

Review Article

Diabetes mellitus linked Alzheimer's disease – A review on sporadic form of Alzheimer's disease

Ramu Sathiya* , Anita Murali, Jayaraman Anbu

Department of Pharmacology, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, Bangalore, Karnataka, India

Abstract

This review mainly deals with scientific data related to sporadic Alzheimer's disease (AD) particularly related to diabetes mellitus (DM). AD is divided into sporadic AD and familial AD. It is known to be the most common cause of dementia. Sporadic form of AD results from multiple etiologic factors including metabolic, environmental and genetic factors. DM linked AD is known to be one of major challenges to health care system in these days. Both type 1 and type 2 DM is strongly related to cognitive impairment and known to be a major risk factor in the development of probable Alzheimer's disease. In this review, the various mechanisms involved in the development of neuronal degeneration associated with chronic hyperglycaemia are discussed.

Keywords:

Diabetes mellitus;
Alzheimer's disease;
Hyperglycemia

Received: 11 Jan 2018

Accepted: 20 Sep 2018

*Correspondence to:

R. Sathiya

Tel: +91-8023603947

Email:

sathiya.pg.ph@msruas.ac.in

Introduction

Diabetes mellitus (DM) is a disorder of glucose regulation which is characterized by hyperinsulinemia, hyperglycaemia and wilted insulin receptor responsiveness. It is the common disease in recent days with various complications such as cardiovascular diseases, central nervous system dysfunction, kidney failure and retinopathy (Liu et al., 2013). Neurodegeneration, memory and cognitive impairment are revealed to be the major complications of DM (Kodl and Seaquist, 2008). Studies show that both type 1 and 2 is strongly related to cognitive impairment (Duarte et al., 2007; Stewart and Liolitsa, 1999). Thus DM is known to be a major risk factor in the development of probable Alzheimer's disease (AD) (Biessels et al., 2006). A report released by WHO on September 2012 states that 347 million people worldwide are suffering from DM. It is predicted that 300 million of world population

will be affected by particularly with type 2 DM by the year 2025 (WHO, 2012).

The memory impairment caused by DM is correlated to the impairment of central insulin modulation in hippocampus (Liu et al., 2013). Insulin and insulin like growth factor are having a major role in the regulation of amyloid beta (A β) protein. Clinical epidemiological studies show that diabetic patients are twofold prone for AD when compared to non-diabetic individuals. Thus, chronic hyperglycemia is observed to be one of the major causes of diabetic encephalopathy (Liu et al., 2013).

AD is a common, progressive and devastating neurodegeneration of human brain structure which is characterized by loss of neurons, cognition and a progressive loss of functions. It is known to be one of the major challenges to the modern health care system (Ghanemi, 2015; Sun et al., 2012; Mount and Downton, 2006; Janson et al., 2004). AD is associated with the aggregation of A β protein and tau protein. A β protein cumulates into small, toxic senile

plaques. The accumulation of senile plaque leads to activation of microglial cells and proinflammatory cytokines which are responsible for inflammatory responses in neocortex and hippocampus. Imbalance between kinases and phosphatases causes hyperphosphorylation of tau protein that results in neuronal loss and degeneration. The hyperphosphorylated or pathologically modified tau protein aggregate into neurofibrillary tangles in brain and contributes to neuronal loss and degeneration (Ghanemi, 2015; Saido, 2013; Belluti et al., 2013; Thota et al., 2007).

Diabetic encephalopathy is a condition triggered by DM, which is characterized by electrophysiological, structural and neurochemical changes in the brain leading to cognitive impairments. The most common altered cognitive function in early onset of DM is memory impairment (Liu et al., 2008). The prominent common pathological feature in DM and AD is extracellular aggregation of insoluble amyloid beta proteins.

Common pathological features between diabetes mellitus and Alzheimer's disease

Amyloidogenesis

DM and AD are known to be amyloid forming diseases. The pathological hallmark of AD is the extracellular amyloid plaque. The primary component of this amyloid plaque is the A β peptide 1–42. A β is derived from the amyloid precursor protein (APP) by proteolytic cleavage. APP is the base of molecular pathology of which impairs glucose metabolism and tolerance in brain (Bigl et al., 2003). The deposition of amyloidogenic peptide is also seen in the islets of Langerhans in DM in the same manner. The islet amyloid deposit is known as Islet Amyloid Polypeptide (IAPP) or amylin which is a 37 amino acid peptide.

