteases when blood glucose or amino acid concentration increases. Active insulin is consisted of two chains, bound together with disulfide bonds [79]. Insulin performs its duty by binding to its specific receptors known as insulin receptors (IR). Insulin binds to the α-subunit of the receptor and activates the tyrosine phosphorylation of β-subunit of the receptor [80, 81]. This process activates two important signaling pathways: Akt (also known as protein kinase B [PKB]) and MAPK (mitogen activated protein kinase) [82, 83]. Akt signaling regulates cell growth, proliferation, survival, and protein synthesis; while MAPK signaling activates cell differentiation, proliferation and death (Fig. 1).

Insulin Signaling in Diabetes and AD

Activation of Akt results in phosphorylation of 3′-OH group of inositol thus generating PIP2 and PIP3 (phophoinositide phosphates) that further activates serine/threonine kinases, 3′-phosphoinositide-dependent kinase-1 (PDK-1), PKB/Akt, and MAPK regulatory pathways [84, 85]. As Akt and MAPK are major pathways involved during insulin signaling through tyrosine phosphorylation on insulin receptors, defects in insulin receptors, insulin receptor substrates (IRS) and these pathways lead to complications that are hall mark of diabetes, AD and their related abnormalities [86, 87].

Defects in Insulin Receptors

A decrease in tyrosine kinase activity of insulin receptors was observed in T2DM suggesting a post-receptor defect with reduced association of the insulin receptor with p85 subunit of Akt leading to impairment of insulin stimulating glucose disposal and glycogen synthesis. This also leads to defects in glucose transportation and lower level of GLUT4 mRNA in muscles. Glucose may undergo glycolytic pathway or glycogen synthesis after phosphorylation through hexokinases (HK-I to -IV) [67, 88, 89]. Increased insulin induces glycogen synthesis, while decreased glycogen synthesis in muscle cells due to insulin resistance is hallmark in T2DM especially in skeletal muscles [67, 90]. Rare mutations on IRS especially IRS-2 may lead to insulin resistance in T2DM patients as chances of diabetes were more in IRS-2 mouse mutants compared to IRS-1 [91]. Insulin receptors found in the brain's hippocampus and cerebral cortex play important role in memory and learning [8, 92]. Mutated mice lacking IRS-2 show improved premature mortality and Aβ deposition lead to the IR role in AD pathology [93, 94]. A reduced insulin signaling was observed in brains of AD patients. Aβ also has the ability to induce insulin resistance by down regulating the IRS expression [74].

Akt Signaling

The binding of Akt with insulin receptors is affected by serine phosphorylation of IRS that decreases the tyrosine phosphorylation of IRS due to several mechanisms such as hyperglycemia, inflammation, hyperinsulinemia, hyperlipidema and mitochondrial dysfunction. It may lead to disassociation of Akt from IRS or IRS from insulin receptors [95, 96]. Circulating free fatty acids (FFA) and tumour necrosis factor (TNF) may induce serine phosphorylation in muscle cells leading to IRS dysfunctioning [97, 98]. Although the mechanism of insulin signal impairment through FFA is still unclear, the intracellular lipid metabolites such as diacylglycerol (DAG) and acetyl CoA lead to insulin resistance through IRS serine/threonine phosphorylation via protein kinase C (PKC) and may result in endothelial dysfunction in T2DM [99, 100]. DAG that induced the PKC is also observed in muscles during lipid infusions and fat feeding. FFA also induces PKC phosphorylation independent of

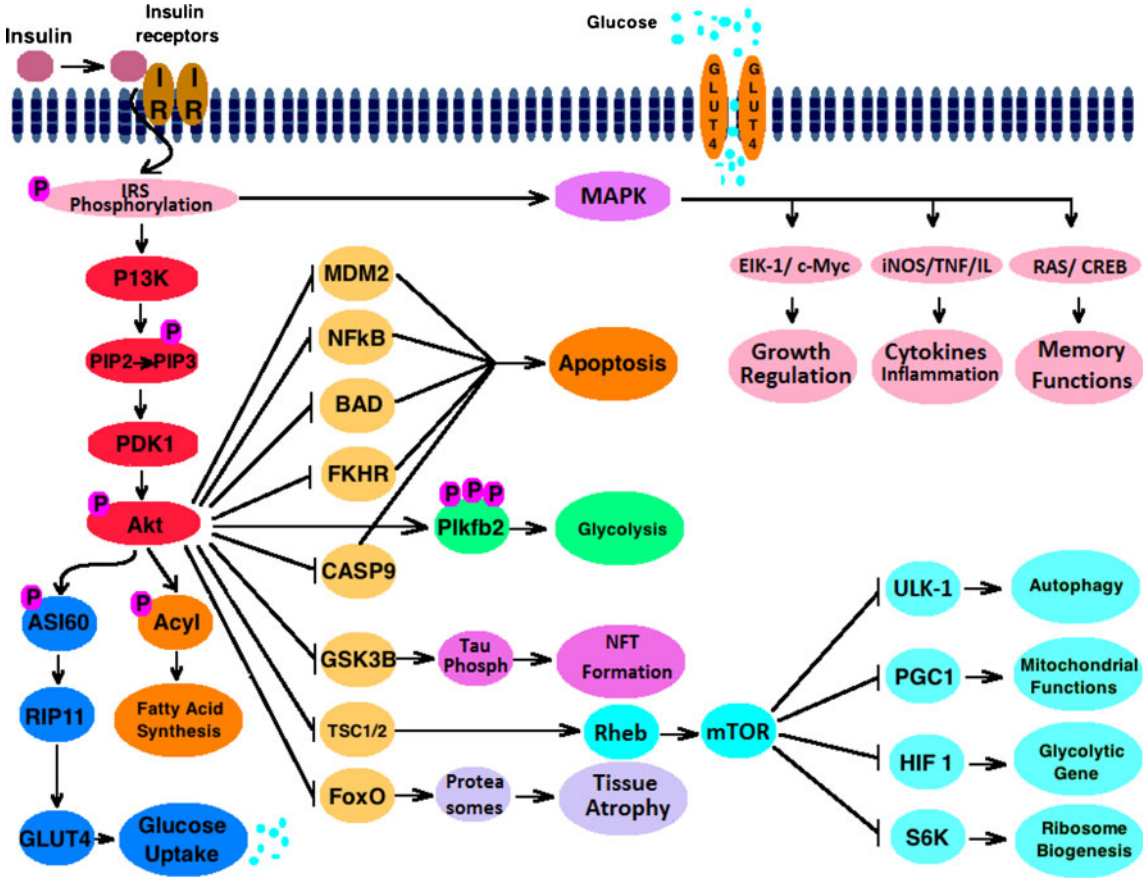

Fig. 1 Linking insulin-signaling mechanism with diabetes and AD. Impaired insulin signaling due to insulin resistance or defects in insulin receptors and Akt phosphorylation lead to activation of all pathways that remain block during normal signaling. Deactivation of Akt triggers several transcription factors that resulted in abnormal cell functions, apoptosis, neuronal cell death via NFT production, tissue atrophy and inflammation. These are major hallmarks in patients with AD and diabetes

PDk1 and translocates PKC to the nucleus and inhibits IR gene transcription [101, 102]. A recent study by Liu et al. [103, 104] has observed the decreased levels of insulin signaling components, increased hyperphosphorylation of tau and reduced *O*-GlcNAcylation (OGlcNAc) levels in the brain of patient suffering from T2DM. Decreased brain glucose levels are resulted in reduced *O*-GlcNAc levels that regulate phosphorylation of tau inversely. Interestingly, *O*-GlcNAc modification also regulates the AKT phosphorylation [103, 104]. It is interesting to know that at first insulin induced IDE expression in hippocampal neurons, while IDE decrease is associated with reduction of Akt p85 subunit. This observation lead to the hypothesis that IDE reduction by insufficient insulin action might increase the chances of AD, as brain IDE activity reduced in hyperinsulinemia conditions [105, 106].

