Common Cellular and Molecular Mechanisms Underlying Alzheimer's Disease and Type 2 Diabetes: A Knowledge-Driven Approach

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Abstract: The relationship between the two age-related diseases namely, Alzheimer's disease (AD) and type II diabetes mellitus (T2DM), is gaining much attention in research because of the alarming forecast on both increasing incidence and economic burden. Recent research studies have identified some of the existing links, between AD and T2DM, such as the dysfunctional glucose metabolism and insulin signaling, stress and inflammation, defective protein processing and the role of advanced glycation end products. It is, therefore, crucial to understand the cellular and molecular mechanisms to identify the common linking mechanisms involved in the pathogenesis of both AD and T2DM. Genome wide association studies may lead to identification of novel targets and provide clues for possible interventional strategies to limit the progression of these two age-related diseases. Hence, the purpose of the present review is to provide an update, on the various possible linking cellular and molecular mechanisms, including our experience on the use of high throughput applications to investigate the molecular mechanisms underneath the neurodegeneration in animal models. Besides, using this knowledge-driven approach, we discuss how the current technological advancements can effectively be used to identify possible associations between these age-related diseases.

Keywords: Alzheimer's disease, type II diabetes mellitus, amyloid-β protein, inflammation, advanced glycation end products.

INTRODUCTION

Ageing is a manifestation of the weariness of the cells over time resulting in functional decline and disease susceptibility. Most organs and tissue homeostasis become altered leading to metabolic, cardiovascular, neurological, renal, skeletal and cancer related disorders [1-4]. Ageing and its associated diseases are, therefore, expected to become immense social and economic burden.

Of age related diseases, Alzheimer's disease (AD) is fast emerging as a serious global problem, afflicting not only the individuals in terms of health related adverse effects, but also affecting their families and the nation's economy at large. AD is a progressive neurodegenerative disorder characterized by dementia, neurodegeneration, and the presence of senile plaques and neurofibrillary tangles in the brain tissue, which are, mainly, made up of amyloid β (Aβ) and hyperphosphorylated tau protein [5]. The projected forecast that AD would quadruple by the year 2050 from the estimated 26.6 million in 2006 [6] and the fact that the annual cost for its management in the United States alone is around 172 billion US dollars [7] are indeed alarming. Strategies that would help to delay the progression of AD would obviously be easing the impending global burden. As such, AD research is currently pursued with much vigour than ever before so as to leave no stone unturned in (a) understanding the cellular and molecular mechanisms involved, (b) identifying additional risk factors if any, (c) devising efficient screening methods to enable early detection, (d) employing computational techniques to study their association with other diseases, (e) identification of possible gene targets, and (f) devising novel therapeutic methods.

In parallel with AD, type 2 diabetes mellitus (T2DM), a well-known metabolic disorder also shows a rising trend afflicting the obese and the elderly. T2DM is the most common form of diabetes and is characterized by hyperglycaemia, insulin resistance or relative lack of insulin. Apart from the common vascular, neurological, renal

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complications seen in young adults with diabetes, the geriatric patients may also suffer from co-morbid conditions such as general debility, mood disorders and cognitive impairment [8].

The relationship between T2DM and AD remains complex, and more research in this area is necessary to understand the underlying mechanisms. In contrast to the earlier studies with conflicting data [9-12], more recent studies have identified T2DM to be an associated risk factor in the pathogenesis of AD [13-17]. Earlier transcriptome and proteome analysis of the pancreas revealed some similarities in the type of proteins that are either up or down regulated, with that of the brain [18]. Moreover, improvement in cognition as well as prevention of neurodegenerative effects of AD by insulin [19] and acceleration of AD pathogenesis following insulin deficiency [20] clearly indicate that there exists a link between T2DM and AD (Fig. **1**). As such various other underlying mechanism(s) linking T2DM and AD are actively researched to identify possible methods to slow down the progression of AD. The availability of high throughput technology and the possibility of genome-wide association studies will provide additional insights into the overlapping mechanisms at the molecular level leading to the development of novel interventional strategies.

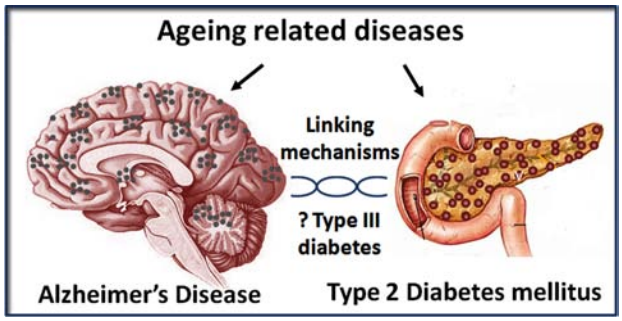

Fig. (1). Schematic representation of the two major age related diseases namely the Alzheimer's disease (AD) and type II diabetes mellitus (T2DM). Evidences indicate that AD and T2DM have common linking cellular and molecular mechanisms.

We had earlier used the genome-wide molecular analysis method to identify the relationship between a cholesterol transport-inhibiting agent (U18666A) and induction of neuronal apoptosis in the primary cortical neurons in a mouse model of neurodegenerative disease. We consider the use of high throughput techniques to be extremely helpful in genome wide association studies of different disorders and to identify common links between various diseases. In the present review, we aim to provide a comprehensive update of the currently understood mechanistic links between AD and T2DM followed by discussion of our earlier work and potential future applications.

CELLULAR AND MOLECULAR MECHANISMS IN T2DM AND AD

Numerous mechanisms have been postulated in the risk associated between T2DM and AD (Fig. **2**). Common defects include insulin signaling, cerebrovascular dysfunction, receptor for advanced glycation end products (RAGE), SorCS1 dysfunction, inflammatory mediators, apoplipoprotein E (APOE), cholinesterase proteins, mitochondrial dysfunction and oxidative stress. Some of these important linking mechanisms are discussed below.