IAPP is co secreted with insulin. Together with the insulin and glucagon IAPP acts as a satiety and adiposity signal in regulation of food intake and body weight. The human A β 1-42 and IAPP are highly susceptible for aggregation and thus they can easily lead to the formation of polymers (Yang and Song, 2013; Sun et al., 2012).

Aggregates of A β oligomers and also their early intermediate assemblies provoke toxicity to neurons. Similarly, aggregates IAPP produces toxicity to β -

cells of islets of Langerhans (Porat et al., 2003). IAPP oligomers reacts same way toward cultured β cells as how A β oligomers react to neurons (Zhao and Townsend, 2009).

Impairment in energy metabolism

Glucose is the main source of energy for the neurons in the brain. Thus any impairment in the utilization and glucose metabolism forms the pathological basis of DM (Hoyer, 1990). In total body glucose, 18-30% is consumed by brain. Disruption in the supply, transport or utilization of glucose can lead to neuronal damage and functional deficits in brain. Neuronal death always accompanies insulin resistance in developing human brains which may even cause permanent brain damage (Dunne et al., 2004; Strachan et al., 1997; Tun et al., 1990; Richardson, 1990). This gives a clear indication that cognitive function is affected by disruption in glucose metabolism.

Clinical studies have revealed that AD patients had severely impaired glucose metabolism in their cerebral cortex. In early stages, the hypometabolism was found to be prominent in parietotemporal and the posterior cingulate regions, as the disease progresses it is observed spread to the prefrontal cortex (Mosconi et al., 2008; Small et al., 2000). AD genetic risk factor is strongly correlated to abnormal glucose metabolism. Metabolic reduction of glucose in posterior cingulate regions of AD transgenic animal model was reported by Valla et al. (2008).

The association between impaired glucose transport and neurodegeneration links the major glucose GLUT1 which is selectively expressed in the endothelium of the blood brain barrier. Significant reduction of GLUT1 is seen in aged humans and AD transgenic mice model coinciding with hippocampal atrophy (Hooijmans et al., 2007)

Oxidative stress and high level of advanced glycation end products (AGEs)

Non-enzymatic glycation and oxidation of cellular proteins, nucleic acids and lipids by reducing sugars leads to accumulation of AGEs in chronic hyperglycemia. Accumulated AGEs binds to the receptor "RAGE" expressed on various cells such as microglia, vascular smooth muscle cells, mononuclear phagocytes and endothelial cells. AGEs interact with RAGE and triggers signalling cascade

leading to increased oxidative stress by up-regulating transcription factor NF- κ B. This leads to increased secretion or production of inflammatory cytokines such as TNF- α and IL-6. Thus the interaction of RAGE-AGE is depicted as a major source of oxidative stress and inflammation which is correlated with diabetic complications as well as neurodegenerative diseases.

AGE is known to be an accelerating factor for A β aggregation (Reddy et al., 2002). Evidence suggest that the neurofibrillary tangles are stabilized by glycation of tau protein which actually results from accumulated AGE products. Thus AGE contributes to amyloidosis and neurofibrillary tangle formation in brain. Abnormally hyperphosphorylated tau protein localised in neuronal axons is known to be the major component in neurofibrillary tangles (Zhao and Townsend, 2009; Smith et al., 1995).

Role of insulin receptor and insulin receptor substrates

Modulation of synaptic plasticity and cognition are the major functions of insulin receptor in brain (Zhao and Townsend, 2009). The abundant distribution of insulin receptors in cerebral cortex, amygdala and hippocampus are the evidences for their involvement in cognitive process and synaptic activity. Studies have shown that animals with increased amount of insulin receptor and insulin receptor substrate-1 in the hippocampal synaptic membranes show better spatial memory compared to the diabetic animals which showed reduction in hippocampal insulin receptor. Accumulated A β competes with insulin to bind to the insulin receptor and interferes with insulin signalling. Impaired insulin signalling is reported to be a main cause of reduced clearance of A β oligomers (Yang and Song, 2013).