Akt signaling may be blocked by PTEN (tensin homologue deleted on chromosome ten) and tumour suppressor protein phosphatase resulted in dephosphorylation of PIP2 and PIP3 [107, 108]. Imbalances among the Akt subunits p85 and p110, and their heterodimer p85–p110 are also responsible for insulin resistance. Akt p85 unit competes with p85–p110 (as this heterodimer unit is responsible for Akt activity) and the p85 induction is caused by human placental growth hormone. This type of resistance is observed in pregnant women with T2DM [109–111]. Akt triggers downstream effects leading to glycogen synthesis, hepatic glucose production and on/off switch of many transcriptional factors. Studies in mice have shown that deletion of Akt leads to insulin resistance ending up with diabetes phenotype as humans. Upon activation, Akt blocks apoptosis related genes such as BAD, caspase 9, GSK3, FoxO family transcription factors, CREB and NF-κB. It also blocks the MDM2 activity by blocking p53 [106, 112]. Furthermore, Akt phosphorylation allows the translocation of GLUT4 (glucose transportor) to the plasma membrane by AS160 phosphorylation [113]. The mutated Akt was unable to phosphorylate downstream targets and inhibition of gluconeogenic through phosphoenolpyruvate carboxykinase (PEPCK) [114, 115]. Another factor regulating gluconeogenesis and its related genes PEPCK and G-6-pase is FoxO protein 1 and 3 in patients with hyperglycemia. A reduction in Akt activity leads to decreased phosphorylation on FoxO allowing its entrance to the nucleus and activation of its

transcription factors in T2DM. Phosphorylation of FoxO regulates gene transcription and inhibits apoptosis to promote neural growth and survival through phosphorylation of BAD (Bcl-2 associated death promoter protein) [116–118].

Akt also initiates protein synthesis by p70s6k phosphorylation that may shutdown IRS activity by direct phosphorylation of IRS through mTOR (overactive mammalian target of rapamycin) signaling triggering by Rheb (GTPase RAS homolog enriched in brain). Akt also regulates the binding of TSC1 protein from TSC2 (tuberous sclerosis protein 1 and 2). Upon phosphorylation, TSC2 is released and activates Rheb and mTOR pathway [119, 120]. mTOR further activates initiation factor 4E-BPs (4E-binding proteins) phosphorylation and inhibits its binding with elF (eukaryotic initiation factor) and promotes elF4E cap-dependent translation that control cell growth and survival. This event also activates adipocyte differentiation transcription factors, PPARγ, CCAAT enhancer binding protein α (E/EBP), etc., that leads to adipogenesis, obesity and insulin resistance if not properly controlled [121–124]. Activation of p70S6 protein regulates ribosomal function by phosphorylating ribosomal proteins and initiates amino acid addition to newly synthesized peptides. In T2DM, effected kidney tissues, induced mTOR levels were observed with matrix expansion and renal hypertrophy [125, 126].

Under normal conditions Akt signaling phosphorylate the glycogen synthase kinase 3B (GSK3B) and inactivates glycogen synthase. Insulin resistance leads to dephosphorylation and activation of GSK3B. Increased expression of GSK3 was observed in patients with neurodegeneration and was associated with Tau hyperphosphorylation [127, 128]. A study by Schubert et al. reported high tau phosphorylation with significantly reduced phosphorylation of Akt and GSK3 in NIRKO mouse brains [129, 130]. Hyper tau phosphorylation via GSK3 impairment is associated with NFT formation in brain, which is an important hallmark of AD [131].

In brief, defects in Akt signaling not only lead to defects in glycogen synthesis, gluconeogenesis, glucogenolysis, and amino acid synthesis but also promote AD through hyperphosphorylation of tau and reduction of *O*-GlcNAcylation.

MAPK Signaling in Diabetes and AD

MAPK signaling activates intracellular enzymes that have ability to respond to stimuli from extracellular environment. MAPK pathway runs parallel to Akt and stimulates extracellular signal-regulated kinases 1/2 (ERK1/2) that induce activation of several transcription factors such as ElK-1 and c-Myc that are important in cell growth regulation [132, 133]. The Ras-ERK/MAPK activated cascade is thought to be involved in memory formation by synaptic plasticity [134]. MAPK signaling also activates MK2 (MAPK-activated protein kinase 2) that is further involved in mediating inflammatory response to cellular stress. It is shown by cell culture studies showed that MAPK activation resulted in expression of inflammation-associated iNOS, TNFα and IL-1β genes [135]. MAPK activation also upregulates cytokine production by direct phosphorylation of transcription factors such as CREB (cAMP response element binding). CREB has direct effect on structural changes associated with memory formation [136].

MAPK pathway is involved in excessive tau phosphorylation, neuroinflammation and synaptic plasticity in AD patients. Induced MAPK expression is reported in hippocampal and cortical regions of brain in AD patients when compared with aged-matched healthy individuals. Furthermore, greater immunoreactivity of MAPK is observed in AD post-mortem brains [137, 138]. Moreover, in transgenic mice, tau hyperphosphorylation was found to be directly associated with phosphorylated MAPK. Furthermore, Aβ fibrils in microglia also able to activate MAPK signaling that resulted in inflammatory gene expression and elevated proinflammatory cytokines [139]. Briefly, impaired MAPK signaling is not only associated with neuroinflammation but also leads to the promotion of Aβ and NFTs generation.

Abnormal Glucose Metabolism

Abnormal glucose metabolism is a characteristic of T2DM and is mechanistically linked with AD [52]. Metabolic abnormalities due to impaired glucose consumption and energy metabolism in AD almost resemble with T2DM. In addition, impaired glucose metabolism and insulin resistance also lead to memory and synaptic dysfunction in patients suffering from diabetes (Fig. 2) [140, 141]. Furthermore, increased ratio of plasma insulin levels to decreased CSF was reported in AD patients [13]. These findings lead to the conclusion that normal glucose metabolism is associated with standard cognitive response and any defects in glucose metabolism lead to cognitive system decline. Brain neurons are unable to produce and store glucose, and require continuous glucose transportation through the BBB by glucose transporters (GLUTS). Glucose transporters, isoforms 1, 3, 4 and 8 are abundant in the brain. GLUT 1 expressed on BBB endothelial cells and cortical membranes, GLUT 3 expressed on neurons while GLUT 4 and GLUT 8 expressed in intracellular compartments of neurons [10, 142, 143]. Reduced levels of GLUT1 observed in AD patients as well as in transgenic mice lead to reduced supply of glucose from peripheral transport system [8]. Reduced GLUT 1 and 3 levels and decreased glucose utilisation are likely to be associated with tau hyperphosphorylation, increased density of NFTs, and reduction in *O*-GlcNAcylation [144–146].