Defects in Insulin Signalling

Insulin, primarily secreted by the β-cells of the pancreas regulates and maintains normal blood glucose level and its final degradation is catalysed by insulin degrading enzyme [21]. Apart from its peripheral action *via* its peripheral receptors, insulin is also known to cross the blood brain barrier [22] and exert significant functions by interacting with the insulin receptors (IRs) found in different regions of the brain. They mainly include the regulation of food intake acting through the IRs located in the olfactory bulb and hypothalamus [23], as well as learning and memory *via* receptors in the hippocampus and cerebral cortex [24]. Binding of insulin to its receptor initiates phosphorylation of the β-subunit and activation of the Src homology collagen mitogen-activated protein kinase pathway or its binding to the IR substrates (IRS-1 and IRS-2) activates the phosphatidylinositol 3-kinase (PI3K) and extracellular signal-regulated kinase (ERK) signaling. Both signalling mechanisms are involved in neuronal cell growth and synaptic plasticity that underlies learning and memory [25-27], thus providing a mechanistic link between *T2DM* and *AD*. In addition, glycogen synthase kinase (GSK) 3β involved in glycogen synthesis is also known to induce hyperphosphorylation of the 'tau' protein and neurofibrillary tangle (NFT) formation [28]. Moreover, hyperglycemia and insulin resistance activates the c-Jun NH_2-terminal kinase (JNK), and the protein 'Janus interacting protein 1' otherwise known as 'islet brain 1' that is mainly expressed in the brain is known to regulate JNK activity [29], which in turn leads to hyperphosphorylation of the 'tau' protein associated with in AD [30].

An elegant study by Takeda *et al*. [31], in which two new mice models were established by crossing APP23 transgenic mice model of AD and ob/ob (leptin deficient) or NSY (spontaneous diabetic) mice models of T2DM, demonstrated that there was AD like cognitive impairment without an increase in brain amyloid-β deposition. The APP^+-ob/ob mice showed early-onset of obesity, severe hyperglycemia, hyperinsulinemia, glucose intolerance, hyperlipidemia and cerebrovascular inflammation compared to APP^+ mice [31]. Likewise, APP^+-NSY had severe glucose intolerance and memory deficits following high-fat diet compared to NSY mice [31]. Analysis of both cross bred animal models thus provides insights into some of the common underlying mechanisms between *T2DM* and *AD*.

Ke *et al*. [32] demonstrated massive deposition of hyperphosphorylated, insoluble tau following streptozotocin (STZ) induced diabetes in pR5 transgenic mice that has pre-existing tau pathology compared to non-transgenic mice indicating that DM can accelerate onset and increase the severity of disease in individuals with existing predisposition to develop AD. STZ induced diabetes in AD transgenic mice (5XFAD model) also showed (a) significant decrease in brain insulin levels without affecting insulin receptor expression level, (b) increased cerebral Aβ deposition, (c) upregulated levels of both b-site APP cleaving enzyme 1 (BACE1) and full-length APP indicating that insulin deficiency may predispose to β-amyloidogenesis [20]. In contrast to the use of genetically modified animals, Bitel *et al*. [16] demonstrated that alloxan induced diabetes in