Insulin resistance

The declined ability of insulin receptor to respond to insulin stimulation is known as insulin resistance. Insulin resistance is an early feature of DM and it could be detected 10-20 years before the actual episode of clinical hyperglycemia. Even though brain insulin receptors are having a different structure when compared to the peripheral receptors, studies suggest that reduction in insulin level leads to functional debility (Zhao and Townsend, 2009). Impaired insulin receptor signalling is known to be a

mediator of cognitive impairment in both DM and AD. It activates glycogen synthase kinase 3 β and hyperphosphorylation of tau protein and reduces phosphatidylinositol-3-kinase/ Akt pathway signalling (Liu et al., 2013; Liu et al., 2008).

Inflammation

DM is projected to be an autoinflammatory disease where inflammation plays a major role in the development of insulin resistance. Patients with type 2 DM are reported to have elevated levels of circulating cytokines and chemokines. In addition elevated level of B-cell, IL-1 β , islet-associated macrophages and reduced IL-1 receptor antagonist are observed in such patients reflecting inflammation in the pancreatic islet. Evidence suggests that insulin resistance has a strong connection to circulating levels of inflammatory mediators. Serum C reactive protein is one such example for inflammation marker. Similarly post-mortem AD brains had shown up-regulation in the levels of chemokines, complement proteins and cytokines. This indicates the association of AD to the wide range of immune and inflammatory pathways (Mushtaq et al., 2015).

Hepatic insulin resistance caused by elevated cytokine level gives the clue for the correlation of inflammation to DM in obese individuals. Over-expression of TNF- α derived from activated macrophages in adipose tissues of obese mice was revealed by Aziz et al. (2012). Peraldi and Spiegelman (1997) reported that TNF- α impairs insulin signalling by inhibiting insulin receptor tyrosine kinase activity and tyrosine phosphorylation of IRS-1.

An overview of studies on DM and the related memory impairments

This part of review deals with studies reported on streptozotocin (STZ) induced DM and the related memory impairments and also the effect of DM and the prediabetic state on synaptic plasticity.

The modifications caused by STZ mainly result from its ability to induce diabetic state. Rahigude et al. (2012) have reported that high-fat diet for two weeks and a low dose of STZ (35mg/kg) leads to diabetes related memory impairment. Liu et al. (2013) have used STZ in the dose 65mg/kg to induce diabetes related brain encephalopathy. The STZ induced diabetic state was reported to increase A β protein

level 1- 40 in the brain by Liu et al. (2008). Li et al. (2012) correlated administration of STZ to tau over-expression and hyperphosphorylation and also ultra-structural changes in nucleus and nucleolus. Sasaki-Hamada et al. (2012) revealed that hippocampal synaptic plasticity is influenced by diabetes in STZ-treated rats. They also highlighted that the age of diabetes onset is also important in the pathophysiology of diabetes-induced cognitive difficulties as it varies with onset.

Liu et al. (2013) studied the neuroprotective effect of Liuwei Dihuang decoction on cognition deficits of diabetic encephalopathy in STZ-induced diabetic rat. In this study, a high glucose fat diet and STZ in the dose of 40mg/kg was used to produce a model of diabetic encephalopathy.

Soares et al. (2013) investigated the link between hippocampal dysfunction and the presence of spatial learning and memory deficits in a prediabetic animal model. The authors concluded that prediabetic state induced by 9 weeks sucrose consumption induced short and long term spatial memory deficits. Thus, this study evidenced that the prediabetic state is related to spatial memory impairments.

Jolivald et al. (2012) reported that type 1 DM and Alzheimer's disease are known to have a similar pattern of peripheral neuropathy in mouse models. They examined insulin signalling in the sciatic nerve of APP over-expressing transgenic mice and insulin-deficient mice. The data obtained from this study depicted that there are deficits in the insulin signalling pathway in both the diseases.

Another study conducted by Ariza et al. (2014) interconnected early peripheral sensorimotor neuropathy to experimental diabetes in neonatal mice. Sciatic nerve and tibial nerve was taken as an index to measure the extent of peripheral neuropathy. They reported a decrease in the number of myelinated fibers, its thickness, size and decrease in nerve conduction velocity. This study indicated type 1 diabetes induced early peripheral neuropathy as a preferable model to assay pharmacological therapy in the treatment of diabetic neuropathy.