Functional neuroimaging technique positron emission tomography (PET) has been found best to monitor neuronal

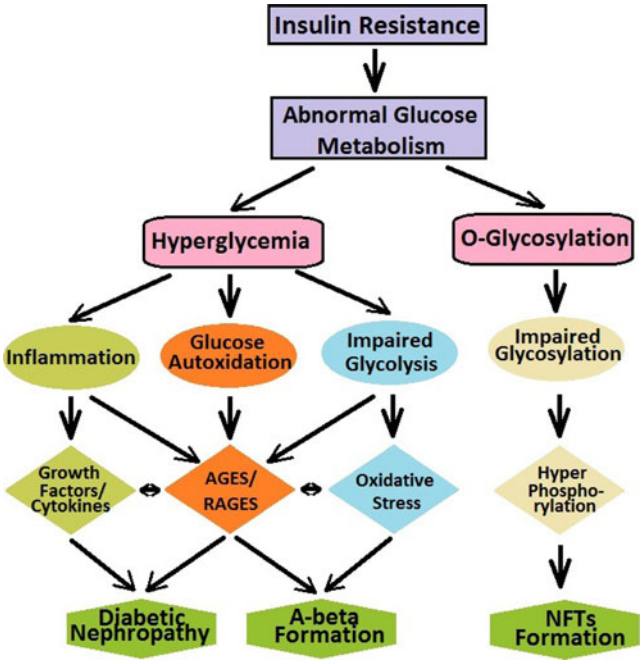

Fig. 2 Hyperglycemia-prompted activation of molecular pathways associated with AD, and diabetes. Defects in insulin signaling pathway and/or in production of insulin lead to hyperglycemia. Hyperglycemia promote production of AGES, oxidative stress, and induce levels of various growth factors and cytokines that accumulatively endorse the AD and diabetic complications

activity and specific biological processes at tissue levels in vivo. PET with 2-[^{18}F]fluro-2-deoxy-D-glucose (FDG) is used to estimate qualitative and quantitative changes in cerebral metabolic rate of glucose (CMRglc) [147]. Several studies have reported the cerebral metabolism decline before the attenuation of cognitive functions. In AD, reduced CMRglc has been reported in hippocampus, parietal–temporal and prefrontal regions of brain when compared with age-matched health individuals [148, 149]. Decreased CMRglc metabolism may lead to mitochondrial dysfunction, hyperglycemia and inflammation within the brain. A 55–65 % decrease in cerebral glucose utilization was observed not only in AD patients and in transgenic models but also in individuals carrying the apolipoprotein 4 allele. ApoE4 allele can lead to reduced glucose metabolism and energy production within brain [21, 150, 151]. Reduced activity of mitochondrial proteins mainly associated with TCA cycle such as α-ketoglutarate dehydrogenase, pyruvate dehdrogenase, and isocitrate drhydrogenase was observed in AD patient's brain tissues. This reduced activity was resulted in the release of cytochrome *c* from mitochondria, and caspase-3 activation leading to neuronal cell death. Moreover, these changes were positively associated with the degree of clinical disability in AD [152, 153]. Furthermore 50 % decrease in ATP production from glucose was also reported in early AD. All these findings suggest that ATP-dependent energy generation is vital for normal cell performance [154].

Although glucose is the least reactive reducing sugar, it may lead to non-enzymatic Amadori products through Schiff base formation by reacting with free amino groups of proteins, lipids and nucleic acids. These Amadori products accumulate on proteins and initiates process of advanced glycation [155, 156]. Hyperglycemia resulting from insulin resistance promotes the production of AGEs that are involved in AD pathogenesis. Although this process occurs in normal aging, it becomes highly accelerated in diabetes. AGEs are accepted as active contributors in AD progression and induce Aβ and tau glycation that lead to Aβ aggregation and NFTs formation in the brain [157, 158].

AGEs implement their functions and induce several biological processes through binding with RAGEs (receptors for AGEs). RAGEs not only interact with AGEs but also bind and interact with Aβ. Activation of RAGEs through binding with these ligands may initiate ROS production and inflammation [159, 160]. Levels of RAGEs were increased in RAGE-bearing cells from AD patients when incubated with Aβ that resulted in increased oxidative stress through NADPH oxidase-like mechanism, and activated NF-κB pathway [161]. Furthermore, Aβ transportation across the BBB was associated with RAGE that was blocked by using anti RAGE IgG or sRAGE (soluble RAGE). Moreover, RAGE associated transport of Aβ and induction of tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and heme oxygenase type 1 was also observed in mice neuronal cells. Mice administrated with sRAGE showed decreased Aβ production and accumulation in brain parenchymal regions [162].

It is suggested that vascular remodelling in diabetes and AD linked cerebrovascular amyloid angiopathy (CAA) are both associated with RAGE expression [163]. Aβ-RAGE interaction also has effects on cerebral blood flow in murine models. Infusion of Aβ into peripheral circulation resulted in reduced cerebral blood flow that was prevented by sRAGE, RAGE IgG or RAGE specific inhibitor (FPS-ZM$_1$) administration [162, 164]. Furthermore, induced levels of vasoconstrictor mediator endothelin-1 were induced to block Aβ-associated suppressed cerebral blood flow. A recent study by Xiong et al. [165] reported that RAGE expression in human umbilical vein endothelial cell line (ECV-304) had prevented the endothelial cell membrane repair by activating β-catenin levels that resulted in reduced F-actin stress fibres and attenuated plasma membrane resealing [165].

Impaired glucose metabolism also plays a very important role in NFTs formation by promoting hyperphosphorylation of tau protein. Tau protein undergoes many posttranslational modifications (PTMs) particularly phosphorylation and glycosylation. Tau phosphorylation has been thought to inhibit

the binding of tau protein from microtubules, while hyperphosphorylation leads to self-aggregation of tau filaments and NFTs formation. *O*-glycosylation (addition of one molecule of *N*-acetylglucosamine to serine or threonine residue) is thought to regulate tau phosphorylation reciprocally by competing phosphate groups on single or proximal Ser/Thr residues [166, 167]. Although exact mechanism by which *O*-glycosylation regulates tau phosphorylation is unknown, *O*-glycosylation is thought to be associated with glucose metabolism. Furthermore, STZ-induced diabetic rat showed reduced *O*-glycosylation levels that were restored after insulin treatment [168]. Decreased GLUTs levels and *O*-glycosylation have also been reported in the AD brain when compared to normal [20, 169]. A recent study by Yuzwa et al. [170] has observed that *O*-glycosylation at tau protein not only delays neurodegeneration but also hinders tau oligomerization. These observations suggest *O*-glycosylation as a potential therapeutic target to slow down AD progression and this mechanism also provides evidence of shared pathology between diabetes and AD.

Inflammation

Insulin resistance in diabetes and AD also leads to inflammation. Vascular inflammation mediated by RAGE has been proposed as a possible mechanism for vascular dysfunctions in AD and diabetes. Furthermore, the levels of inflammatory mediators IL-6 and C-reactive proteins were raised in diabetic, and AD patients [171]. It is reported that diabetes accelerates memory dysfunction via promoting Aβ aggregation and cerebrovascular inflammation by up regulating RAGE in diabetic mice AD models [2]. Ramasamy et al. [172] and Srikanth et al. [173] extensively reviewed the role of AGEs and RAGE in development of AD. Briefly, RAGE can be activated by many ligands as described earlier. AGEs and Aβ synergistically induce the expression of the proinflammatory cytokines IL-6, TNF-α and M-CSF (macrophage colony-stimulating factor). Aβ-mediated persistent activation of microglial cells due to proinflammatory state is resulted in neuronal cell death and disease progression in AD. Interestingly, inflammation induced levels of both Aβ and AGEs. Stimulation of TNF-α accelerates BACE1 expression and resulting in enhanced amyloidic processing of APP in astrocytes and formation of Aβ in diabetic models of AD [172, 173].

Summary of the Section

Impaired insulin signaling and glucose metabolism is not only risk for diabetes but also for AD. Peripheral insulin dysfunctions induce impairments to insulin functions in brain that result in Aβ aggregation and NFTs formation. Furthermore, abnormal glucose metabolism not only promotes oxidative stress, Aβ aggregation and NFTs formation but is also responsible for vascular angiopathy and inflammation in AD as well as in diabetes. Additionally, AGEs and RAGE both promote AD and diabetic complications and provide a common link between these two diseases. In the words of Kroner et al. [174], "co-existence of brain insulin deficiency and resistance suggest that AD might be form of diabetes i.e., type 3 diabetes."

Linking Lipids with AD and Diabetes

AD and diabetes are not only characterized by insulin metabolism impairments but also by dyslipidemia. Lipid-mediated signaling regulates many physiological processes like trafficking and proteolytic activities of membrane bound protein [175, 176]. Fatty acids (FAs) are mostly synthesized in all body cells, stored and circulated as triglycerides. FAs can be degraded by lipases such as phospholipase (PL) and lipoxygenase (LOX), and resynthesized in the form of phospholipids [177]. Increased levels of FFA, triglycerides, cholesterol and low density lipoproteins (LDL), and reduced levels of high density lipoproteins (HDL) are well-described risk factors not only for diabetes but also for neurodegenerative diseases like AD [178–181]. Induced FFAs levels in brain were also linked with mitochondrial dysfunction, and IDE inhibition that resulted in increased Aβ production [182, 183].