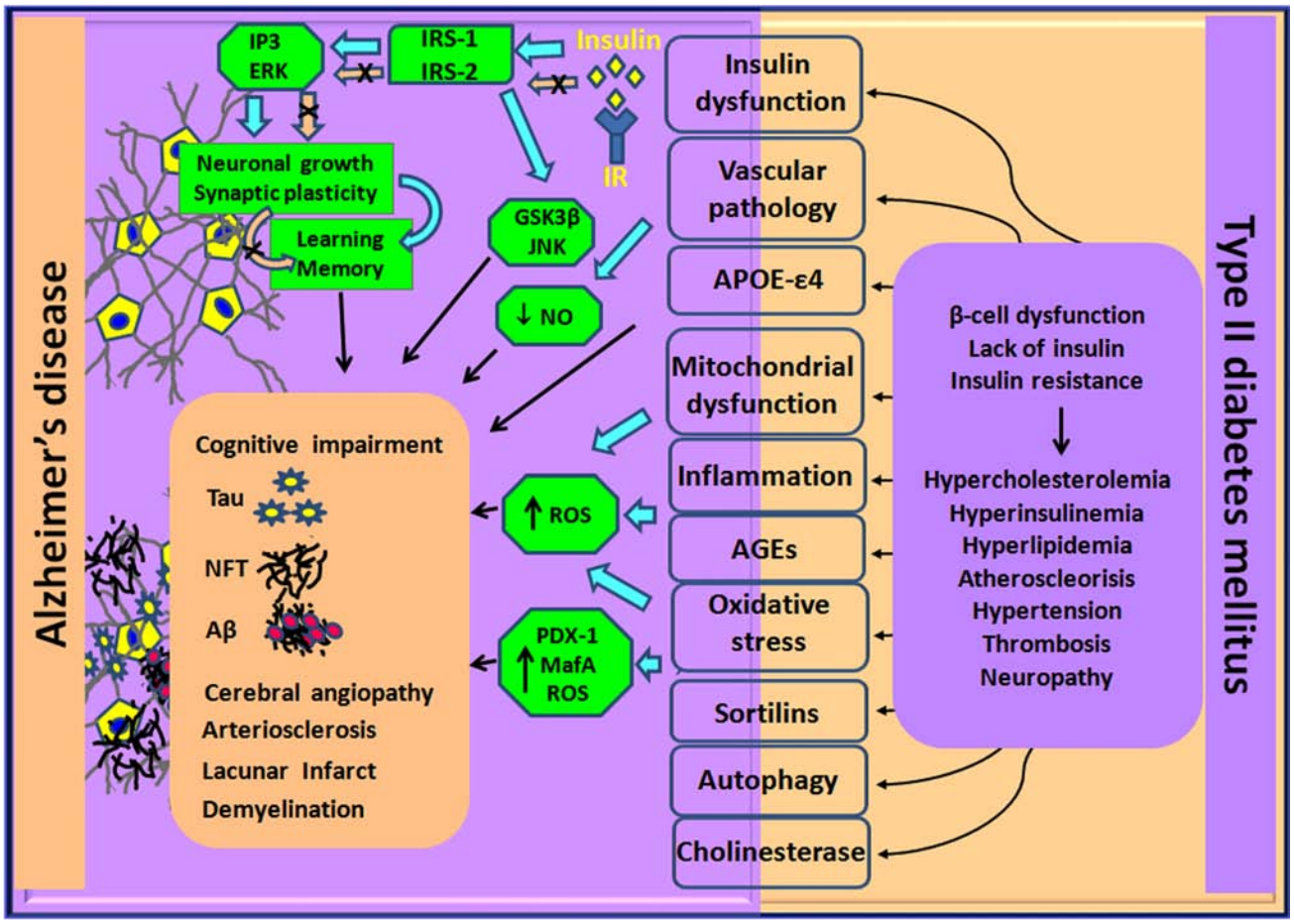

Fig. (2). Schematic representation showing the possible linking mechanisms and mediators between type II diabetes mellitus (T2DM) and Alzheimer's disease (AD). T2DM is characterized by insulin resistance or lack of insulin and hyperglycemia and leading to organ and metabolic dysfunctions. The pathology seen in T2DM is also involved in the pathogenesis of AD. Abbreviations: APOE - apopliprotein-E; AGEs - advanced glycation end products; IR - insulin receptor; IRS-1/IRS-2 - insulin receptor substrates; IP3 - phosphatidylinositol 3-kinase; ERK - extracellular signal-regulated kinase; GSK - glycogen synthase kinase; JNK: c-Jun NH2-terminal kinase; NO - nitric oxie; ROS - reactive oxygen species; tau - hyperphosporylated 'tau' protein; A β - Amyloid β protein; NFT - neurofibrillary tangle; PDX-1 - pancreatic and duodenal homeobox 1 gene; MafA - β-cell-specific activator of insulin gene.

genetically unmodified rabbits led to nearly 5-fold increase of Aβ in the cortex and hippocampus. Phosphorylated-tau was also elevated and the retinal cell layers showed deposition of Aβ [16]. All the above studies identify a clear link of dysfunctional insulin signaling and neurodegeneration in AD.

Cerebrovascular Dysfunction

Vascular pathology of the brain is well known to be associated with neurodegenerative changes and cognitive impairment in the elderly. In a recent study, analysis of 135 brain biopsy samples of patients confirmed to have dementia before death, identified arteriosclerosis and amyloid angiopathy as early features followed by myelin loss and lacunar infarcts [33]. Further, study of 1352 participants without dementia from the prospective Framingham Offspring cohort identified midlife, hypertension, diabetes, obesity and smoking as strong risk factors in the progression of vascular brain injury [34]. Treatment with simvastatin, a well-known anticholesterol agent, is known to rescue the vascular pathology in part by increasing nitric oxide levels [35]. It is also shown to improve both short and long term memory in adult transgenic mice models of AD without many changes in Aβ deposition and plague formation [35]. T2DM has a high prevalence of vascular complications leading to cerebrovascular changes and alteration in brain insulin signaling resulting in vascular dementia. The possible link between T2DM and AD is clearly demonstrated using a cross bred animal model of T2DM and AD, namely APP+-ob/ob mice, in which, dense amyloid deposition was observed in small arteries, arterioles and capillaries. Moreover, Aβ40 being significantly increased in APP+-ob/ob mice compared to APP+ mice in an age dependent manner [31]. Therefore, it is clear from all above studies that cerebrovascular dysfunction is indeed involved in the pathogenesis of T2DM and AD.

Apolipoprotein E (APOE-ε4)

The human 'apoE' protein is expressed by several cell types including the CNS [36]. In addition, other lipoproteins

such as 'apoA1 and 'apoJ', also known as clusterin, exist in the CNS [37]. The common isoforms of 'apoE' are 'apoE2, apoE3, and apoE4' [38] have a different structure and function [39]. Of the isoforms, apoE4 was identified to be a strong genetic risk factor for AD and cerebral amyloid angiopathy [40]. Recently, 'apoJ' have also been identified to be a risk factor for AD [41]. It has been suggested that physical interaction of apoE with Aβ plays a pivotal role in AD and cerebral amyloid angiopathy. Furthermore, the apoE4-positive middle-aged and elderly individuals are more likely to have brain amyloid than apoE4-negative individuals [42]. It is understood that apoE isoforms differentially affect Aβ clearance before Aβ deposition with E4 resulting in clearance that is slower than E3 and E2 [43].

Diabetes is also associated with hypercholesterolemia thereby increasing the risk of vascular pathology leading to cognitive impairment. ApoE is involved in the transport of cholesterol among various cells of the body, and the isoform apoE-ε4 is identified to be implicated in atherosclerosis [44]. Recently, using diabetic mutant mice expressing human apoE ε 4 together with human low density lipoprotein receptor gene, it was demonstrated that diabetes-induced pro-inflammatory changes and accumulation of cholesterol in the macrophages synergistically triggered atherosclerosis [45]. Considering the role of apoE-ε4 in development of vascular pathology and the cerebral amyloid angiopathy, a common link exists between T2DM and AD. Understanding the mechanistic link between T2DM and AD pathogenesis is likely to provide novel insights to limit the progression of AD.

