

Diabetes and Alzheimer's Disease: The Unresolved Connection

Suraiya Saleem*

*Neuroscience Lab, Molecular and Nanomedicine Research Unit, Sathyabama Institute of Science and Technology, (Deemed to be University), Jeppiaar Nagar, Rajiv Gandhi Salai, Chennai, 600119, Tamil Nadu, India.

Received December 23, 2020; Revised February 8, 2021; Accepted February 11, 2021

ABSTRACT

Diabetes is mainly a metabolic disorder while Alzheimer's disease is a neurodegenerative disease (AD). Diabetes mellitus is mainly specified by impaired insulin signaling and increased blood glucose levels. AD on the other hand is one of the most common causes of dementia and is characterized by amyloid beta plaques and neurofibrillary tangles in the brain. Clinical data reveals that patients suffering with diabetes are more vulnerable to Alzheimer's AD. However, the exact correlation between the two diseases is still obscure. The specific markers which may denote the link between the two pathologies have not been identified yet. Interestingly, several metabolic studies have pointed out towards indirect pathophysiological links between diabetes and AD. One of the major links among others is the insulin signaling pathway which is found impaired in both the diseases. Abnormal protein aggregation, mitochondrial dysfunction and ER stress are some of the other clinical pathologies common between the diabetes and AD. This review focuses on bringing out the various possible molecular links between AD and Diabetes to create an understanding for identifying potential biomarkers and better treatment strategies for the two diseases.

Keywords: Metabolic disease, Neurodegeneration, Insulin, Amyloid beta, Molecular link

INTRODUCTION

Diabetes and Alzheimer's have been linked to each other for quite some time [1]. Both the diseases share common pathology which includes deregulated glucose homeostasis and impaired brain function. Impaired glucose tolerance impacts cognitive processes leading to loss in processing speed and verbal memory. Extensive research suggests that a connection exists between the two and that correction in the dysregulation in the blood sugar level should prove to be an effective strategy to prevent or treat AD. Though a clarified explanation is not yet available yet however, research suggests that people with diabetes mellitus are at a higher risk of developing Alzheimer's like dementia [2]. The failure in the clinical trials stage for AD drugs may be mainly attributed to the approach to therapeutic strategy. The scientific community has so far focused their entire attention on one particular solution for AD. Since multiple factors are responsible for the development of this complex neurodegenerative disease a multitude of strategies should be employed as a therapeutic strategy. This approach for curing AD somehow remains ignored.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disease. The pathological hallmarks of AD include extracellular A β plaques and cerebral A β

angiopathy, hyperphosphorylated tau, synaptic loss and neuronal death [3,4]. Clinical characterization of AD includes gradual impairment of cognitive functions ultimately culminating in death. Regions of the brain affected in AD include the hippocampus, the amygdala, the frontal and temporal cortex. A German psychiatrist and neuroanatomist, Alois Alzheimer reported the presence of peculiar severe disease process of the cerebral cortex in the brain samples of his patient Mrs. Auguste Deter [5]. Her symptoms at the time of admission to hospital included paranoia, progressive sleep and memory disorders, phrenic malfunctioning, aggression, delirium and protein accumulations. Onset of the autosomal dominant form of AD occurs at an early age which could be attributed to mutations in amyloid precursor protein (APP), Presenilin1

Corresponding author: Suraiya Saleem, Molecular nanomedicine and neuroscience department, Centre for nanoscience and nanomedicine. Sathyabama Campus Road, Jeppiaar Nagar, Rajiv Gandhi Salai, Semmancheri, Chennai, Tamil Nadu 600119, India. Tel: +917044548637; E-mail: suraiyasaleem.mnru@sathyabama.ac.in, suraiya.saleem171@gmail.com

Citation: Saleem S. (2021) Diabetes and Alzheimer's Disease: The Unresolved Connection. J Ageing Restor Med, 4(1): 150-158.

Copyright: ©2021 Saleem S. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

(PS1) and Presenilin2 (PS2) [6]. These mutations cause alterations in APP processing resulting in abnormal production of amyloid β ($A\beta$) peptides. Genetic variations occurring in APP causing increased production of it could be the cause of late onset AD. Sequential processing of the APP protein leads to the generation of amyloid peptides. Amyloid beta is cleaved into 39-42 amino acid peptide by proteolytic cleavage of APP by β secretase and γ secretase respectively [7]. Of these the 1-42 amyloid beta peptide has been shown to have more toxic effects than the other shorter species. Alzheimer's disease being a multifactorial disease is caused by complex interactions between genetic, epigenetic and environmental components. The extracellular $A\beta$ plaques exert toxicity by acting as physical hindrances to synaptic transmissions and by activating pathogenic cellular cascades [8]. Source of toxicity is not limited to the extracellular amyloid plaques. The soluble amyloid beta accumulating in the cells also exert huge neurotoxicity and cause death of cells. This intracellular abnormal accumulation of $A\beta$ is the result of an imbalance between three mechanisms linked to amyloid beta processing, $A\beta$ (i) production, (ii) aggregation and (iii) clearance [9]. Targeting intracellular $A\beta$ may prove to be a promising therapy for AD. The neurofibrillary tangles consist of hyperphosphorylated tau protein. The physiologic function of Tau is to stabilize the microtubules, regulate microtubule dynamics, axonal transport and neurite outgrowth. Once phosphorylated dysfunctional tau now acts as a determining factor for AD pathogenesis. Abnormal hyperphosphorylation tau along with its incorporation into neurofibrillary tangles (NFTs), presence dystrophic neurites surrounded by neuritic plaques (NP) and neuropil threads are the other major pathological hallmarks of AD [10]. The pathognomonic features of AD are abundant in the entorhinal cortex, hippocampus, amygdala, frontal, temporal and parietal lobes, and subcortical nuclei.