Phospholipase isoform A2 (PLA2) hydrolyses the phospholipids and converts them to arachidonic acid (AA) which further can be converted to various signaling molecules required for cellular metabolism [177]. Several studies have found that induced levels of LOX and PLA2 are associated with higher intensity of Aβ, and cognitive decline in transgenic mice models [184, 185]. Furthermore AA also activates NADPH, a major source of ROS production in neurons that consequently activates cytoplasmic PLA2 (cPLA2) [186, 187]. cPLA2 regulates AA release at synapses. In neurons, AA is involved in synaptic functions and it's over production can trigger depolarization of neuronal cells via calcium dependent apoptosis [188]. FAs metabolism through LOX also produces ROS and is very sensitive to glutathione (GSH) a major antioxidant in mitochondria. GSH can be depleted under high concentrations of LOX [189]. A reduction in Aβ production has been reported in LOX deleted transgenic mice [184]. Moreover, LOX metabolites such as 5-hydroperoxy eicosatettraenoic acid and leukotriene have been reported to positively induce Aβ production in cultured cell lines [190]. AA can also be converted to inflammation mediators, eicosanoids; such as prostaglandins by the action of cyclooxygenase (COX) [191]. Elevated levels of PL2, LOX and COX are reported in patients with AD and diabetes [192]. These data suggest

that diabetes can mediate AD through lipid metabolism as increased FFAs levels are reported in diabetes and derivatives of AA may be responsible for Aβ production in AD [131].

Hypercholesterolemia also contributes to the pathology of AD and diabetes. Hypercholesterolemia is associated with increased risk of type 2 diabetes, and more than 70 % patients diagnosed with type 2 diabetes have hypercholesterolemia. High levels of cholesterol and other fatty acids lead to arthrosclerosis and vascular lesions [193, 194]. In the brain, unesterified cholesterol is present in cellular membranes and myelin sheets of astrocytes and neurons. As the majority of lipoproteins cannot cross BBB, cholesterol in the brain is derived from de novo synthesis [195]. In the brain excess cholesterol is converted to cholesteryl esters by enzyme acyl CoA: cholesterol acyltransferase 1 (ACAT1) or oxysterol 24S-hydroxycholesterol (24OHC). 24OHC can be easily transported to peripheral circulation through BBB. Moreover, 27S-hydroxycholesterol (27OHC) which is produced outside the brain has the ability to cross the BBB and is reported to increase in AD patients [196–198]. Brain lipoproteins that transport lipids resemble to HDL particles present in CSF and apolipoprotein E is the most studied lipid carrier in AD pathology discussed later [199]. Induced levels of ACAT1 associated with increased Aβ generation and vice versa in mouse models suggests direct association of cholesterol esters with Aβ production and AD promotion [200, 201]. Furthermore, cholesterol also modulates the BACE1 and secretase activities. Reduction in cholesterol levels lead to decreased activities of BACE1 and secretase that resulted in reduced Aβ production. Moreover, association of BACE1 with lipid rafts is found to be positively linked with amyloidic processing of APP, and production of Aβ is decreased after cholesterol depletion [202, 203].

ApoE is well-established risk for the late-onset AD. ApoE that is significant for lipid transport also plays an important role in Aβ clearance as well as stimulation of IDE which is also involved in Aβ degradation [204]. Normal individuals have 77 % ApoE3 allele and 15 % ApoE4. ApoE4 allele is significantly higher in AD patients, and normal individuals carrying ApoE4 allele have 3- to 4-fold more chances to develop AD when compared to non carriers [193]. Furthermore, diabetic patients who are ApoE4 allele carrier have 2-fold more chances to develop AD than non-diabetic individuals [205]. Aβ clearance in the brain is ApoE isoform specific (ApoE4<ApoE3<ApoE2). High levels of ApoE4 were associated with induced Aβ generation [206]. Moreover, transgenic over expression of ApoE4 in neurons increases the tau phosphorylation suggesting that ApoE4 is also involved in development of NFTs by unknown mechanism [207]. Diabetes and ApoE4 synergically increase the risk for AD. Various studies linked type 2 diabetes to brain pathology particularly in individuals with ApoE4 allele (reviewed by Luchsinger et al. [208]). Low lipid clearance characteristic of ApoE4 may also make it an independent risk factor for type 2 diabetes. A study by Chaudhary et al. [209] has found that ApoE4 allele has influence on lipid plasma levels and is associated with diabetes with or without coronary artery disease.

Intracellular cholesterol trafficking is mainly thought to be modulate by ATP-binding cassette (ABC) transporter family proteins such as ABCA [210]. ABCA1 primary function is the transportation of cholesterol efflux onto lipid-poor ApoE. Mutations in human ABCA1 allele result in Tangier disease (absence of HDL in plasma with increased cardiovascular risk) and cause significantly low levels of ABCA1 and ApoE in brain [211]. ABCA1 deficiency in mice lead to 80 % decrease in brain ApoE levels. Thus poor lipidation of ApoE due to decreased ABCA1 levels is resulted in increased Aβ production and vice versa [212]. A recent study by Wang et al. has reported high cholesterol levels in STZ-induced rat brain with decreased expression of ApoE mRNA. However, they have observed decreased cholesterol levels and high ABCA1 expressions in peripheral tissues [213]. These results suggest that in case of diabetes, the body tends to decrease cholesterol levels by expressing ABAC1. Moreover diabetes also results in high cholesterol levels in the brain.

The above data suggests that impaired lipid metabolism is as important as insulin dysfunctions in AD and diabetes. Although much attention is given to ApoE but still lipid metabolism association between AD and diabetes has not been fully addressed till date. More research is required to explore the role of fatty acids in the formation of Aβ plaques and NFTs in AD, as this mechanism is still unclear. Figure 3 represents a way how impaired fatty acid metabolism may be responsible for diabetes and AD promotion. Secondly, very limited studies are available on any correlation between human amylin and ApoE in diabetes as well as in AD. Although one study found that amylin fibrillation could be prevented by lowering the ApoE4 levels in T2DM [214], no further evidence came from this side.

Mitochondrial Dysfunctions

Aerobic organisms mostly produce energy in the form of ATP utilizing oxygen and nutrients. Mitochondria produce over 90 % of cellular ATP through oxidative phosphorylation, which is also the major source of ROS production. Furthermore mitochondria also regulate other physiological processes and cellular functions like cell survival and death, intracellular calcium homeostasis, cell cycle regulation and synaptic plasticity [215, 216]. AD and diabetes are associated with mitochondrial dysfunctions. Especially as neurons require high energy to perform their functions, limited glycolytic activity