Advanced Glycation End Products

Advanced glycation end products (AGEs) are formed *via* the Mailard reaction, which occurs when reducing sugars react non-enzymatically with amino groups of proteins, lipids and nucleic acids [46]. Increasing accumulation of AGEs occurs in various pathological conditions including diabetes [47] and AD [48]. Hemoglobin A1c, which serves as an indicator of blood glucose level, to monitor the diabetic status, a well-recognized early glycation product. Glycation of the proteolytic enzymes in diabetes is known to reduce their efficiency leading to further build of AGEs [49]. High expression of AGEs, receptor for AGEs (RAGE) in the human brain tissue obtained in patients with DM and AD by immunohistochemistry implies a clear link between T2DM and AD [50]. Furthermore, a comparative study of the brain tissue in normal and AD patients' demonstrated the presence of higher AGEs [51] and sufficient evidence shows that RAGE enables transport of amyloid peptides *via* the blood-brain barrier [52].

Mitochondrial Dysfunction

Mitochondria are the main organelles involved in the cellular production of adenosine triphosphate utilizing oxygen and glucose and any dysfunction will lead to the generation of reactive oxygen species (ROS) leading to cellular damage. Mitochondrial dysfunction and oxidative stress are implicated in AD, and in fact, oxidative stress is known to appear early in the pathogenesis of AD, before the Aβ deposition [53]. Mitochondria isolated from the brains of T2DM were more susceptible to neurotoxic Aβ protein exposure in aged diabetic rats [54]. Involvement of the mitochondrial mechanism between T2DM and AD was further supported, as the mitochondrial bioenergetics and oxidative status in the brain, compared between triple transgenic AD and wild type mice fed with 20% sucrose-sweetened water showed similar impairment of the respiratory chain and significant increase in Aβ protein levels [17].

Oxidative Stress

Diabetes leads to increase in the production of free radicals namely the ROS, which can hamper the antioxidant capacity of a cell leading to oxidative stress [14]. Non-enzymatic glycosylation and the electron transport chain in the mitochondria are the main sources of ROS production and oxidative stress associated with T2DM. The pancreatic β-cells become vulnerable to oxidative stress due to low expression of antioxidant enzymes namely the catalase and glutathione peroxidase leading to deterioration of β-cell function [55]. Oxidative stress and impaired glucose tolerance are, in fact, attributed to the neuropathological complications seen in T2DM [56]. Moreover, as a result of β-cell glucose toxicity there is marked reduction in expression and function of insulin gene transcription factors, pancreatic and duodenal homeobox 1 (PDX-1) that is necessary for β-cell maturation and MafA, a β-cell-specific activator involved in insulin gene transcription [57]. Production of ROS can lead to apoptotic cell damage [58] and also vascular injury in multiple organs leading to impairment in their function.

Oxidative stress is also implicated in the pathogenesis of AD. The cross talk between mitochondrial dysfunction, ROS production and the closely associated endoplasmic reticulum (ER) is involved in neurodegeneration associated with AD. Generation of hydroxyl radical in general causes DNA strand breaks, and in the ER, stress leads to activation of the unfolded protein response leading to synaptic dysfunction and neuronal death [59]. Protein and lipid peroxidation following free-radical-mediated injury, leads to the generation of stable products such as 3-nitrotyrosine, malondialdehyde, trans-4-hydroxy-2-nonenal, and F2-isoprostanes, and these are found to be expressed in the brain in close association with NFT, senile plaques and in biological fluids of AD patients [60-62]. It was recently demonstrated that the ROS generation led to alteration in the tertiary structure of p53 protein in immortalized lymphocytes derived from early onset AD and patients with AD mutation compared to cells from normal healthy subjects [63]. In addition, ROS scavenging activity of superoxide dismutase and glutathione reductase was reduced in the above pathological cells compared to normal [63]. Oxidative stress and ROS are, therefore, identified to be a common determinant in T2DM, AD and ageing.

Inflammatory Mediators

Chronic low grade inflammation is a common phenomenon in the pathogenesis of both T2DM. In diabetes, inflammation is associated with β-cell dysfunction, insulin resistance, increased AGE formation, micro and macro vascular diseases; while in AD inflammation is implicated in

NFT, Aβ deposition, activated astrocytes and microglia formation. Increased expression of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and other mediators such as c-reactive protein and α-1-antichymotrypsin were identified to be associated with both AD and T2DM [14, 64, 65]. As such, anti-inflammatory agents may prove to be useful in limiting the pathogenesis in T2DM and AD [64].

Recently prostaglandin E2 (PGE2) signaling was implicated in early pathogenesis of AD [66], and this was well observed in an *in vivo* model, Aβ (42) peptide induced sub-acute neuroinflammation, where deletion of PGE2 EP3 receptor led to reduction in proinflammatory gene expression, oxidative stress and inflammatory cytokines [67]. This was further confirmed in the APPSwe-PS1ΔE9 model of familial AD, where deletion of the same receptor had similar effects, in addition to decrease in Aβ, peptides and β-secretase levels [67]. Although, inhibition of the PGE2 signaling led to partial protection against the diabetogenic toxicity in a mice model of STZ induced Type I diabetes [68], the role of prostaglandin signaling and cyclooxygenase inhibitors in T2DM yet remains unknown. However, another class of drugs such as the glucagon-like peptide-1 analog, exendin-4, led to reduction in stress induced neurotoxicity *in vitro* and also Aβ and tau levels in, transgenic AD (3xTg-AD) mice model [69]. Moreover, increased levels of Aβ and tau in the brain of 3xTg-AD mice treated with STZ were significantly reduced by treatment with exendin-4 [69]. Another drug that belongs to the same class namely liraglutide led to 50% reduction of the activated microglia that results due to cortical inflammation in APPswe/PS1ΔE9 AD mice [70] thereby clearly providing a mechanistic link between T2DM and AD. Other agents, such as the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists that are known to reduce both insulin resistance and inflammation [71] or the natural PPAR-γ activator amorfutins [72] might be useful in alleviating both T2DM and AD.