DIABETES

Type 2 diabetes is one of the most common chronic metabolic disorders. Diabetes can be classified into three broad types. Type 1 diabetes, Type 2 diabetes and Gestational diabetes (GDM) [11]. Type 1 diabetes mellitus (T1DM) accounts for approximately 5% to 10% of Diabetic cases and is characterized by an autoimmune anomaly which causes destruction of self-insulin-producing beta cells in the islets of the pancreas [12]. This results in a deficiency of insulin in the system. The autoimmunity may be developed due to genetic vulnerability and the impact of environmental factors such as viral infection, toxins, or some dietary factors [13]. T1DM is most commonly prevalent in children and adolescents though it can develop at any age. Around 90% of diabetic patients suffer Type 2 diabetes mellitus (T2DM). Insulin resistance i.e., a diminished response to insulin is generally observed patients suffering with T2DM [14]. In this condition, in order to maintain glucose homeostasis initially an increased insulin production by the system tries to overcome the ineffective insulin. However, over time, the

production of insulin decreases, thus resulting in T2DM [15]. T2DM is most commonly seen in older population though cases among children, adolescents are also reported. The third type is the Gestational Diabetes Mellitus (GDM) [16]. This is detected during pregnancy and is also known as hyperglycemia. GDM may be accompanied by several complications like hypertension, preeclampsia, and hydramnios which may require operative interventions [17]. In T1DM the autoimmune destruction of pancreatic cells is cellular mediated and is generally genetically predisposed. The major histocompatibility complex (MHC), also known as human leukocyte antigens (HLA), is reported is reported accountable for familial aggregation of T1DM [18]. Latent autoimmune diabetes seen in adults (LADA) is another rare form of T1DM observed [19]. It generally has a slow onset and exemplifies in adulthood. The autoimmunity developed in the system is strong enough to detect antibodies against islet cells, insulin, glutamic acid decarboxylase-65 (GAD-65), and zinc transporter 8 (Zn T8) in the patient's serum [20]. These antibodies destroy the beta cells thus curbing the amount of insulin secreted by the pancreas. T2DM on the other hand is an insulin-resistance condition which is also associated beta-cell dysfunction. Initially, the system tries to compensate for the loss by increase in insulin secretion. This maintains glucose levels in the normal physiologic range. However, as the disease progresses, more and more dysfunctional beta cells are produced. The system's compensatory mechanism is unable to maintain the increased insulin production, impairing glucose homeostasis, producing hyperglycemia [21]. It is observed that the diabetic patients are generally obese having high body fat deposition [22]. This INCREASED store of adipose tissue is responsible for promoting insulin resistance through mechanisms which include inflammation high release of free fatty acid and adipokine impairment [23]. The complications arising in diabetes affect several organs simultaneously. These include the eye, brain, kidney, liver and heart [24,25]. Diabetic conditions have been studied to regulate atherosclerosis arising in the cerebral arteries which may in turn lead to changes in cerebral blood flow.

UNDERSTANDING THE LINK BETWEEN AD AND DIABETES

Growing epidemiological evidence shows patients suffering with diabetes are more likely to develop AD. Vascular dementia is caused by diabetes as it is known to cause damage to blood vessels. This results in reduced blood flow to the brain thus damaging it which in turn might lead to dementia. People suffering with diabetes undergo changes in the brain which are similar to those observed in Alzheimer's or dementia [26]. Scientists are coming to believe that each condition fuels the causes that result in damage of the other condition. Diabetes has been found guilty in inducing Mild Cognitive Impairment (MCI) [27]. This may lead to adverse dementia observed in AD. Results indicate that there is an imbalance of oxidation and antioxidant capacity in diabetic

patients [28,29]. This condition further worsens the situation leading to more oxidative stress, disruption of fission and fusion of mitochondria, anomalies in the biological functions and mutations in the mitochondrial DNA. As a result of these events brain energy supply is insufficient thus making the brain more vulnerable to cognitive dysfunction and memory impairments [30,31].

There is enough ongoing research aiming to understand the link between diabetes and dementia. The link might lie in the manner diabetes regulates the brain and other body tissues to utilize glucose and respond to insulin. Research is being carried on to understand the connection between the two, however the recent clinical trial of intranasal insulin showed no effect in improving cognition [32].

Molecular Connections

Abnormalities in diabetes lead to overproduction of advanced glucose end products (AGES) and reactive oxygen species (ROS) [33]. Both these pathologies are a common feature observed in aging. The role of insulin has been quite interesting in contributing to the link between the two diseases. Experiments suggest that Insulin acts as a neurotrophic factor having several neurotrophic properties in the brain [34]. Clinical evidence proves that patients suffering with Alzheimer's disease have low levels of insulin in their cerebrospinal fluid [35]. Interestingly clinical hyperinsulinism has been identified as a risk factor for AD [36]. If insulin is neurotrophic then its excess availability should not affect the functioning of the brain. This paradoxical finding can be explained simply through the concept of competition [37].

Key player

IDE: Though insulin is a neurotrophic factor, yet increased levels of it leads to competition with amyloid beta for insulin degrading enzyme (IDE) [38,39]. IDE is a very prominent clearance mechanism for amyloid beta [40]. IDE being highly selective for insulin ultimately leads to reduced clearance of amyloid beta. Moreover, hyperglycemia and hyperinsulinism exacerbates both oligomerization of amyloid beta and hyperphosphorylation of tau [41,42].