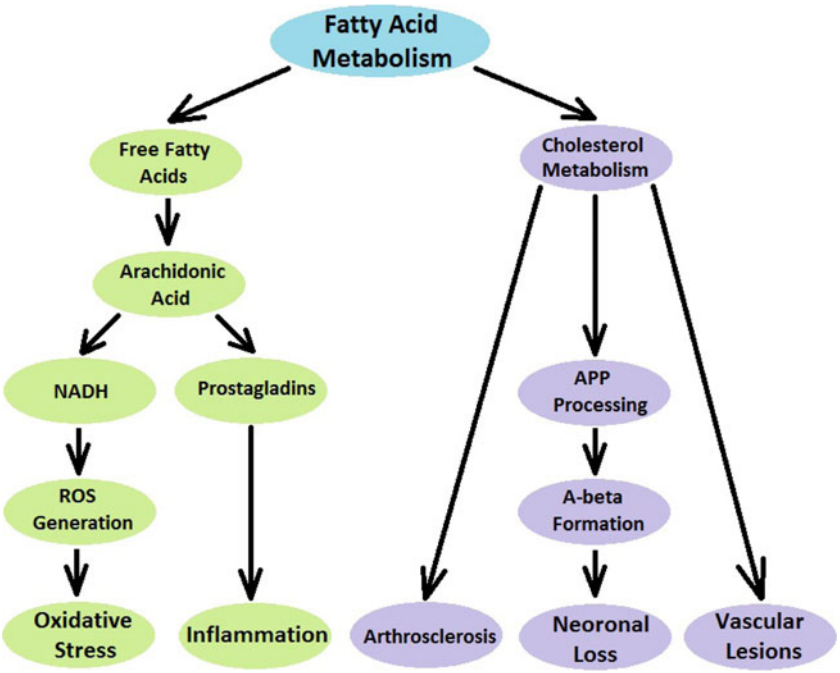

Fig. 3 Lipid metabolism in AD and diabetes. Production/accumulation of excessive free fatty acid and cholesterol lead towards several complication like oxidative stress, inflammation, arthrosclerosis, vascular lesions, and neuronal loss that are major hallmarks of these diseases

of neuronal cells makes them highly dependent on mitochondrial energy production and any changes associated with mitochondrial impairment lead to neuronal dysfunction and neurodegeneration [217, 218]. Mitochondrial abnormalities like over oxidative stress and impaired calcium homeostasis are reported in AD and diabetes.

Oxidative Stress

According to Perez-Matute et al. [218], "living with the risk of oxidative stress is a price that aerobic organisms must pay for more efficient bioenergetics." Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are important oxidants in living organisms. These ROS produced can be converted to many forms and have the ability to permeate through inner and outer mitochondrial membranes (OMM) to enter in cytoplasm. However, most ROS produced in mitochondria can be converted into water or oxygen in the presence of metal-dismutases either in mitochondria or in cytoplasm as described later [219, 220]. The oxygen-derived pro-oxidants (ROS) can be classified into two groups; radicals and nonradicals. The radicals are superoxide ($O^{\cdot}{}_2^{-}$), alkoxyl ($RO^{\cdot}$), peroxyl ($ROO^{\cdot}$), hydroxyl ($OH^{\cdot}$), hydroperoxyl ($HO_2^{\cdot}$) and nitric oxide ($NO^{\cdot}$). The reactive, oxygen-containing nonradicals include hydrogen peroxide (H_2O_2), organic peroxides (ROOH), aldehydes (HCOR), hydrochlorous acid (HOCL), and peroxynitrite ($ONOOH/ONOO^{-}$) [221–224].

Several hypotheses have been proposed to explain the role of oxidative stress in AD and diabetes pathophysiology, while the combination of high-energy demand, relatively low antioxidant levels and a high concentration of iron makes the brain particularly vulnerable to oxidative stress [221, 225]. In AD pathology, decline in synaptic activities and defects in low energy metabolism with comparatively increased amount of ROS are observed [226, 227]. Moreover, reduced levels of antioxidants enzymes like Cu/Zn SOD, gluthatione (GSH) and catalase are found in frontal and temporal cortex. Furthermore presence of Aβ and NFTs lead to mitochondrial dysfunctions, generation of oxidative stress and neuronal cell death [78, 228–230]. Meanwhile, diabetic patients exhibit a number of oxidative stress markers including F_2-isoprostane and nitrotyrosine in urine, plasma and tissue, leading to the hypothesis that oxidative stress is also a hallmark of diabetes [231, 232]. Although mitochondria are capable of generating ROS/RNS by themselves however, in AD and diabetes, other sources/mechanisms like misfolded proteins (Aβ and hIAPP), accumulated NFTs (tau plaques), hyperglycemia and AGEs also promote ROS generation [56, 233, 234]. We will briefly discuss the generation of ROS by these sources.

Generation of Oxidative Stress by Mitochondrion Itself

Many authors have reviewed the production of ROS and RNS in mitochondria in detail [235–239]. Here we briefly describe the ROS/RNS generation in mitochondria. In total, nine different types of enzymes in mitochondria have the capacity to produce ROS by converting molecular oxygen to either superoxide anion or hydrogen peroxide. Cytochrome *b5* reductase and monoamine oxidases (MAO) are located on OMM, whereas dihydroorotate dehydrogenase (DHOH, α-glycerophosphate dehydrogenase (α-GDH), succinate dehydrogenase (SDH), aconitase, α-ketoglutarate dehydrogenase

complex (KGDHC), complex I and complex III are present on inner mitochondrial membrane (IMM). MAO, DHOH, α-GDH and KGDHC produce H_2O_2 via direct or indirect biochemical reactions, while cytochrome b5, complex I and complex III produce superoxides. Aconitase localized in the mitochondrial matrix generates hydroxyl radical upon oxidation of its iron–sulphur cluster by superoxide. PDHC and KGDHC have also been reported to generate superoxide and hydrogen peroxide when isolated and purified from bovine heart, and mouse brain mitochondria.

Generation of Oxidative Stress by Aβ, Tau and hIAPP

Aβ insertion in mitochondria has been reported to disrupt the electron transport chain, reducing energy production and increased ROS production [240]. Reduced activity of complex IV in AD patients is well documented and Aβ is believed to inhibit the functions of complex IV. Aβ has been shown to produce hydrogen peroxide (H_2O_2) and release thiobarbituric acid reactive substances (TBARS) mainly associated with hydroxyl radicals (OH) via metal ion reduction [241, 242]. Furthermore, Aβ can also act directly on mitochondria. Aβ plaques interact with Aβ-binding alcohol dehydrogenase (ABAD) resulting in increased mitochondrial membrane permeability and reduced activities of respiratory proteins [243–245]. The oxidation of proteins at lysine, arginine, proline and histidine residues via peroxynitrite generates protein carbonyls and nitrile, both of which cause increase in NFTs, non-tangle bearing neurons and glia of AD patients [243].

Even though, several studies report the association of Aβ and oxidative stress, few studies have looked at the role of hIAPP. However, two studies have reported the elevation of oxidative stress markers using immortalised beta cell lines when treated with hIAPP exogenously [246, 247]. Furthermore, β-cells of patients with diabetes have shown higher oxidative stress with increased levels of hIAPP. A study by Zraika et al. [56] reported that amyloid deposition on mice islets is associated with increased ROS levels and beta cell apoptosis. Although treatment with antioxidants prevents ROS generation, it does not reduce amyloid formation. In contrast, amyloid inhibition reduces ROS generation as well as beta cell apoptosis. This information leads to the conclusion that hIAPP also induce oxidative stress and apoptosis although the exact mechanism is still unknown.

Hyperglycemia Induced ROS Generation

Hyperglycemia due to insulin impairment in diabetic patients is associated with many biochemical pathways including glucose mediated ROS production, protein kinase activation, formation of AGEs and cytokine secretion [233]. In glucose autoxidation, glucose forms enediol radicals and is converted to reactive ketoaldehydes and superoxide; consequently hydroxyl radicals are produced in presence of transition metals via H_2O_2 if not degraded by catalase or glutathione peroxidase [248, 249]. Hyperglycemia drives the inner mitochondrial membrane potential upward through generation of excessive electron donors in the Kreb's cycle [250]. Hyperpolarization of the mitochondrial inner membrane leads to an increased ATP/ADP ratio, which inhibits electron transport to complex III leaving coenzyme Q in a reduced state. Coenzyme Q can pass electrons to molecular oxygen to generate the partially reduced derivative, superoxide [155, 251]. This superoxide overproduction causes a 66 % decrease in GAPDH (glyceraldehyde-3-phosphate dehydrogenase) activity, PARP (poly-ADP ribose polymerase) activation, and NAD^+ depletion [252]. Overproduction of superoxidase radicals is countered by superoxide dismutases (SODs) and by uncoupling proteins (UCPs). In hyperglycemia, over expression of UCPs blocks glucose induced cell death by preventing mitochondrial hyperpolarization and ROS formation [253, 254]. Hyperglycemia was found to be responsible for cognitive decline in diabetic patients. Impaired antioxidant system with increased oxidative/nitrosive stress in hyperglycemic conditions has been observed in brain of STZ diabetic rats. Authors have also reported about reduced activity of ETC. complexes III, IV and V, and ATP synthesis [255]. Moreover in another study, 12-week older STZ-induced diabetic rat also showed lower ATP contents and calcium accumulation ability. A recent study by Cardoso et al. and Raza et al. also has reported increased ROSRNS levels, reduced antioxidant activity and decreased activities of mitochondrial enzymes such as complex III, complex IV in cortical and hippocampal mitochondria as well as pancreas of STZ induced diabetic rats [256, 257].