Sortilin-Related VPS Domain Containing Receptor 1 (SorCS1) Dysfunction

SorCS1 and sortilin-related receptor 1 (*SorL1*) are members of the sortilin and vacuolar protein sorting-10 family of proteins, and are known to be associated with AD [73, 74]. SorCS1, located on chromosome 10q23.3, a region of interest in AD [75] is also genetically associated with T2DM [76]. Recently, Lane *et al*. [77] demonstrated that the total secreted Aβ was decreased by 35% following over expression of APP and SorCS1β-myc in human embryonic kidney cell line (HEK293) compared to empty vector control. *In vivo* endogenous levels of total $A\beta_{40}$ and $A\beta_{42}$ were increased in the brains of female *Sorcs1* hypomorphs in comparison to wild-type females but showed no difference when compared to the male and female grouped wild type, indicating possible sexual dimorphic effects [77]. Genetic association of SorCS1 was found to be strongly associated in women with both T2DM and AD [78, 79]. Possible interaction between the SorCS1 and APOE-ε4 was demonstrated by the analysis of 1198 subjects comprising 598 AD patients and 600 healthy controls for involvement of SorCS1 polymorphism that showed significant differences in the genotypes and allele frequencies upon data stratification with APOE-ε4 [75]. Moreover, AD genetic markers from a web-based collection and their analysis of shared biological pathways identified up to 15 genes including APOE, SorL1, IL8, LDLR, SorCS1 and TNF [80]. These genes are significantly associated with cholesterol metabolism, intracellular transport of Aβ precursor and autophagy [80].

Autophagosomes

Insulin resistance, commonly seen in T2DM is well recognized as an etiological factor for AD. Recently, the study by Son *et al.* (2012), shares an additional insight into underlying mechanisms between the two age related diseases. The effect of insulin resistance on amyloid β precursor protein (APP) processing was compared between *db/db* diabetic mice and high-fat diet fed mice. It was observed that Aβ formation, the BACE1/β-secretase and γ-secretase activities were all increased, in addition to the accumulation of autophagosomes in brains of both mice models [81]. They followed this up with an *in vitro* study of insulin resistance using human neuroblastoma and cortical neural cells, and identified that the autophagosome accumulation was mediated by the inhibition of mammalian target of rapamycin [81]. Using rosiglitazone an insulin sensitizing agent or 3-methyladenine an autophagy inhibitor, the effects observed with insulin resistance were reversed [81], thereby clearly identifying a role of insulin resistance and autophagosome accumulation in processing of APP leading to AD.

Cholinesterases

Elevated levels of cholinesterases are predicted to be involved in the pathogenesis of T2DM and AD [82]. Both brain tissue and the gastrointestinal-pancreatic tissue have cholinergic innervations. The cholinergic connections of the basal forebrain and the medial septum at the cerebral cortical and hippocampal regions are associated with cognition, learning and memory [83]. In the gastrointestinal system, vagal secretion of acetylcholine plays a role in glucose homeostasis as this is known to enhance insulin secretion in response to the presence of food in the gastrointestinal tract [84]. This augmented insulin secretion is mediated by inositol trisphosphate receptor signaling and requires the presence of ankyrin-B [85]. Both T2DM and AD are characterized by chronic low grade inflammation and are associated with levels of inflammatory mediators such as C-reactive protein, IL-6 and TNF-α. Acetylcholine is also known to have an anti-inflammatory effect, and the decrease or absence was considered to be associated with AD [86]. The enzyme cholinesterase catalyze the hydrolysis of acetylcholine into choline and acetic acid, and there are two known cholinesterases namely, the acetylcholinesterase and butyrylcholinesterase [86]. Elevated cholinesterases may lead to decrease in acetylcholine levels and trigger the inflammatory process in both T2DM and AD. It is interesting to note that butyrylcholinesterase K variant is associated with a slow decline of cognitive function in AD [87]. Medicinal compound 'SK0506' was shown to reduce the butyrylcholinesterase levels significantly in skeletal

muscle and adipose tissue [88] and also the levels of triglyceride and cholesterol associated with high fat diet in Sprauge-Dawley rats [89], thereby providing leads to target the butyrylcholinesterase mediated inflammatory pathway in the management of T2DM and AD. Furthermore, attempts are made to discover novel cholinesterase inhibitors using pharmacophore and molecular docking studies as the currently available cholinesterase inhibitors are only useful to a limited extent in the management of AD [90].

