POSSIBLE LINKS BETWEEN DIABETES MELLITUS AND ALZHEIMER'S DISEASE

TARUN BHATIA, SONALIKA BHATTACCHARJEE

Department of Pharmaceutical Sciences and Technology
Institute of Chemical Technology, India

Received on December 24, 2013; Revised Manuscript accepted on August 5, 2014

Abstract: While both Diabetes Mellitus (DM) and Alzheimer's disease (AD) have been regarded as separate, independent disorders with their own mechanism of pathology and treatment, it is only recently that certain biochemical and pathophysiological links have been found between the two diseases. Both of these are leading causes of morbidity and mortality among the aged patients. Currently available in vitro and in vivo studies point toward a strong association between the presence of type 2 diabetes mellitus (T2DM) and the presence of beta amyloid (Aβ) plaques. It has also been reported that insulin signaling and its impairment positively correlates between the two diseases and that neuronal activity gets affected because of this impairment. Cholinesterases and 'tau' phosphorylation were found to be a common link between the two diseases and may be the underlined etiology. The role of apolipoproteins in diabetes and dementia, along with the role of inflammatory mediators has also been determined. Certain classes of anti-diabetic drugs like peroxisome proliferator-activated receptor gamma (PPARγ) agonists are now being tried-and-tested in clinical trials for their effects in cognitive impairment, among other treatment options. This paper reviews some of the advances made in linking these two diseases with an insight into the caveats involved and the prospects of future studies.

Keywords: Diabetes Mellitus (DM), Alzheimer's disease (AD), beta amyloid (Aβ) plaques, insulin, cholinesterases, 'tau', apolipoproteins, peroxisome proliferator-activated receptor gamma (PPARγ) agonists

Introduction:

1.1. Type 2 Diabetes Mellitus:

Type 2 diabetes mellitus (T2DM) is a condition in which a high blood glucose level results from increased hepatic glucose production, impaired insulin production by pancreatic β-cells, impaired insulin release or 'insulin resistance' (inadequate response to insulin by target cells).[1]

Neuropathy is among the most frequent complication of diabetes mellitus, with diabetic neuropathy being the most common form of neuropathy in the western world. [2]

Central nervous systemcomplications can include stroke and possibly cognitive impairment. [3] Persistent blood glucose elevation contributes to atherosclerosis that impairs blood flowto the brain. Such damage might be associated with vascular dementia.[4]

1.2. Alzheimer's Disease:

Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by numerous neuritic plaques and neurofibrillary tangles. Several studies have attempted to link serum insulin levels with the pathogenesis of Alzheimer disease. Early studies reported decreased serum glucose levels, and higher insulin levels, after oral glucose tolerance tests in Alzheimer patients compared to aged-matched non-Alzheimer patients. [5]

2. Possible links:

2.1. Insulin processing and insulin receptors:

Disturbances in insulin signaling appear to be the main common impairment that affects cell growth and differentiation, energy metabolism, and glucose utilization. Insulin not only regulates blood sugar levels but also acts as a growth factor on all cells including neurons in the CNS. Impairment of insulin signaling therefore not only affects blood glucose levels but also causes numerous degenerative processes.[6]

Insulin regulates cholesterol biosynthesis. Cholesterol levels also play a crucial role in AD and high levels are considered a risk factor. Hypercholesterolemia is also a known risk factor of T2DM. [7]High levels of cholesterol affect β-amyloid (Aβ) synthesis and Aβ deposition. [6]

Neurons rely on glucose for energy, but only a small percentage of the glucose supply to neurons is delivered via insulin-dependent transport mechanisms. The rest of the glucose is obtained through non-insulin-dependent mechanisms. Further, insulin receptors are found in high density in some regions of brain, but in only low density in other regions of the brain. This uneven distribution is somewhat correlated with neuronal activity and, hence, with the energy demands (glucose requirement) of neurons. [5]

2.2. Role of Acetylcholine:

Recent research suggests a possible link between blood sugar, insulin resistance and inadequate production of acetylcholine (ACh). [1]

Quantitative studies that used Nissl-stained tissue to mark cholinergic neurons have revealed up to a 90% reduction in basocortical cholinergic neurons in AD. [8]