AGEs Induced ROS Generation

AGEs found in senile plaques also produce free radicals by chemical oxidation and degradation, by binding with their receptors (RAGE) or interacting with microglia that surround senile plaques and results in respiratory blast and production of ROS and RNS. AGEs particularly produce superoxides and hydrogen peroxides, and their production is associated with related proteins and sugars oxidative insult. Furthermore, AGEs also produce ROS by the metal-catalysed Fenton reaction that result in site-specific attack on proteins and lipid peroxidation [173, 258–260].

Consequences of Oxidative Stress in AD and Diabetes

Impaired Insulin Signaling

Some studies reported that high concentrations of H_2O_2 are able to activate insulin signaling and induce insulin-

associated metabolic actions leading to increased glucose uptake, stimulation of GLUT4 translocation and lipid synthesis [261, 262]. Furthermore, under oxidative stress, stress-associated signaling cascades like MAP kinase become activated and induce phosphorylation of insulin receptors (IRS) resulting in protein degradation and the release of IRS from membrane pools [263, 264]. All these processes accumulatively result in impaired insulin signaling.

Lipids and Protein Oxidation

Lipids and proteins are important constituents of nutrition and growing body of literature points out changes in their respective metabolism in AD and diabetes. Several lipid and protein oxidative products and their derivatives are consequences of oxidative stress in AD and diabetes, and might be able to predict the onset and progression of these diseases. Cell lipids especially cholesterol and polyunsaturated fatty acids (PUFAs) are most susceptible to oxidative stress and their oxidized derivatives are more reactive than parent compounds [265, 266]. Oxidation of cells, plasma and tissue proteins is also very prominent in AD and diabetes. Oxidative damage to proteins promote unfolding and conformational changes that lead to loss of proteins functions and aggregation of cross-linked protein structures [267]. Protein carbonylation, nitration, gluthathionylation, lipid–protein interactions and AGEs formation are well described oxidative end products, and their accumulation results in the disruption of cellular functions and pathways leading to apoptosis and necrosis [243].

Oxysterols are important oxidation products of cholesterol in brain and are associated with proinflammatory, proapoptotic and profibrogenic effects [268, 269]. Furthermore, oxysterols are also involved in up-regulating APP and BACE1, and induction of Aβ peptides when studied in SH-SY5Y human neuroblastoma cells [270].

PUFAs are important constituents of membrane phospholipids and play an important role in enzyme activities and membrane fluidity. Two forms of PUFAs; PUFA ω-3 and ω-6 are essential for brain homeostasis and decreased ω-3/ω-6 ratio are early markers of AD [271, 272]. α-Linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic (DHA) are well known types of ω-3 PUFAs while linoleic acid (LA) and arachidonic acid (AA) are important forms of ω-6 PUFAs [265]. Non-enzymatic peroxidation of PUFAs resulted in unstable peroxyl radical intermediates, which further converts to endoperoxides. Further reduction of chain after the insertion of second oxygen yielded in different isoforms of isoprostanes (IsoPs) like F2-IsoPs, F3-IsoPs and F4-IsoPs, and aldehydes such as malonildialdehyde (MDA), acrolein and hydroxyalkenals especially 4-hydroxynonenal (HNE) in AD as well as in diabetes [273, 274].

Induced levels of F2-IsoPs and F4-IsoPs have been reported in hippocampus, frontal, temporal, parietal, and occipital lobes of AD patients when compared with normal individuals. As IsoPs increased to the same extent in mild cognitive impairment as well as in late one AD, these are not considered as reliable indicators of disease progression [275, 276].

Although MDA are popular oxidative stress markers, these are not considered as specific AD markers due to their presence in mild cognitive impairment as well as in healthy elderly persons. However, MDA was reported to induce oxidative stress by inhibiting ETC. complexes I, II and V, and other respiratory enzymes such as pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and superoxidodismutase [277, 278].

Other oxidative aldehyde products acrolein and HNE have been detected in the brains of AD patients and are thought to be molecular mediators in AD pathogenesis [279]. Acrolein adducts are usually found in NFTs and induce tau oligimerization that results in aggregation of paired helical filaments. Furthermore, tau oligimerization is promoted during tau phosphorylation; and acrolein is thought as NFTs promoter [280, 281].

Most attention is given to HNE as it is highly reactive and makes bonds with amino and thiol groups of proteins [282]. These protein-bound HNE are considered as important contributors in formation of NFTs [283]. Moreover, HNE are also involved in production of short Aβ peptides which are also a source of oxidative stress in AD [284]. Furthermore, HNE also disrupts the binding of histones to DNA and increase chances of DNA oxidation in AD brain [285].

The oxidation of proteins at lysine (Lys), arginine (Arg), proline (Pro), threonine (Thr) and histidine (His) residues via peroxynitrite generates protein carbonyls and nitrile, both of which have shown increase in NFTs, non-tangle bearing neurons and glia of AD patients [243].

Amino acids like His, Lys. Arg, Pro and Thr are major targets for carbonylation and resulted in the formation of AGEs and products of lipid peroxidation. Protein carbonyls are generally stable compounds and used as markers to determine the degree and damage due to oxidative modifications in vitro and in vivo [286, 287].

Nitrosive stress is also reported in patients with AD. Amino acids Cys, Met, Tyr and Phe are major targets for protein nitration thus causing impaired redox cell signaling, inflammatory response and protein phosphorylation [288, 289].

Protein glutathionylation resulted in disulfide bonding of thiol with protein Cys residue is important in redox signaling. Although it occurs in normal conditions, excessive glutathionylation due to oxidative stress may cause impairment in cell sense and stress responses [290, 291].

Novel advanced oxidation protein products (APOPPs) that induce proinflammatory cytokines are also being used

as reliable markers of protein oxidation in AD as well as for diabetes. These are structurally similar to AGEs and generate during oxidation with chlorinated oxidants [292–294].

Oxidation of LDL is also important mechanism in AD and elevated LDL is associated with brain Aβ levels. Furthermore, paraoxonase 1 (PON1) that contributes as antioxidant for LDL has also been reported significantly low in AD patients [295, 296].

DNA Oxidation

DNA is also susceptible to oxidative stress and their oxidative damage plays an important role in aging as well as AD. Mitochondrial DNA (mtDNA) and nuclear DNA oxidation has been reported in parietal cortex of AD patients. ROS attack on DNA can be result in strand break, sister chromosome exchange, DNA–protein cross-linking, translocation and formation of more than 20 oxidized base adducts [297–299]. DNA mutations due to base modifications can lead to impaired protein synthesis and functions. Several studies have reported the induction of oxidized base adducts such as 8-hydroxyguanine (8-OHG), 8-hydroxyadenine (8-OHA), 5-hydroxyuracil (5-OHU) and 5-hydroxycystosine (5-OHC). Furthermore, failure of 8-OHG repairs has also been reported in patients with AD [298, 300, 301].