Kamboj et al. (2009) exposed that synaptosomal membrane fluidity and activity of membrane bound enzymes can be altered by hyperglycemia and related oxidative stress. The results of this study clearly suggested disquiets in membrane fluidity and lipid composition as a major factor in the

development of diabetic encephalopathy.

Conclusion

It is clear that AD and DM share a number of molecular processes that involves in neuronal degeneration; however, the exact molecular mechanism underlying the link between DM and AD still remains subtle. Impairment in energy metabolism, amyloidogenesis, oxidative stress, advanced glycation end products, impairment of insulin signalling as well as inflammation are highlighted in the present review. Although each could mediate its distinctive effect on AD pathology, it is likely that a combination of several of these factors acts in a synergistic way in promoting the development of AD. Evidences also support that DM and prediabetic state are strongly connected to related memory impairments.

Acknowledgments

The authors are thankful to Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences for providing the required facilities and support.

Conflict of interest

The authors declare there are no conflicts of interest.

References

- Ariza L, Pagès G, Garcia-Lareu B, Cobianchi S, Otaegui PJ, Ruberte J, et al. Experimental diabetes in neonatal mice induces early peripheral sensorimotor neuropathy. *Neuroscience* 2014; 274: 250-9.
- Aziz KS, Rishi P, Kavita K, Firoz CK, Kamal MA. Spectrum from obesity to neurodegenerative disorder. *Am J Neuroprot Neuroregen* 2012; 4: 31-9.
- Belluti F, Rampa A, Gobbi S, Bisi A. Small-molecule inhibitors/modulators of amyloid- β peptide aggregation and toxicity for the treatment of Alzheimer's disease: a patent review (2010 - 2012). *Expert Opin Ther Pat* 2013; 23: 581-96.
- Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006; 5: 64-74.
- Bigl M, Apelt J, Eschrich K, Schliebs R. Cortical glucose metabolism is altered in aged transgenic Tg2576 mice that demonstrate Alzheimer plaque pathology. *J Neural Transm (Vienna)* 2003; 110: 77-94.
- Duarte JM, Osés JP, Rodrigues RJ, Cunha RA.