Synthesis of ACh involves the enzyme acetylcholine transferase (ChAT).[1]

Interestingly, insulin signaling- related proteins coexist with ChAT in terminal buttons located in hippocampal pyramidal cells and this finding raises the possibility that the insulin and the cholinergic systems of the hippocampus

interact in the mediation of cognitive function.[9]

ChAT expression increases with insulin stimulation. Therefore, low insulin levels and insulin resistance can contribute to a decrease in ACh levels, which represents a possible biochemical link between diabetes mellitus and AD. [1]

2.3. Role of Apolipoprotein E and dyslipidemia:

Dyslipidemia is a major cardiovascular risk factor in T2DM. Risk relates to raised triglycerides (TG) and decreased high density lipoproteins (HDL) as well as raised low density lipoproteins (LDL). [10]

Several genes regulating cholesterol homeostasis have been reported to be associated with AD, including ApoE. ApoE plays an important role in lipid transport throughout the body. [11]In the brain, it is primarily synthesized and secreted within HDL particles by astrocytes, and mediates the efficient transport and recycling of cholesterol within the CNS. [11, 12, 13, 14]

Three different ApoEalleles (ε2, ε3, and ε4) give six phenotypes. [10]Studies have shown ε2 as positive and ε4 as negative factor for the progression of diabetic nephropathy.[10, 15, 16]

Individuals with both diabetes and an ApoE ε4 allele are more likely to develop dementia than either those with diabetes alone or non-diabetic individuals who carry the ApoE ε4 allele.[17]

The mechanism by which ApoE ε4 modifies the risk remains unknown, but has been postulated to play a role in Aβ clearance and deposition.[11]

While isomeric differences in the CNS have yet to be entirely elucidated, ApoE ε4exerts less protection against oxidative stress and contributes to cholinergic dysfunction in AD.[1, 18]

The lipidation of ApoE is carried out primarily by the ATP-binding cassette A1 (ABCA1). ABCA1 is a lipid transporter that mediates the loading of ApoE with phospholipids and cholesterol. ApoE acts as a structural scaffold for the formation of HDL particles. ABCA1 acts to regulate ApoE function in the CNS.[11, 12, 13]
Poor lipidation of ApoE, which can result from transporter ABCA1 deficiency, confers a heavier amyloid burden, while overexpression of ABCA1 results in significant reduction of Aβ plaque formation.[1, 19]

Genetic studies have shown that ABCA1 might be a candidate gene of T2DM. Several genetic variants were associated with diabetes and prediabetic intermediate traits. [20]
One possibility for the modification of the association between diabetes and cognition by the presence of one or more ApoE ε4 alleles relates to increased Aβ deposition in individuals with diabetes. Insulin-degrading enzyme (IDE) degrades Aβ. Thus, the increased insulin levels

associated with diabetes may result in less IDE available for the regulation of Aβ. [17, 21]

It has been suggested that increased Aβ deposition may result both from the decreased expression of IDE in individuals with an ApoE ε4 allele and the decreased IDE levels caused by increased use of IDE for insulin regulation in individuals with diabetes, thus leading to higher levels of Alzheimer's disease pathology in participants with both diabetes and increased expression of ApoE. [17, 22]

However, diabetes has been associated with other brain changes, including white matter lesions [17, 23]and the ApoE ε4 allele has been associated with increased deposition of both Aβ plaques and neurofibrillary tangles. [17, 24, 25] Therefore, the decreased levels of cognitive function observed for the diabetic ApoE ε4 carriers may be due to increased levels of vascular pathology in diabetic individuals and Aβ plaque deposition in ApoE ε4 carriers.[17]

2.4. Role of "Tau":

The Aβ interacts with signaling pathways that regulate the phosphorylation of the tau protein, leading to hyperphoshorylation of tau and aggregation of neurofibrillary tangles in neurons. [1, 26]

Tau phosphorylation in both AD and T2DM involves activation of glycogen synthase kinase-3 (GSK-3), which phosphorylates glycogen synthase in the rate-limiting step of glycogen biosynthesis. [1, 27, 28, 29]GSK-3 is a crucial step in formation of neurofibrillary tangles, and therefore, GSK-3 inhibition could be a common target treatment of both AD andT2DM. [1, 30, 31]