RNA Oxidation

The bases in RNA are more prone to oxidation than those in DNA as they are more exposed in the single-stranded RNA molecule and are not as well protected as DNA, which uses histones as, dedicated packaging proteins. The noncoding RNAs are also involved in synapses, neuronal specification and differentiation, and regulation of dendritic spine development. So their damage due to oxidative stress contributes to development of neurodegenerative diseases, especially AD [302–304]. Nunomura et al. [303] extensively has reviewed the RNA oxidation in neurodegenerative diseases and has discussed the biological significance and cellular mechanisms that protect against RNA oxidation.

Antioxidant Therapy for AD and Diabetes

An effective antioxidant treatment can minimize the cellular damage and reduce the burden of oxidative insult. Antioxidant mechanism may involve enzymatic or non-enzymatic approach. Several antioxidant such as vitamins, glutathione, catalase, SOD, α-lipoic acid, coenzyme Q_{10}, carotenoids, flavonides, minerals (zinc, manganese, copper and selinium) and cofactors (folic acid) have been tested to reduce the after-effects of oxidative stress in AD and diabetes. Several controversial studies are available on the role of antioxidants to inhibit oxidative stress and reduced AD and diabetes incidence. Unfortunately, till date all large-scale clinical trials have failed to demonstrate any influential benefits for AD and diabetic patients [225, 305–307].

Impaired Calcium Homeostasis

Normal intracellular calcium homeostasis is important for neuronal functions and survival. Impaired calcium homeostasis is also a consequence of mitochondrial dysfunction and intracellular calcium levels in neurons of AD patients containing NFTs were reported higher than normal. Furthermore, neurons containing NFTs susceptible to degeneration also exhibit increased levels of calcium-dependent protease protein kinase II [308]. Calcium homeostasis also regulates transglutaminase activity. Transglutaminases catalyse the formation of covalent bond between proteins that exhibit high resistance to proteolytic degradation. Higher levels of transglutaminase enzyme in prefrontal cortex of AD patients lead to cross linking of tau proteins that resulted in NFTs [309]. Calcium homeostasis abnormalities also lead to induce production of Aβ peptides and increased calcium levels in AD patients which are thought to be involved in enhancement of proteolytic cleavage of APP to produce Aβ [310]. Aβ formation in AD patients leads to mPTP opening also induces mitochondrial calcium uptake and can, in turn, facilitate the Aβ formation and aggregation [78]. Abnormal calcium homeostasis is commonly observed in diabetic patients and high calcium levels in diabetic pancreatic β-cells were found to disrupt insulin secretion [311]. Furthermore, several studies have proposed the impaired calcium homeostasis in diabetic sensory neurons and have observed a steady increase in intracellular calcium levels. Moreover, depolarization of inner mitochondrial membrane was observed in sensory neurons of STZ-diabetic rats under increased calcium flux [312, 313]. These studies confirmed that impaired calcium homeostasis is also an important reason for mitochondrial damage in diabetes and AD.

Summary of the Section

AD and diabetes both result in increased oxidative stress and impaired antioxidant systems. Although many studies suggest oxidative stress as a main cause for AD and diabetes, from the above observations it seems that oxidative stress is a consequence of these diseases and not a cause. Oxidative stress can lead to damage in several metabolic processes and once it starts can promote AD and diabetes which is summarized in Fig. 4. Although several antioxidative stress therapies have been proposed, are zero so far have been useful in the treatment of AD and diabetic patients. This may be due to the involvement and overlapping of several mechanisms at a time such as abnormal

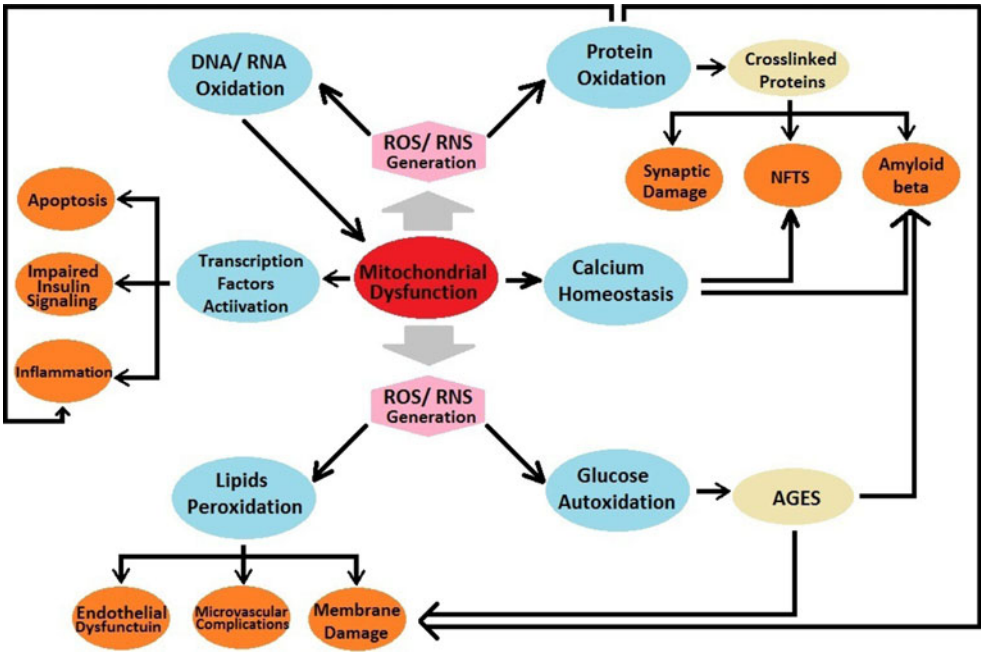

Fig. 4 Schematic description of cellular events linked with mitochondrial dysfunctions especially oxidative stress in diabetes and AD. Oxidative stress not only promotes inflammation and apoptosis but also foster the synaptic damage via membrane damage and enhancing production of NFTs, and amyloid beta. Furthermore, oxidative stress also modulates protein and lipid oxidation that resulted in microvascular complications and endothelial dysfunction in AD and diabetes

glucose, proteins and lipids metabolism, defects in body immune system and inflammation, etc.

Common Therapy for Diabetes and AD

Our above discussion on shared pathology between diabetes and AD leads to the fact that drugs used for diabetes treatment should be helpful for AD patients as rendered by other authors also. Noninsulin hypoglycemic agents such as thiazolidinediones that stimulates peroxisome proliferator-activated receptor-γ (PPARγ) and control lipid and glucose metabolism by regulating insulin-sensitive genes and reduction in insulin resistance; are being used to treat AD, and an improvement in glucose utilization and neuronal mitochondrial biogenesis is observed in AD patients [174, 314]. A recent study by Sato et al. [315] has reported reduced fasting plasma insulin levels, increased insulin sensitivity and improved cognition in mild AD patients with type 2 diabetes when treated with PPARγ agonist pioglitazone. These results have showed that PPARγ agonist might be useful for pre-initial and mild AD patients as well as for AD patients with diabetes [315]. Meanwhile, PPARγ are also involved in regulation of APP-cleaving enzyme BACE1. BACE1 overexpression leads to the formation of amyloidic proteolysis of APP and generation of Aβ plaques [316]. On the other hand, PPARγ agonist ginsenoside Rg1 extracted from ginseng was found to inhibit the transcription and translation of BACE1, overwhelm the BACE1 activity and eventually reduce Aβ plaques generation. Degeneration of oligodendroglia (oligodendrocytes) associated with neuronal support and insulation is important hallmark of AD. Recent research found that these oligodendrocytes require intact insulin/IGF signaling to maintain their functions and survival. PPARγ agonist induces the MAG-1 expression corresponding to oligodendrocytes and enhances DNA repairing [317]. Current studies have showed that PPARγ agonists are also useful in reducing oxidative stress, inflammation and apoptosis in AD patients [318, 319].

Acetylcholine (ACh), a critical neurotransmitter in cognitive function is emerging possible link between AD and diabetes. Impaired insulin mechanism reduced the ACh levels and acetylcholine transferase (ChAT), an enzyme responsible for Ach production. PPARγ agonist induced expression of ChAT that brings improvement in learning, and memory in patients with AD [8, 320].