PROTEIN PERTURBATIONS

Protein accumulation is a common feature in AD and other neurodegenerative diseases. In AD, aggregations occur of the amyloid beta peptides which are the cleaved product of APP. These accumulations can be both intracellular and extracellular. Intracellular aggregations are generally soluble in nature but highly toxic [43]. They not only alter the oxidation levels of cells but also lead to dysregulation of intracellular protein trafficking ultimately leading to death of cells. The extracellular aggregations are more commonly referred to as the amyloid plaques which act as physical obstructions to synaptic transmissions leading to memory impairment [44]. The role of Insulin in activating protein

biosynthesis, inhibiting protein decomposition and improving protein metabolism is well established [45]. However, since insulin secretion is itself compromised in diabetic conditions the protein synthesis mechanism also suffers thus leading to protein metabolic disorders [46]. Islet amyloid peptide (IAPP) or amylin is a key protein responsible for protein pathogenesis in T2DM [47].

Key players

hIAPP & A β : Amyloid Precursor Protein (APP) is sequentially cleaved by the β and the γ secretases to produce the toxic amyloid beta peptide (42 amino acids) [48]. This peptide then aggregates to form oligomers and fibrils within the cell and plaques outside the cell [49]. Similar to amyloid beta accumulations in the AD brain, there occurs islet amyloid deposits in the pancreas of patients with diabetes [50]. The amyloid that aggregates in the islets is a product of proteolytic processing of the human islet amyloid polypeptide (hIAPP) and is 37 amino acids long [51]. Almost 90% of the patients suffering with diabetes also have pancreatic islet amyloid accumulations [52]. These amyloid aggregates in the pancreas are generally associated with decreased β cell mass. The hIAPP fibrils resemble both structurally and morphologically to the amyloid beta fibrils in AD [53]. The APP possesses some vital physiological functions like neurite growth and long-term potentiation (LTP) by controlling release of calcium ions [54,55]. Similarly, the hIAPP has been reported to inhibit glucose-stimulated insulin secretion. Mice lacking hIAPP show enhanced insulin secretion thus display improved glucose tolerance [56]. Both amyloid beta and hIAPP form early aggregate intermediates [57,58]. Further, just as amyloid beta oligomers are more toxic and cause cellular perturbations in the neurons the soluble hIAPP oligomers have been reported to induce apoptosis of the beta cells [59,60]. Reports also suggest a similarity in the mechanism of action of toxicity induction between amyloid beta and hIAPP [61,62].

MITOCHONDRIAL DYSFUNCTION

Mitochondria generally considered as the powerhouse of the cell play significant physiologic functions including production of free radicals, oxidative respiration, metabolism of energy and apoptosis [63]. The efficient role of mitochondria in delaying ageing and neurodegenerative diseases has also been reported [64]. The mitochondria of the brain function overtime to supply the high brain energy demand thus making themselves more vulnerable to mitochondrial disorders [65]. Once the functionality of the mitochondria is disrupted, they tend to produce more reactive oxygen species (ROS), reactive nitrogen species (RNS), super oxide dismutase (SOD) and less of ATP which resembles the oxidative imbalance observed in AD [66]. A dysregulated mitochondrion leads to disruption of calcium homeostasis, causes apoptosis, abnormalities in the electron transport chain and memory impairment [67]. Interestingly,

it has been observed that the mitochondrial genes are missing in Type II Diabetes (T2D) animal models [68-72]. Both AD and diabetic patients display an increased expression of ROS and RNS [73].

Key Player

(PGC-1 α): Proteins such as peroxisome proliferator activated receptor gamma coactivator 1 α (PGC-1 α) plays a role in the biosynthesis of the mitochondria [74]. Interestingly, decreased levels of PGC-1 α proteins are observed in both AD patients [75] and diabetic mice [76] which could be responsible for decreased biosynthesis of mitochondria and impaired peroxidation of mitochondrial fatty acids [77].

ANOMALIES IN LIPID METABOLISM

Brain lipid composition is high [78]. The various types of lipid found in the brain are glycerophospholipids, sphingolipids, and cholesterol [79]. Presence of adipose inclusions have been reported in AD patient brain samples [80] whereas, high lipid oxidation products are observed in brain tissues from AD mice models [81]. Similarly, diabetic patients display increased adiposity, triglycerides, hyperlipidemia and low-density lipoprotein cholesterol (LDL-C) and decreased high-density lipoprotein cholesterol (HDL-C) [82]. Thus, abnormal lipid metabolism is a common feature of both AD and diabetes. Hypercholesterolemia arising due to impaired lipid metabolism may promote pathogenesis attributed to amyloid beta in the brain. 3xTg-AD mice fed with a high-fat diet have been observed to display increased inflammation in the brain, glucose intolerance, tau phosphorylation, increased soluble amyloid beta concentration and impaired memory [83]. Most interestingly, a single dose of insulin helped reverse the deleterious effects partly by mediating amyloid beta production and clearance [84].

Key player

APOE4: Reports implicate the role of Apolipoprotein E allele4 in AD as well as diabetes [85]. It has been shown to bind to amyloid beta peptide and thus regulate its aggregation [86-88]. Expression of APOE4 in a diabetic condition increases more than five times the vulnerability of developing AD [89,90]. Abnormal Lipid metabolism is therefore a common pathogenesis in both AD and diabetes.