- Modification of purinergic signaling in the hippocampus of streptozotocin-induced diabetic rats. *Neuroscience* 2007; 149: 382-91.
- Dunne MJ, Cosgrove KE, Shepherd RM, Aynsley-Green A, Lindley KJ. Hyperinsulinism in infancy: from basic science to clinical disease. *Physiol Rev* 2004; 84: 239-75.
- Ghanemi A. Alzheimer's disease therapies: Selected advances and future perspectives. *Alexandria J Med* 2015; 51: 1-3.
- Hooijmans CR, Graven C, Dederen PJ, Tanila H, van Groen T, Kiliaan AJ. Amyloid beta deposition is related to decreased glucose transporter-1 levels and hippocampal atrophy in brains of aged APP/PS1 mice. *Brain Res* 2007; 1181: 93-103.
- Hoyer S. Brain glucose and energy metabolism during normal aging. *Aging (Milano)* 1990; 2: 245-58.
- Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes* 2004; 53: 474-81.
- Jolivald CG, Calcutt NA, Masliah E. Similar pattern of peripheral neuropathy in mouse models of type 1 diabetes and Alzheimer's disease. *Neuroscience* 2012; 202: 405-12.
- Kamboj SS, Chopra K, Sandhir R. Hyperglycemia-induced alterations in synaptosomal membrane fluidity and activity of membrane bound enzymes: beneficial effect of N-acetylcysteine supplementation. *Neuroscience* 2009; 162: 349-58.
- Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. *Endocr Rev* 2008; 29: 494-511.
- Li L, Zhang ZF, Holscher C, Gao C, Jiang YH, Liu YZ. (Val⁶) glucagon-like peptide-1 prevents tau hyperphosphorylation, impairment of spatial learning and ultra-structural cellular damage induced by streptozotocin rat brains. *Eur J Pharmacol* 2012; 674: 280-6.
- Liu JP, Feng L, Zhang MH, Ma DY, Wang SY, Gu J, et al. Neuroprotective effect of Liuwei Dihuang decoction on cognition deficits of diabetic encephalopathy in streptozotocin-induced diabetic rat. *J Ethnopharmacol* 2013; 150: 371-81.
- Liu Y, Liu H, Yang J, Liu X, Lu S, Wen T, et al. Increased amyloid β peptide (1-40) level in brain of streptozotocin-induced diabetic rats. *Neuroscience* 2008; 153: 796-802.
- Mosconi L, De Santi S, Li J, Tsui WH, Li Y, Boppana M, et al. Hippocampal hypometabolism predicts cognitive decline from normal aging. *Neurobiol Aging* 2008; 29: 676-92.
- Mount C, Downton C. Alzheimer disease: progress or profit?. *Nat Med* 2006; 12: 780-4.
- Mushtaq G, Khan JA, Kumosani TA, Kamal MA. Alzheimer's disease and type 2 diabetes via chronic inflammatory mechanisms. *Saudi J Biol Sci* 2015; 22: 4-13.
- Peraldi P, Spiegelman BM. Studies of the mechanism of inhibition of insulin signaling by tumor necrosis factor- α . *J Endocrinol* 1997; 155: 219-20.
- Porat Y, Kolusheva S, Jelinek R, Gazit E. The human islet amyloid polypeptide forms transient membrane-active prefibrillar assemblies. *Biochemistry* 2003; 42: 10971-7.
- Rahigude A, Bhutada P, Kaulaskar S, Aswar M, Otari K. Participation of antioxidant and cholinergic system in protective effect of naringenin against type-2 diabetes-induced memory dysfunction in rats. *Neuroscience* 2012; 226: 62-72.
- Reddy VP, Obrenovich ME, Atwood CS, Perry G, Smith MA. Involvement of Maillard reactions in Alzheimer disease. *Neurotox Res* 2002; 4: 191-209.
- Richardson JT. Cognitive function in diabetes mellitus. *Neurosci Biobehav Rev* 1990; 14: 385-8.
- Saido TC. Metabolism of amyloid β peptide and pathogenesis of Alzheimer's disease. *Proc Jpn Acad Ser B Phys Biol Sci* 2013; 89: 321-339.
- Sasaki-Hamada S, Sacai H, Oka JI. Diabetes onset influences hippocampal synaptic plasticity in streptozotocin-treated rats. *Neuroscience* 2012; 227: 293-304.
- Small GW, Ercoli LM, Silverman DH, Huang SC, Komo S, Bookheimer SY, et al. Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proc Natl Acad Sci U S A* 2000; 97: 6037-42.
- Smith MA, Sayre LM, Monnier VM, Perry G. Radical aging in Alzheimer's disease. *Trends Neurosci* 1995; 18: 172-6.
- Soares E, Prediger RD, Nunes S, Castro AA, Viana SD, Lemos C, et al. Spatial memory impairments in a prediabetic rat model. *Neuroscience* 2013; 250: 565-77.
- Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment and dementia. *Diabet Med* 1999; 16: 93-112.
- Strachan MW, Deary IJ, Ewing FM, Frier BM. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care* 1997; 20: 438-45.
- Sun X, Bromley-Brits K, Song W. Regulation of β -site APP-cleaving enzyme 1 gene expression and its role in Alzheimer's disease. *J Neurochem* 2012; 120: 62-70.
- Thota H, Rao AA, Reddi KK, Akula S, Changalasetty SB, Srinubabu G. Alzheimer's disease care and management: role of information technology. *Bioinformation* 2007; 2: 91-5.
- Tun PA, Nathan DM, Perlmutter LC. Cognitive and affective disorders in elderly diabetics. *Clin Geriatr Med* 1990; 6: 731-46.
- Valla J, Gonzalez-Lima F, Reiman EM. FDG autoradiography reveals developmental and pathological effects of mutant amyloid in PDAPP transgenic mice. *Int J Dev Neurosci* 2008; 26: 253-8.
- WHO (2012) media centre: diabetes fact sheet available at <http://www.who.int/mediacentre/factsheets/fs312/en/>.
- Yang Y, Song W. Molecular links between Alzheimer's disease and diabetes mellitus. *Neuroscience* 2013; 250: 140-50.
- Zhao WQ, Townsend M. Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. *Biochim Biophys Acta* 2009; 1792: 482-96.