Acetylcholinesterase inhibitors are widely used in treatment of AD. A recent has study observed that tacrine (a drug form of acetylcholinesterase inhibitors) might reduce the diabetes induced cognitive deficits in mice model by dysfunction of central cholinergic system [321].

A latest study in 2012 has showed that antineoplastic agents such as bexarotene previously used for lung and breast cancer have been found to reduce Aβ plaques more than 50 % within 72 h treatment [322]. ApoE gene expression that normally promotes the Aβ plaques generation is regulated by ligand activated nuclear receptors PPARγ and LXRs (liver x receptors) and their binding with RXRs (retinoid X receptors) [323, 324]. Bexarotene is RXR agonist and reduced Aβ plaques in an ApoE manner by increasing its expression. We hypothesize the use of Bexarotene will be useful for diabetic patients as RXR agonists also functions as insulin sensitizers and can reduce hyperinsulinemia and hyperglycemia [325].

Metformin is a famous anti diabetic drug and have some contradictory results on AD pathogenesis. Chen et al. [326] observed the induced Aβ formation through AMPK pathway in N2a695 cell line. This induction was inhibited through AMPK pathway pharmacological inhibitor Compound C [326]. On the other hand metformin was shown to be induce activity of PP2A and reduction in tau phosphorylation in human tau transgenic mice and the authors suggest a beneficial role of metformin for AD therapy [327]. A recent study by Gupta et al. [328] showed that metformin restored acetylcholine esterase activity and inhibited GSK3β and ERK activity, and reduced Aβ production in patients with AD by sensitizing neuronal insulin resistance.

ABAD as described earlier has an important role in mitochondrial membrane permeability, converting estradiol to estrone. Optimal levels of estradiol are important for neuronal survival. A current study has found that inhibition of Aβ using AG18051; restores the Aβ induced deregulation of estradiol and reduced ROS. Furthermore, when AG18051 was tested for hIAPP toxicity, partial protection was observed in type 2 diabetic pancreas. This study also pointed out a shared pathological relationship between AD and diabetes [244].

In summary, the above information lead to the assumption that AD and diabetes shared common pathology; and treatment for one disease may be useful for the other due to the overlapping of shared metabolic pathways.

Future Directions

The fact that some drugs developed to treat diabetes also have a positive effect on Alzheimer's patients supports the view that there is a common metabolic basis for both disorders. The suggestion that Alzheimer's should be referred to "type-3 diabetes" was first proposed in 2005 but the name was not widely accepted. The resurgence of metabolic research in the form of metabolomics has coincided with renewed interest in a metabolic basis of AD and there is a question mark that whether it represents a neural form of diabetes or not.

A system biology approach to study the animal metabolism will benefit our understanding of diseases of old age, but the mouse, which is the traditional model for diabetes and Alzheimer's, is not the most amenable to systems biology research. In contrast, *Caenorhabditis elegans* may provide an excellent model for system biology of metabolism, but is not typically used as a model of these diseases. However, the use of *C. elegans* in age related diseases like diabetes and AD has gained greater importance in recent years due to shorter lifespan and ease to handle [329]. The formation of misfolded proteins, AGEs, mitochondrial disorders, generation of oxidative stress, insulin resistance and abnormal glucose metabolism are main hallmarks of diabetes and AD. *C. elegans* showed the presence of AGE formation, high oxidative stress and reduced lifespan when exposed under high glucose concentrations. In addition, high caloric diet also induces the Aβ formation in *C. elegans* [330]. Moreover insulin signaling pathway present in *C. elegans* is well defined and many groups studied the genes and subpathways involved in insulin signaling in *C. elegans* and found that reducing insulin signaling decreases Aβ toxicity [73]. In recent years, several studies used *C. elagans* as model of drug research/screening for diabetes and AD. They studied the effect of diabetic drugs on AD *C. elegans* models and vice versa. Here, we briefly describe the results of these studies.

Traditional Chinese medicine *Ginkgo biloba* is found to reduce insulin resistance by lowering glucose levels by significant increase and improved insulin concentration in

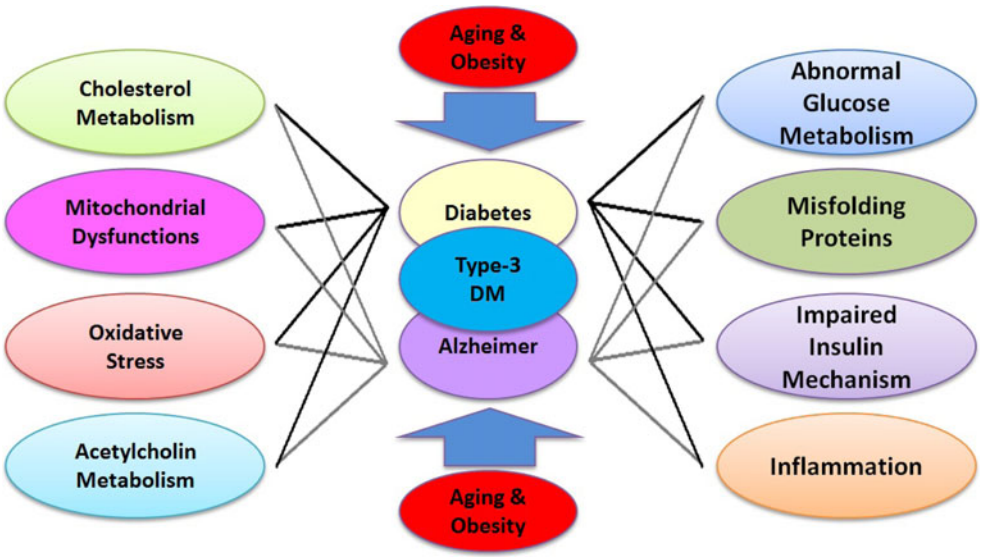

Fig. 5 Schematic illustration of the common links between diabetes and AD. These common links lead toward the hypothesis that AD may be an another type of diabetes "type-3 diabetes"

patients with diabetes. It was also capable to reduce lipid and protein oxidation in diabetic patients [331]. *G. biloba* extract increases stress resistance and extends life span of *C. elegans*. Study using *G. biloba* leaf extracts showed reduction in Aβ induced paralysis in transgenic *C. elegans* [332]. Furthermore, increase in lifespan was observed when metformin was used in type 2 diabetic *C. elegans* model system [333]. A recent study using *C. elegans* as model by Saharia et al. [334] found that reserpine (FDA-approved drug for AD whose mode of action and pathways activation was unknown) acts through acetylcholine mechanism. This information lead to the conclusion that *C. elegans* not only used to study the known drugs effects but may also help to elucidate the mechanisms and actions of newly developed drugs and formation of new drugs on basis of these results.

The above discussion reveals that diabetes especially T2DM and AD follow the same pathological mechanisms resulting in misfolded proteins, insulin impairment, abnormal glucose metabolism, abnormal fatty acid metabolism, mitochondrial dysfunction, and high oxidative stress. These shared metabolic profiles, and diabetes as extreme risk factor for AD lead to the assumption that AD may reflect type-3 diabetes (Fig. 5). Recent studies also have observed the mechanistic links of the other pathways such as ApoE 4 allele, decreased acetylcholine synthesis, PPARγ activation, and activation of inflammatory genes also shares their roles in AD and diabetes pathology. Conclusively, both AD and diabetes are resulted from metabolic abnormalities, and impaired insulin mechanism is the main reason for these defects. Future studies need deep exploration of energy metabolism associated with these mechanisms as recent studies observed direct link between lower energy metabolisms, induced lifespan, and reduced aging. Although model system *C. elegans* has some drawbacks and may not perfectly stand for the human diseases pathophysiology, it may be used as powerful model for screening drugs, and studying diabetes and AD pathophysiology due to conserved insulin signaling and other metabolic pathways.

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