2.5. Inflammation:

Insulin resistance, a key aspect of T2DM, is associated with inflammation, specifically with elevated levels of the inflammatory mediators' interleukin-6 (IL-6) and C-reactive protein. Likewise, inflammatory products accumulate at different rates in Alzheimer's patients compared with healthy control subjects, IL-6 is present in senile plaques of AD patients, and elevated immunoreactivity to IL-6 is found in lumbar and ventricular CSF in patients with AD. At least two studies link C-reactive protein with an increased risk of AD.[1]

A key hallmark of AD brain is the presence of chronic neuroinflammation. It was posited that activation of microglia and the concurrent production of inflammatory molecules may deteriorate and accelerate the progression of AD and therefore the neuronal loss.[32, 33]

2.6. Mitochondria and Oxidative Stress:

There is increased oxidative stress in T2DM, with reduced antioxidant capacity,[1, 34] which has been suggested can lead to neuronal injury with mitochondria as specific targets.[1, 35]

Oxidative changes in nucleic acids, lipids and mitochondrial proteins amplify production of reactive oxygen species and trigger cells to generate Aβ, tau phosphorylation and formation of neurofibrillary tangles. [1, 36]

2.7. Role of Advanced glycation end-products (AGE's):

AGE formation starts with the reaction of the amino groups of proteins, particularly the side chains of lysine, arginine and histidine, with reducing sugars. [37]

In diabetes, accelerated AGE formation is caused primarily by a higher level of plasma glucose. However, accumulation of extracellular AGEs in AD is more likely caused by accelerated oxidation of glycated proteins.[37, 38]

In any event, the commonality of AGE modifications and free radical damage in T2DM and AD suggests that common therapeutic rationales might be considered.[39]

2.8. Role of Iron:

Iron is a strong pro-oxidant which catalyzes several cellular reactions that yield reactive oxygen species. This property, while essential for its metabolic functions, makes iron potentially hazardous.[40]

In addition to the induction of oxidative stress, iron may also impede insulin extraction in the liver, impair pancreatic insulin secretion, and interfere with insulin action and glucose uptake in adipocytes. A reduction in iron overload has been shown to reverse or improve glycemic control in T2DM. [40, 41]

An important pathological finding of AD is the iron accumulation that occurs in the same brain regions characterized by Aβ peptide deposition. [40, 42]

3. Drugs linked to Diabetes and Alzheimer's Disease:

3.1. Peroxisome proliferator-activated receptor-gamma(PPARγ) agonists:

PPARγis a key neuromodulator found in increased amounts in the brain of AD patients. PPARγplays a role in multiple processes thought to be involved in the pathogenesis of both diabetes and AD, including inflammatory and metabolic processes, cell growth and differentiation.[1]