ER STRESS

The endoplasmic reticulum (ER) is regarded as the site of synthesis of proteins. It is responsible for folding of all types of proteins, secreted or membrane-bound proteins. Some of the important factors required for proper protein folding to facilitate disulphide-bond formation are ATP, Ca²⁺ and an optimum oxidizing environment. The ER therefore is highly vulnerable to stresses that possess the ability to disturb the cellular energy levels, the physiological redox levels or Ca²⁺ concentration of the cell [91]. Such stresses adversely affect

the ER, they impair its protein folding capacity, thus leading to accumulation and aggregation of unwanted unfolded proteins [92,93]. This condition is referred to as ER stress [94]. Accumulation of unwanted proteins within the cell is toxic. Recent studies indicate the active role of Endoplasmic Reticulum stress in promoting apoptosis and autophagy of cells [95,96]. In order to overcome the exacerbating effects of ER stress, cells have evolved a collection of protective strategies, referred to as the unfolded protein response (UPR) [97]. The protective UPR is mediated through three of the ER transmembrane receptors, namely pancreatic ER kinase (PKR)-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1 (IRE1) [98]. Under normal conditions all the ER stress receptors remain inactive in association with the ER chaperone, glucose-regulated protein78 (GRP78) [99]. Under stress conditions GRP78 disrupts the association with the three receptors and dissociates from them thus leading to the upregulation of the UPR [100]. The UPR is mainly a protective mechanism however, if there occurs a continuous unresolvable aggregation of proteins the UPR renders ineffective leading to death of cells [101]. The molecular mechanisms involved in these events are not quite well studied and are only emerging now. The role of a pseudokinase, Tribbles 3 is of interest in this scenario [102].

Key player

Trib3: Trib3 is a mammalian ortholog of the *Tribbles* gene found in the *Drosophila* [103]. Trib3/TRB3/Tribbles3 is a pseudokinase which is upregulated in response to ER stress [104]. Though it is responsible for several physiologic functions including glucose regulation and tumor cells migration it has also been reported to increase expression levels in several stress conditions induced by hypoxia, 6-hydroxy dopamine, deprivation of growth factor, anoxia and ethanol exposure [105,106]. Once upregulated it activates a cascade of genes downstream which are responsible for cell death [107]. Trib3 has been reported to inhibit Akt resulting in increased autophagy and apoptotic death of neuronal cells [108-110]. Upregulation of Trib3 has been observed in both AD [111] and diabetes [112]. Trib3 impairs insulin signaling by increasing phosphorylation of insulin receptor 1 (IRS-1) at the serine residue and reducing activation of Akt [113]. It further reduces activation of Akt induced via insulin by physically binding with Akt and reducing exposure of the serine threonine active sites [114,115].

CONCLUSION

Epidemiological studies have revealed that diabetes is associated with AD and patients suffering with diabetes are at a higher risk of developing AD [116]. In spite of presence of several links into the metabolic anomaly of the two diseases, the exact specific mechanism which might link the two is still elusive. Diabetes leads to impaired insulin signaling, mitochondrial dysfunction and vascular changes in the brain [117,118]. While neurodegeneration in AD leads

to increased amyloid deposition and tau phosphorylation, hyperglycemia and accelerated rate of advanced glycation end product (AGE) formation [119]. Further, it must be borne in mind that both the diseases are highly heterogeneous [120,121]. A multitude of factors may be acting simultaneously to bring about the overt connection. Focusing on a single factor may prove ineffective when actually several interactions at molecular, cellular and systemic levels are at play. Extensive studies in this area are required to unravel the complexities of this association.

REFERENCES

- Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, et al. (2011) Diabetes mellitus and Alzheimer's disease: Shared pathology and treatment? *Br J Clin Pharmacol* 71(3): 365-376.
- Gudala K, Bansal D, Schifano F, Bhansali A (2013) Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. *J Diabetes Investig* 4(6): 640-650.
- Gouras GK, Olsson TT, Hansson O (2015) β -Amyloid peptides and amyloid plaques in Alzheimer's disease. *Neurotherapeutics* 12(1): 3-11.
- Iqbal K, Liu F, Gong C-X, Grundke-Iqbal I (2010) Tau in Alzheimer disease and related tauopathies. *Curr Alzheimer Res* 7(8): 656-664.
- Hippius H, Neundörfer G (2003) The discovery of Alzheimer's disease. *Dialogues Clin Neurosci* 5(1): 101-108.
- Bekris LM, Yu C-E, Bird TD, Tsuang DW (2010) Genetics of Alzheimer disease. *J Geriatr Psychiatry Neurol* 23(4): 213-227.
- O'Brien RJ, Wong PC (2011) Amyloid precursor protein processing and Alzheimer's disease. *Annu Rev Neurosci* 34: 185-204.
- Phillips JC (2019) Why A β 42 Is Much More Toxic than A β 40. *ACS Chem Neurosci* 10(6): 2843-2847.
- Tabaton M, Piccini A (2005) Role of water-soluble amyloid-beta in the pathogenesis of Alzheimer's disease. *Int J Exp Pathol* 86(3): 139-145.
- Bloom GS (2014) Amyloid- β and tau: The trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol* 71(4): 505-508.
- American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. *Diabetes Care* 33 Suppl 1(Suppl 1): S62-S69.
- Atkinson MA, Eisenbarth GS, Michels AW (2014) Type 1 diabetes. *Lancet* 383(9911): 69-82.
- Kawasaki E (2014) Type 1 diabetes and autoimmunity. *Clin Pediatr Endocrinol* 23(4): 99-105.
- Wilcox G (2005) Insulin and insulin resistance. *Clin Biochem Rev* 26(2): 19-39.
- Smushkin G, Vella A (2010) What is type 2 diabetes? *Medicine (Abingdon)* 38(11): 597-601.
- Alfadhli EM (2015) Gestational diabetes mellitus. *Saudi Med J* 36(4): 399-406.
- Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH (2018) The Pathophysiology of Gestational Diabetes Mellitus. *Int J Mol Sci* 19(11): 3342.
- Wucherpfennig KW (2003) MHC-linked susceptibility to type 1 diabetes: A structural perspective. *Ann N Y Acad Sci* 1005: 119-127.
- Pieralice S, Pozzilli P (2018) Latent Autoimmune Diabetes in Adults: A Review on Clinical Implications and Management. *Diabetes Metab J* 42(6): 451-464.
- Lee SA, Lee WJ, Kim EH, Yu JH, Jung CH, et al. (2011) Progression to insulin deficiency in Korean patients with Type 2 diabetes mellitus positive for anti-GAD antibody. *Diabet Med* 28(3): 319-324.
- Rau C-S, Wu S-C, Chen Y-C, Chien P-C, Hsieh H-Y, et al. (2017) Stress-Induced Hyperglycemia in Diabetes: A Cross-Sectional Analysis to Explore the Definition Based on the Trauma Registry Data. *Int J Environ Res Public Health* 14(12): 1527.
- Chobot A, Katarzyna G-K, Sokołowska M, Przemysława J-C (2018) Obesity and diabetes-Not only a simple link between two epidemics. *Diabetes Metab Res Rev* 34(7): e3042.
- Sears B, Perry M (2015) The role of fatty acids in insulin resistance. *Lipids Health Dis* 14: 121.
- Bouhairie VE, McGill JB (2016) Diabetic Kidney Disease. *Mo Med* 113(5): 390-394.
- Vieira-Potter VJ, Karamichos D, Lee DJ (2016) Ocular Complications of Diabetes and Therapeutic Approaches. *Biomed Res Int* 2016: 3801570.
- Biessels GJ, Despa F (2018) Cognitive decline and dementia in diabetes mellitus: Mechanisms and clinical implications. *Nat Rev Endocrinol* 14(10): 591-604.
- Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW (2016) Diabetes and Cognitive Impairment. *Curr Diab Rep* 16(9): 87.
- Giacco F, Brownlee M (2010) Oxidative stress and diabetic complications. *Circ Res* 107(9): 1058-1070.
- Yan L-J (2018) Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. *Animal Model Exp Med* 1(1): 7-13.