Genome-Wide Link Between T2DM and AD

The objective of this review is to provide genome-wide common cellular and molecular signature underlying between T2DM and AD. Neuronal death by apoptosis is believed to be one of the key events involved in AD, a major dementia in the elderly, and other neurodegenerative diseases [91]. We had earlier reported the genome-wide molecular analysis to identify the U18666A-mediated neuronal apoptosis in primary cortical neurons that provided insights to understand the mechanisms of neurodegenerative diseases, in the mouse model [92, 93]. U18666A, a cholesterol transport-inhibiting agent leads to apoptosis and intracellular cholesterol accumulation in primary cortical neurons. Recent findings also suggest that cholesterol imbalance in the brain might be linked to the development of neurological disorders such as AD and Niemann-Pick disease type C (NPC) [94, 95]. In order to integrate this dataset with T2DM, Gene Expression Atlas (GXA) was extracted and the data for T2DM of a mouse model, available in the public database was analysed. The data was obtained for both up-regulated and down-regulated genes in the mouse, separately, to integrate with mouse primary cortical neurons mimicking neurodegenerative conditions (Fig. **3**). The common genes involved in molecular mechanism associated with AD and T2DM are listed in Table **1**. Cluster analysis demonstrated the commonly expressed genes in AD and T2DM, (Fig. **4**) and the cluster dendrogram matched our earlier expression profiles of U18666A-mediated neuronal apoptosis in primary cortical neurons at different time points for the common genes obtained between the neurodegenerative and T2DM conditions. The Database for Annotation, Visualization and Integrated Discovery (DAVID) analysis further revealed the significantly overrepresented Biological Processes (BP) and Canonical Pathways (CP) that are common between T2DM and neurodegenerative conditions in mice (Fig. **4**). Correlations for genome-wide patterns between T2DM and neurodegenerative conditions may offer insights into the common biomarkers in these conditions. The link may provide further clues to the aetiology and pathogenesis of AD, and the cellular mechanisms underlying other neurodegenerative diseases, including NPC. Although *in vitro* studies, in model systems, may not directly represent the physiological conditions of T2DM and AD, they offer causal links as well as common molecular mechanisms taking place in these systems.

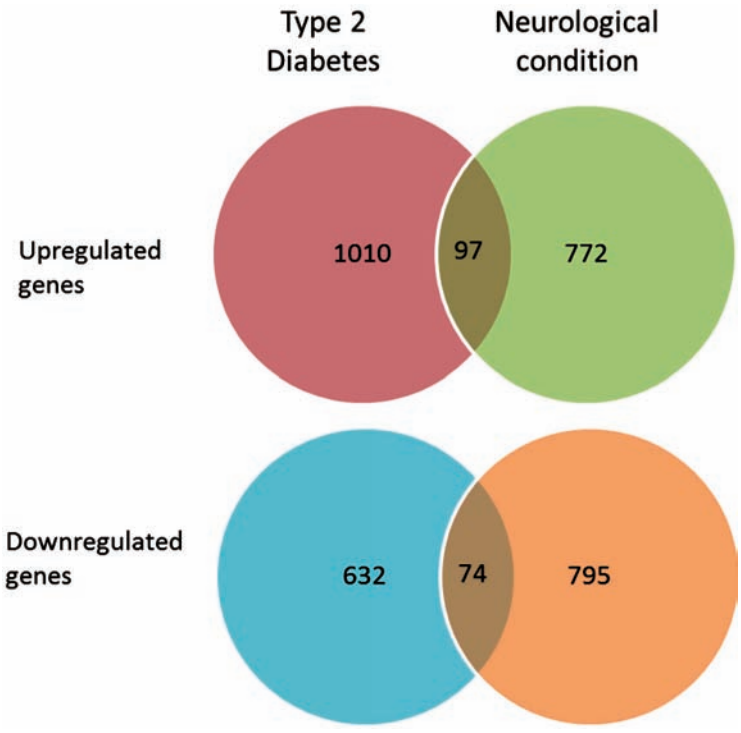

Fig. (3). Venn diagram showing the common differentially regulated genes between T2DM and Neurodegenerative condition in mice. Differentially expressed genes for T2DM in mice were extracted from Gene Expression Atlas (GXA) and are correlated with our previously published transcriptomic data from mouse primary cortical neurons mimicking neurodegenerative condition. Venn diagram shows the up-regulated and down-regulated common genes involved in both conditions. The diagram was generated by Genespring GX 7.3 (Silicon Genetics, Redwood City, CA). The numbers in the regions between overlapping circles represent the number of genes that were differentially expressed by both T2DM and neurodegenerative condition. The numbers in the non-overlapping regions of each circle represent the number of genes that were exclusively differentially expressed after either of the condition.

Table 1. List of Common Genes Involved in Molecular Mechanism Associated with AD and T2DM

Gene Symbol	Gene Name
Upregulated Genes in Both T2DM and Nuerodegentaive Condition in Mice	
Nnat	neuronatin
KLF3	Kruppel-like factor 3 (basic); similar to BKLF
lamp2	lysosomal-associated membrane protein 2
Prdx6	similar to Peroxiredoxin-6 (Antioxidant protein 2)
gpi1	glucose phosphate isomerase 1
SSBP4	single stranded DNA binding protein 4
BCL2L11	BCL2-like 11 (apoptosis facilitator)
CNBP	cellular nucleic acid binding protein
Apeg3	paternally expressed 3; antisense transcript gene of Peg3
SLC16A1	solute carrier family 16 (monocarboxylic acid transporters), member 1
H2-Bl	histocompatibility 2, blastocyst; predicted gene 8810
nfix	nuclear factor I/X
Gadd45g	growth arrest and DNA-damage-inducible 45 gamma
Nr1h2	nuclear receptor subfamily 1, group H, member 2
Hist2h2ac	histone cluster 2, H2ac
PITPNB	phosphatidylinositol transfer protein, beta
CFLAR	CASP8 and FADD-like apoptosis regulator pseudogene; CASP8 and FADD-like apoptosis regulator
ddit4	DNA-damage-inducible transcript 4
Zfp787	zinc finger protein 787
sh3glb1	SH3-domain GRB2-like B1 (endophilin)
KIF16B	kinesin family member 16B
CSRP1	cysteine and glycine-rich protein 1
tmed7	transmembrane emp24 protein transport domain containing 7
MAPKAPK2	MAP kinase-activated protein kinase 2
pten	phosphatase and tensin homolog
qk	similar to Quaking protein; quaking
FOS	FBJ osteosarcoma oncogene
SPSB1	splA/ryanodine receptor domain and SOCS box containing 1
ALDH2	aldehyde dehydrogenase 2, mitochondrial
FGFR2	fibroblast growth factor receptor 2
kcna3	potassium voltage-gated channel, shaker-related subfamily, member 3
tm7sf2	transmembrane 7 superfamily member 2
Vcam1	vascular cell adhesion molecule 1
MFGE8	milk fat globule-EGF factor 8 protein
mgst1	microsomal glutathione S-transferase 1
GLO1	glyoxalase 1
zfp36l1	zinc finger protein 36, C3H type-like 1
Mt1	metallothionein 1
prss23	protease, serine, 23
Tubb2a	tubulin, beta 2A