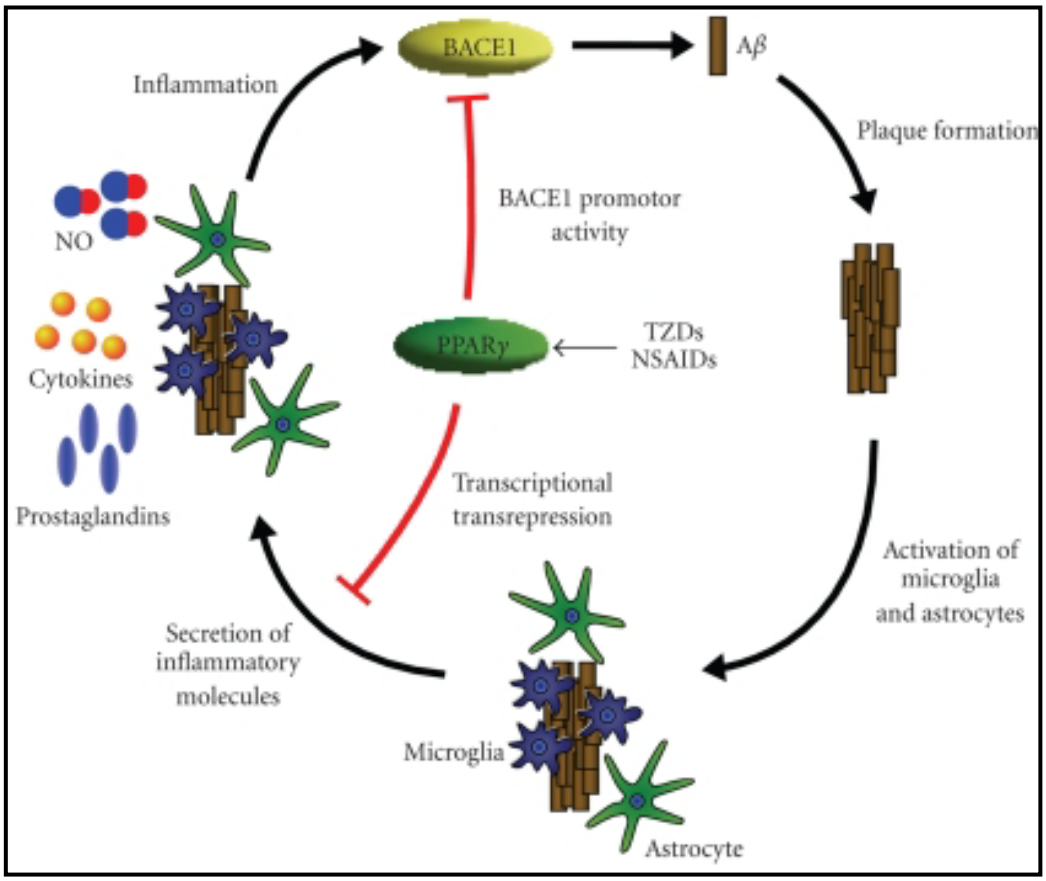
Synthetic thiazolidinediones (TZDs)including pioglitazone and rosiglitazone which are commonly prescribed for the treatment of T2DM, are selective PPARγ ligands.[32]
Pharmacological treatment with TZDs may offer some therapeutic relief of AD by lowering peripheral insulin and enhancing insulin sensitivity, reducingAβ accumulation and inflammatory reactants and exhibit neuroprotective effects. [43, 44]

3.1.1. Effect of PPARγ on Aβ metabolism:

As shown in figure 1, formation of amyloid plaques induces the activation of microglia as well as astrocytes which respond with the secretion of proinflammatorymolecules like NO, cytokines and prostaglandins. [32]
When neuroblastoma cells (stably transfected with human amyloid precursor protein, APP) were stimulated with inflammatory cytokines,

they activated the APP processing enzyme BACE1, resulting in an increase in Aβ secretion. There is a PPARγ response element in the promoter region of the BACE1 gene, and binding of PPARγ to this response element suppresses BACE1 expression and inhibits Aβ production. [11]

Figure 1: Effects of PPARγon Aβ metabolism.[32]



3.1.2. Energy metabolism:

There is ample documentation that glucose utilization is impaired in brain regions involved in memory and cognition in AD patients. PPARγ plays critical roles in energy metabolism due to its direct effects on mitochondrial function and ultimately ATP production. [11]

3.1.3. Rosiglitazone:

Recently, rosiglitazone has been shown to increase brain IDE levels in an animal model of AD. [45]

More than 500 patients with mild to moderate AD were treated for 6 months with rosiglitazone, resulting in a statistically significant improvement in cognition in those patients that did not possess an ApoE ε4 allele.[46]

Patients with ApoE ε4 did not respond to the drug and showed no improvement in standard cognitive tests. As an explanation it was suggested that rosiglitazone acts on mitochondria in the brain, increasing their metabolic efficiency and number.[47]

3.2. Metformin:

Metformin (*N*,*N*dimethylimidodicarbonimidicdiamide) is an orally active biguanide that lowers blood glucose levels by suppression of hepatic gluconeogenesis. It also increases insulin sensitivity and peripheral uptake, increases fatty acid oxidation, and decreases gastrointestinal absorption of glucose. [1]

A recent study reported that metformin reduced phosphorylation of tau protein incortical neurons of mice. [48, 49]