30. Seaquist ER (2015) The Impact of Diabetes on Cerebral Structure and Function. *Psychosom Med* 77(6): 616-621.
31. Duarte JMN (2015) Metabolic Alterations Associated to Brain Dysfunction in Diabetes. *Aging Dis* 6(5): 304-321.
32. Sridhar GR, Lakshmi G, Nagamani G (2015) Emerging links between type 2 diabetes and Alzheimer's disease. *World J Diabetes* 6(5): 744-751.
33. Vitek MP, Bhattacharya K, Glendening JM, Stopa E, Vlassara H, et al. (1994) Advanced glycation end products contribute to amyloidosis in Alzheimer disease. *Proc Natl Acad Sci U S A* 91(11): 4766-4770.
34. Cole GM, Frautschy SA (2007) The role of insulin and neurotrophic factor signaling in brain aging and Alzheimer's Disease. *Exp Gerontol* 42(1-2): 10-21.
35. Ferreira LSS, Fernandes CS, Vieira MNN, De Felice FG (2018) Insulin Resistance in Alzheimer's Disease. *Front Neurosci* 12: 830.
36. Hegde V, Dhurandhar NV, Reddy PH (2019) Hyperinsulinemia or Insulin Resistance: What Impacts the Progression of Alzheimer's Disease? *J Alzheimers Dis* 72(s1): S71-S79.
37. Waragai M, Ho G, Takamatsu Y, Wada R, Sugama S, et al. (2020) Adiponectin Paradox in Alzheimer's Disease; Relevance to Amyloidogenic Evolvability? *Front Endocrinol (Lausanne)* 11: 108.
38. Xie L, Helmerhorst E, Taddei K, Plewright B, Bronswijk WV, et al. (2002) Alzheimer's beta-amyloid peptides compete for insulin binding to the insulin receptor. *J Neurosci* 22(10): RC221.
39. Qiu WQ, Folstein MF (2006) Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: Review and hypothesis. *Neurobiol Aging* 27(2): 190-198.
40. Baranello RJ, Bharani KL, Padmaraju V, Chopra N, Lahiri DK, et al. (2015) Amyloid-beta protein clearance and degradation (ABCD) pathways and their role in Alzheimer's disease. *Curr Alzheimer Res* 12(1): 32-46.
41. Chao A-C, Lee T-C, Juo S-HH, Yang D-I (2016) Hyperglycemia Increases the Production of Amyloid Beta-Peptide Leading to Decreased Endothelial Tight Junction. *CNS Neurosci Ther* 22(4): 291-297.
42. Nagai N, Ito Y, Sasaki H (2016) Hyperglycemia Enhances the Production of Amyloid β 1-42 in the Lenses of Otsuka Long-Evans Tokushima Fatty Rats, a Model of Human Type 2 Diabetes. *Invest Ophthalmol Vis Sci* 57(3): 1408-1417.
43. Carrillo-Mora P, Luna R, Colín-Barenque L (2014) Amyloid beta: Multiple mechanisms of toxicity and only some protective effects? *Oxid Med Cell Longev* 2014: 795375.
44. Serrano-Pozo A, Betensky RA, Frosch MP, Hyman BT (2016) Plaque-Associated Local Toxicity Increases over the Clinical Course of Alzheimer Disease. *Am J Pathol* 186(2): 375-384.
45. Biolo G, Wolfe RR (1993) Insulin action on protein metabolism. *Baillieres Clin Endocrinol Metab* 7(4): 989-1005.
46. Pfeifer MA, Halter JB, Porte Jr D (1981) Insulin secretion in diabetes mellitus. *Am J Med* 70(3): 579-588.
47. Mukherjee A, Morales-Scheihing D, Salvadores N, Moreno-Gonzalez I, Gonzalez C, et al. (2017) Induction of IAPP amyloid deposition and associated diabetic abnormalities by a prion-like mechanism. *J Exp Med* 214(9): 2591-2610.
48. Chow VW, Mattson MP, Wong PC, Gleichmann M (2010) An overview of APP processing enzymes and products. *Neuromolecular Med* 12(1): 1-12.
49. Finder VH, Glockshuber R (2007) Amyloid-beta aggregation. *Neurodegener Dis* 4(1): 13-27.
50. Tomita T (2005) Amyloidosis of pancreatic islets in primary amyloidosis (AL type). *Pathol Int* 55(4): 223-227.
51. Chaari A, Ladjimi M (2019) Human islet amyloid polypeptide (hIAPP) aggregation in type 2 diabetes: Correlation between intrinsic physicochemical properties of hIAPP aggregates and their cytotoxicity. *Int J Biol Macromol* 136: 57-65.
52. Mukherjee A, Soto C (2017) Prion-Like Protein Aggregates and Type 2 Diabetes. *Cold Spring Harb Perspect Med* 7(5): a024315.
53. Krotee P, Griner SL, Sawaya MR, Cascio D, Rodriguez JA, et al. (2018) Common fibrillar spines of amyloid- β and human islet amyloid polypeptide revealed by microelectron diffraction and structure-based inhibitors. *J Biol Chem* 293(8): 2888-2902.
54. Masliah E, Mallory M, Ge N, Saitoh T (1992) Amyloid precursor protein is localized in growing neurites of neonatal rat brain. *Brain Res* 593(2): 323-328.
55. Kim HS, Park CH, Cha SH, Lee JH, Lee S, et al. (2000) Carboxyl-terminal fragment of Alzheimer's APP destabilizes calcium homeostasis and renders neuronal cells vulnerable to excitotoxicity. *FASEB J* 14(11): 1508-1517.