(Table 1) contd…..

Gene Symbol	Gene Name
Upregulated Genes in Both T2DM and Nuerodegentaive Condition in Mice	
BCAS2	breast carcinoma amplified sequence 2
Gm9840	ring-box 1; predicted gene 9840
LGALS3	lectin, galactose binding, soluble 3
SCP2	sterol carrier protein 2, liver
GSTA4	glutathione S-transferase, alpha 4
Apcdd1	adenomatosis polyposis coli down-regulated 1
Pik3r1	phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)
SERPINE2	serine (or cysteine) peptidase inhibitor, clade E, member 2
SPP1	secreted phosphoprotein 1
RANBP9	similar to B cell antigen receptor Ig beta associated protein 1; RAN binding protein 9
snrpd3	small nuclear ribonucleoprotein D3
Zfp358	zinc finger protein 358
Downregulated Genes in both T2DM and Nuerodegentaive Condition in Mice	
Atp6v1a	ATPase, H+ transporting, lysosomal V1 subunit A
Gm7665	predicted gene 7665; S100 calcium binding protein A11 (calgizzarin)
HMGCR	3-hydroxy-3-methylglutaryl-Coenzyme A reductase
clpB	ClpB caseinolytic peptidase B homolog (E. coli)
Mettl8	methyltransferase like 8
H6pd	hexose-6-phosphate dehydrogenase (glucose 1-dehydrogenase)
LRP2	low density lipoprotein receptor-related protein 2
AEBP2	AE binding protein 2

The downregulation of tyrosine kinase signalling activity (Fig. **4**) is reported to be associated with impaired neuronal development. Neurite outgrowth following a steroidal saponin, spicatoside was inhibited by tyrosine kinase knockdown with siRNA [96]. Spicatoside is comparable to the nerve growth factor (NGF) which is considered as a treatment option for AD, and both spicatoside and NGF are known to exert their neuronal growth functions *via* tyrosine kinase meidated activation of ERK/PI3 signalling [96]. The upregulation of the cholesterol biosynthesis and angiogenesis related genes (Fig. **4**) are identified to have common linking mechanisms between AD and T2DM as mentioned in earlier part of the review. Severe hyperglycemia, hyperinsulinemia, glucose intolerance, hyperlipidemia and cerebrovascular inflammation were demonstrated in two AD models of mice (APP^+-ob/ob and APP^+-NSY) [31]. Improvement of both short and long term memory in adult transgenic mice models of AD following treatment with an anticholesterol agent simvastatin, helps also to overcome the vascular pathology by increasing nitric oxide levels [35] highlights the common links between T2DM and AD. Additionally, upregulated cholesterol biosynthesis is associated with increased 'apoE4' which in turn is known to be associated with AD and cerebral amyloid angiopathy [40]. Hypercholesterolemia is also associated with high expression of AGEs, and receptor for AGEs (RAGE). The identification of AGEs & RAGE in the human brain tissue of patients with DM and AD by immunohistochemistry implies a clear link between T2DM and AD [50].

CONCLUDING REMARKS

Alzheimer's dementia and diabetes are now recognized to be inter-related diseases and the underlying cellular and molecular mechanisms are complex. Many possible links based on the current literature evidence have been systematically summarized so as to better understand the associated risk factors and also to provide potential leads to develop effective prevention strategies. Systems based analysis of our own data from earlier studies on mouse models of T2DM and AD has also supported many of the mechanistic links between the two age related diseases. Employment of robust screening of the various aetiological agents, intermediate molecules and signaling pathways between T2DM and AD will lead to the development of novel agents to prevent or slow down the progression and ultimately reduce the impending economic consequences of ageing.

Stress related generation of free radicals and chronic low grade inflammation are the hallmarks of both diseases and affects the structure and function of multiple organs. Given its poor antioxidant mechanisms, the brain is especially prone to oxidative stress-induced damage. Taking steps to prevent or control T2DM may help reduce your risk of AD