56. Gebre-Medhin S, Mulder H, Pekny M, Westermark G, Törnell J, et al. (1998) Increased insulin secretion and glucose tolerance in mice lacking islet amyloid polypeptide (amylin). *Biochem Biophys Res Commun* 250(2): 271-277.
57. Raimundo AF, Ferreira S, Martins IC, Menezes R (2020) Islet Amyloid Polypeptide: A Partner in Crime with A β in the Pathology of Alzheimer's Disease. *Front Mol Neurosci* 13: 35.
58. Zhang X, Fu Z, Meng L, He M, Zhang Z (2018) The Early Events That Initiate β -Amyloid Aggregation in Alzheimer's Disease. *Front Aging Neurosci* 10: 359.
59. Bram Y, Frydman-Marom A, Yanai I, Gilead S, Shaltiel-Karyo R, et al. (2014) Apoptosis induced by islet amyloid polypeptide soluble oligomers is neutralized by diabetes-associated specific antibodies. *Sci Rep* 4: 4267.
60. Haataja L, Gurlo T, Huang CJ, Butler PC (2008) Islet amyloid in type 2 diabetes, and the toxic oligomer hypothesis. *Endocr Rev* 29(3): 303-316.
61. Ren B, Hu R, Zhang M, Liu Y, Xu L, et al. (2018) Experimental and Computational Protocols for Studies of Cross-Seeding Amyloid Assemblies. *Methods Mol Biol* 1777: 429-447.
62. Ge X, Yang Y, Sun Y, Cao W, Ding F (2018) Islet Amyloid Polypeptide Promotes Amyloid-Beta Aggregation by Binding-Induced Helix-Unfolding of the Amyloidogenic Core. *ACS Chem Neurosci* 9(5): 967-975.
63. Javadov S, Kuznetsov AV (2013) Mitochondria: The cell powerhouse and nexus of stress. *Front Physiol* 4: 207.
64. Nilsson MI, Tarnopolsky MA (2019) Mitochondria and Aging-The Role of Exercise as a Countermeasure. *Biology (Basel)* 8(2): 40.
65. Safiulina D, Kaasik A (2013) Energetic and dynamic: How mitochondria meet neuronal energy demands. *PLoS Biol* 11(12): e1001755.
66. Kausar S, Wang F, Cui H (2018) The Role of Mitochondria in Reactive Oxygen Species Generation and Its Implications for Neurodegenerative Diseases. *Cells* 7(12): 274.
67. Ježek J, Cooper KF, Strich R (2018) Reactive Oxygen Species and Mitochondrial Dynamics: The Yin and Yang of Mitochondrial Dysfunction and Cancer Progression. *Antioxidants (Basel)* 7(1): 13.
68. Gilkerson R (2016) Commentary: Mitochondrial DNA damage and loss in diabetes. *Diabetes Metab Res Rev* 32(7): 672-674.
69. King AJF (2012) The use of animal models in diabetes research. *Br J Pharmacol* 166(3): 877-894.
70. Pinti MV, Fink GK, Hathaway QA, Durr AJ, Kunovac A, et al. (2019) Mitochondrial dysfunction in type 2 diabetes mellitus: an organ-based analysis. *Am J Physiol Endocrinol Metab* 316(2): E268-E285.
71. Oliveira MT, Garesse R, Kaguni LS (2010) Animal models of mitochondrial DNA transactions in disease and ageing. *Exp Gerontol* 45(7-8): 489-502.
72. Fang J-Y, Lin C-H, Huang T-H, Chuang S-Y (2019) In Vivo Rodent Models of Type 2 Diabetes and Their Usefulness for Evaluating Flavonoid Bioactivity. *Nutrients* 11(3): 530.
73. Ahmad W, Ijaz B, Shabbiri K, Ahmed F, Rehman S (2017) Oxidative toxicity in diabetes and Alzheimer's disease: Mechanisms behind ROS/ RNS generation. *J Biomed Sci* 24(1): 76.
74. Fontecha-Barriuso M, Martin-Sanchez D, Martinez-Moreno JM, Monsalve M, Ramos AM, et al. (2020) The Role of PGC-1 α and Mitochondrial Biogenesis in Kidney Diseases. *Biomolecules* 10(2): 347.
75. Qin W, Haroutunian V, Katsel P, Cardozo CP, Ho L, et al. (2009) PGC-1 α expression decreases in the Alzheimer disease brain as a function of dementia. *Arch Neurol* 66(3): 352-361.
76. Moreno-Santos I, Pérez-Belmonte LM, Macías-González M, Mataró MJ, Castellano D, et al. (2016) Type 2 diabetes is associated with decreased PGC1 α expression in epicardial adipose tissue of patients with coronary artery disease. *J Transl Med* 14(1): 243.
77. Davì G, Falco A, Patrono C (2005) Lipid peroxidation in diabetes mellitus. *Antioxid Redox Signal* 7(1-2): 256-268.
78. Norton WT, Abe T, Poduslo SE, DeVries GH (1975) The lipid composition of isolated brain cells and axons. *J Neurosci Res* 1(1): 57-75.
79. Scandroglio F, Venkata JK, Loberto N, Prioni S, Schuchman EH, et al. (2008) Lipid content of brain, brain membrane lipid domains, and neurons from acid sphingomyelinase deficient mice. *J Neurochem* 107(2): 329-338.
80. Luchsinger JA, Gustafson DR (2009) Adiposity and Alzheimer's disease. *Curr Opin Clin Nutr Metab Care* 12(1): 15-21.
81. Praticò D, Uryu K, Leight S, Trojanowski JQ, Lee VM (2001) Increased lipid peroxidation precedes amyloid plaque formation in an animal model of Alzheimer amyloidosis. *J Neurosci* 21(12): 4183-4187.

82. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H (2016) Diabetes Dyslipidemia. *Diabetes Ther* 7(2): 203-219.
83. Julien C, Tremblay C, Phivilay A, Berthiaume L, Emond V, et al. (2010) High-fat diet aggravates amyloid-beta and tau pathologies in the 3xTg-AD mouse model. *Neurobiol Aging* 31(9): 1516-1531.
84. Vandal M, White PJ, Tremblay C, St-Amour I, Chevrier G, et al. (2014) Insulin reverses the high-fat diet-induced increase in brain A β and improves memory in an animal model of Alzheimer disease. *Diabetes* 63(12): 4291-4301.
85. Peila R, Rodriguez BL, Launer LJ (2002) Type 2 Diabetes, APOE Gene, and the Risk for Dementia and Related Pathologies. *Diabetes* 51(4): 1256-1262.
86. Liu S, Park S, Allington G, Prelli F, Sun Y, et al. (2017) Targeting Apolipoprotein E/Amyloid β Binding by Peptoid CPO_A β 17-21 P Ameliorates Alzheimer's Disease Related Pathology and Cognitive Decline. *Sci Rep* 7(1): 8009.
87. Strittmatter WJ, Weisgraber KH, Huang DY, Dong LM, Salvesen GS, et al. (1993) Binding of human apolipoprotein E to synthetic amyloid beta peptide: Isoform-specific effects and implications for late-onset Alzheimer disease. *Proc Natl Acad Sci U S A* 90(17): 8098-8102.
88. Sanan DA, Weisgraber KH, Russell SJ, Mahley RW, Huang D, et al. (1994) Apolipoprotein E associates with beta amyloid peptide of Alzheimer's disease to form novel monofibrils. Isoform apoE4 associates more efficiently than apoE3. *J Clin Invest* 94(2): 860-869.
89. Liu C-C, Liu C-C, Kanekiyo T, Xu H, Bu G (2013) Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nat Rev Neurol* 9(2): 106-118.
90. Safieh M, Korczyn AD, Michaelson DM (2019) ApoE4: An emerging therapeutic target for Alzheimer's disease. *BMC Med* 17(1): 64.
91. Ozcan L, Tabas I (2012) Role of endoplasmic reticulum stress in metabolic disease and other disorders. *Annu Rev Med* 63: 317-328.
92. Bueter W, Dammann O, Leviton A (2009) Endoplasmic reticulum stress, inflammation, and perinatal brain damage. *Pediatr Res* 66(5): 487-494.
93. Badr CE, Hewett JW, Breakefield XO, Tannous BA (2007) A highly sensitive assay for monitoring the secretory pathway and ER stress. *PLoS One* 2(6): e571.
94. Lin JH, Walter P, Yen TSB (2008) Endoplasmic reticulum stress in disease pathogenesis. *Annu Rev Pathol* 3: 399-425.
95. Deng Y, Srivastava R, Howell SH (2013) Endoplasmic reticulum (ER) stress response and its physiological roles in plants. *Int J Mol Sci* 14(4): 8188-8212.
96. Scull CM, Tabas I (2011) Mechanisms of ER stress-induced apoptosis in atherosclerosis. *Arterioscler Thromb Vasc Biol* 31(12): 2792-2797.
97. Bravo R, Parra V, Gatica D, Rodriguez AE, Torrealba N, et al. (2013) Endoplasmic reticulum and the unfolded protein response: Dynamics and metabolic integration. *Int Rev Cell Mol Biol* 301: 215-290.
98. Szegezdi E, Logue SE, Gorman AM, Samali A (2006) Mediators of endoplasmic reticulum stress-induced apoptosis. *EMBO Rep* 7(9): 880-885.
99. Wang M, Wey S, Zhang Y, Ye R, Lee AS (2009) Role of the unfolded protein response regulator GRP78/BiP in development, cancer, and neurological disorders. *Antioxid Redox Signal* 11(9): 2307-2316.
100. Uddin MS, Tewari D, Sharma G, Kabir MT, Barreto George E, et al., Molecular Mechanisms of ER Stress and UPR in the Pathogenesis of Alzheimer's Disease. *Mol Neurobiol* 57(7): 2902-2919.
101. Jovaisaite V, Mouchiroud L, Auwerx J (2014) The mitochondrial unfolded protein response, a conserved stress response pathway with implications in health and disease. *J Exp Biol* 217(Pt 1): 137-143.
102. Koh H-J, Toyoda T, Didesch MM, Lee M-Y, Sleeman MW, et al. Tribbles 3 mediates endoplasmic reticulum stress-induced insulin resistance in skeletal muscle. *Nat Commun* 4: 1871.
103. LaFerriere H, Zars T (2017) The *Drosophila melanogaster* tribbles pseudokinase is necessary for proper memory formation. *Neurobiol Learn Mem* 144: 68-76.
104. Zhang J, Han Y, Zhao Y, Li Q-R, Jin H-F, et al. (2019) Role of endoplasmic reticulum stress-associated gene TRIB3 in rats following kainic acid-induced seizures. *Int J Clin Exp Pathol* 12(2): 599-605.
105. Cunard R (2013) Mammalian Tribbles Homologs at the Crossroads of Endoplasmic Reticulum Stress and Mammalian Target of Rapamycin Pathways. *Scientifica (Cairo)* 2013: 750871.
106. Zhang J, Han Y, Zhao Y, Li Q, Jin H, et al. (2019) Inhibition of TRIB3 Protects Against Neurotoxic Injury Induced by Kainic Acid in Rats. *Front Pharmacol* 10: 585.
107. Ohoka N, Yoshii S, Hattori T, Onozaki K, Hayashi H (2005) TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death. *EMBO J* 24(6): 1243-1255.

108. Du K, Herzig S, Kulkarni RN, Montminy M (2003) TRB3: A tribbles homolog that inhibits Akt/PKB activation by insulin in liver. *Science* 300(5625): 1574-1577.
109. Zareen N, Biswas SC, Greene LA (2013) A feed-forward loop involving Trib3, Akt and FoxO mediates death of NGF-deprived neurons. *Cell Death Differ* 20(12): 1719-1730.
110. Biswas S, Saleem S (2014) A Dual Role of TRB3 in Neuronal Cell Death in an Alzheimer's Disease Model. *Alzheimer's & Dementia* 10: 4.
111. Saleem S, Biswas SC (2017) Tribbles Pseudokinase 3 Induces Both Apoptosis and Autophagy in Amyloid- β -induced Neuronal Death. *J Biol Chem* 292(7): 2571-2585.
112. Guo L, Guo Z-X, Gong H-P, Shang Y-Y, Zhong M, et al. (2015) Tribbles homolog 3 is induced by high glucose and associated with apoptosis in human endothelial cells. *Mol Med Rep* 12(2): 1963-1970.
113. Jang YY, Kim NK, Kim MK, Lee HY, Kim SJ, et al. (2010) The Effect of Tribbles-Related Protein 3 on ER Stress-Suppressed Insulin Gene Expression in INS-1 Cells. *Korean Diabetes J* 34(5): 312-319.
114. Fischer Z, Das R, Shipman A, Fan J-Y, Pence L, et al. (2017) A Drosophila model of insulin resistance associated with the human TRIB3 Q/R polymorphism. *Dis Model Mech*. 10(12): 1453-1464.
115. Salazar M, Lorente M, García-Taboada E, Gómez EP, Dávila D, et al. (2015) TRIB3 suppresses tumorigenesis by controlling mTORC2/AKT/FOXO signaling. *Mol Cell Oncol* 2(3): e980134.
116. Noreen Z, DeJesus J, Bhatti A, Loffredo CA, John P, et al. (2018) Epidemiological Investigation of Type 2 Diabetes and Alzheimer's Disease in a Pakistani Population. *Int J Environ Res Public Health* 15(8): 1582.
117. Rask-Madsen C, King GL (2013) Vascular complications of diabetes: mechanisms of injury and protective factors. *Cell Metab* 17(1): 20-33.
118. Pinti MV, Fink GK, Hathaway QA, Durr AJ, Kunovac A, et al. (2019) Mitochondrial dysfunction in type 2 diabetes mellitus: An organ-based analysis. *Am J Physiol Endocrinol Metab* 316(2): E268-E285.
119. Aljanabi NM, Mamtani S, Al-Ghuraibawi MMH, Yadav S, Nasr L (2020) Alzheimer's and Hyperglycemia: Role of the Insulin Signaling Pathway and GSK-3 Inhibition in Paving a Path to Dementia. *Cureus* 12(2): e6885.
120. Chornenkyy Y, Wang W-X, Wei A, Nelson PT (2019) Alzheimer's disease and type 2 diabetes mellitus are distinct diseases with potential overlapping metabolic dysfunction upstream of observed cognitive decline. *Brain Pathol* 29(1): 3-17.
121. Karalliedde J, Gnudi L (2016) Diabetes mellitus, a complex and heterogeneous disease, and the role of insulin resistance as a determinant of diabetic kidney disease. *Nephrol Dial Transplant* 31(2): 206-213.