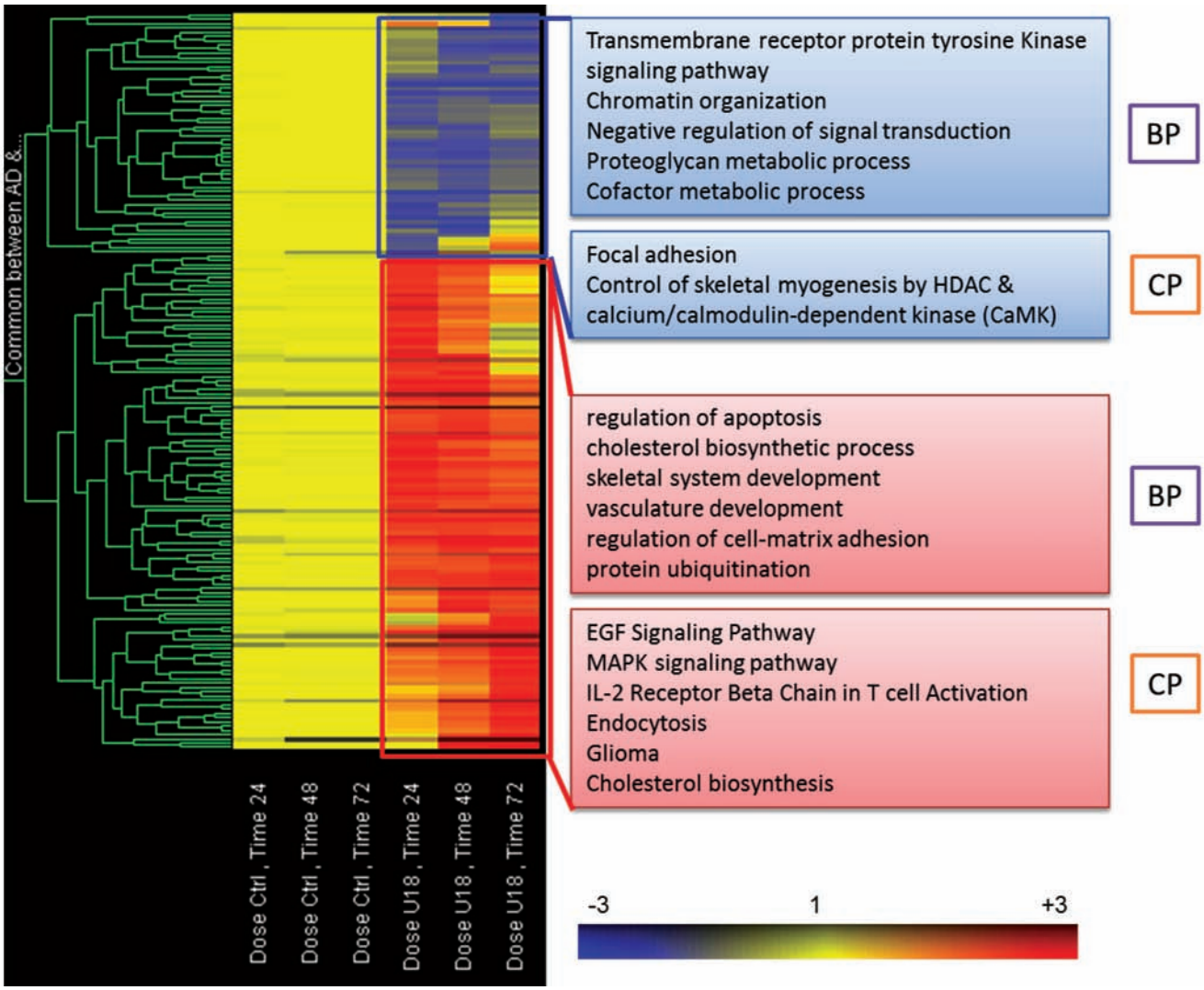

Fig. (4). Functional and pathway analyses of common signatures between T2DM and neurodegenerative condition in mice. Cluster analysis of microarray data obtained from mouse cortical neurons treated with vehicle (Control) or 1mg/mlU18666A for 24h, 48h and 72h. Differentially expressed genes from this data set have been correlated with differentially regulated genes in T2DM from GXA. The common genes were then clustered by agglomerative average-linkage hierarchical for genes using Genespring GX 7.3 (Silicon Genetics, Redwood City, CA) software. The cluster color represents the normalized expression level of a given gene in a particular time point of 18666A treated primary cortical neurons given below and is colored according to the color bar at the bottom. Red denotes up-regulation and blue denotes down-regulation. Rows represent individual genes; columns represent experimental conditions. Blue and pink boxes indicate cluster of relative differentially regulated genes and their significantly altered biological processes (BP) and canonical pathways (CP).

and *vice versa*. The report that six months of aerobic exercises in an aged group reduced stress related effects, improved insulin deficiency and cognition; as well as xanthophyll carotenoid lowered oxidative stress, reduced inflammation mediators and boosted immunity in obese individuals and smokers are some of the basic lifestyle modifications that one can easily adopt. Numerous other natural products reach the pharmaceutical market regularly with claims of anti-oxidant activity, which signifies the importance of anti-oxidants in health. Rather than debating on all the above claims, it would be beneficial to adopt a healthy lifestyle, include a well-balanced diet and practice regular exercises which by itself will have a positive impact in delaying the progression of the both T2DM and AD.

LIST OF ABBREVIATIONS

A β	=	Amyloid β protein
AD	=	Alzheimer's disease
APOE	=	Apopliprotein-E
AGEs	=	Advanced glycation end products
APP	=	Amyloid β precursor protein
ER	=	Endoplasmic reticulum
IR	=	Insulin receptor
IRS-1/IRS-2	=	Insulin receptor substrates
IP3	=	Phosphatidylinositol 3-kinase

ERK = Extracellular signal-regulated kinase

GSK = Glycogen synthase kinase

GXA = Gene expression atlas

IL-1β = Interleukin-1 beta

IL-6 = Interleukin-6

JNK = c-Jun NH2-terminal kinase

NFT = Neurofibrillary tangle

NPC = Niemann-Pick disease type C

NO = Nitric oxide

PDX-1 = Pancreatic and duodenal homeobox 1 gene

ROS = Reactive oxygen species

STZ = Streptozotocin

T2DM = Type II Diabetes Mellitus

TNF-α = umor necrosis factor alpha

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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