Metformin has been shown as a neuroprotectant against apoptotic cell death in primary cortical neurons. [50, 51] It has also been reported to protect the brain against the oxidative imbalance promoted by type 2 diabetes. [50, 52]Increased neuronal viability has been reported by metformin treatment in an in vitro model of ischemia. [50, 53]

Findings that metformin at doses that sensitized neuronal insulin resistance also significantly improved AD-like changes, further potentiates the hypothesis of AD being associated with impaired neuronal insulin actions and justifies the term "type 3 diabetes" given for AD. [50]

3.3. Role of AGE inhibitors:

Inhibitors such as aminoguanidine are currently being assessed in clinical trials for the treatment of diabetic complications. In contrast, their potential for the treatment of AD is only just being recognized. The AGE-inhibitor Tenilsetam has been shown to improve cognitive abilities and memory constantly over a time span of three months in two phase II trials. AGE inhibitors might be able to stop formation of AGE-Aβ deposits or modify their structure thus interrupting the AGE-induced signal transduction pathway at the earliest possible step.[37]

3.4. Role of cholinesterase inhibitors:

These drugs slow the breakdown of synaptic ACh, prolong its ability to stimulate post-synaptic receptors and amplify the natural pattern of ACh release in the brain. [54]

Galantamine is a tertiary alkaloid compound and a reversible selective inhibitor of AChE.[55]

Donepezil is highly selective for acetylcholinesterase, has few side-effects, and in the literature, is said to have beneficial effects on cognition and daily living in AD patients. [56]

Donepezil only inhibits acetylcholinesterase. Galantamine inhibits acetylcholinesterase, modulates presynaptic nicotinic receptors so that they release more acetylcholine, and modulates postsynaptic nicotinic receptors so that the neuron is activated. Despite this, it does not seem to be more effective than donepezil. This could be because donepezil may just be a more powerful drug, despite the relative simplicity of its action.[56]

3.5. Intranasal Insulin:

Peripheral administration of insulin is not viable owing to the risk of hypoglycemia and/or exacerbation of peripheral insulin resistance. In contrast, intranasal administration of insulin provides rapid delivery of insulin to the central nervous system. [57]

In rodent models, intranasally administered insulin binds to receptors in the hippocampus and the frontal cortex within 60 minutes. [58]

In human studies,intranasal insulin increases insulin levels in cerebrospinal fluid (CSF) within a similar time frame and acutely enhances memory. A 3-week trial of daily administration of intranasal insulin improved delayed story recall and caregiver-rated functional status in a small sample of adults with AD. [59]

4. Conclusion & Further Prospects:

The results of epidemiological and basic science investigation have suggested possible associations between T2DM and AD. There are clinical trials testing 'antidiabetic' drugs in AD patients.[1]Based on this, connections between other disorders can also be elucidated.

Table 1 shows the conclusions that can be made from this review:

REFERENCE	MECHANISM	SYNOPSIS
Munch et al[37]	AGE	In diabetes, accelerated AGE formation is caused primarily by a higher level of plasma glucose.
Jansonet al[60]	Amyloid deposition in islet and brain cells	More islet amyloid in AD patients than control subjects. No greater brain amyloid in diabetic patients compared with control subjects. In T2DM patients with brain amyloid, the extent of amyloid increased with longer duration of diabetes
Rivera et al[61]	Low insulin and a decrease in ChAT	Low insulin levels and low insulin sensitivity can contribute to a decrease in acetylcholine synthesis, leading to AD.
Miklossyet al[62]	Amyloid and hyperphosporylated tau	Islet amyloid polypeptide and hyperphosphorylated tau were found in islet cells of the pancreas in T2DM patients (on autopsy).

Table 1: Common pathways between DM and AD[1]

References:

1. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB.,'Diabetes mellitus and Alzheimer's disease: shared pathology and treatment?',*British Journal of Clinical Pharmacology*,71 (3) (2011)365–376.

2. A. Dejgaard, 'Pathophysiology and Treatment of Diabetic Neuropathy', *Diabetes Medicine,* 15 (2) (1998) 97-112.

3. Lin EH, Rutter CM, Katon W, Heckbert SR, Ciechanowski P, Oliver MM, Ludman EJ, Young BA,Williams LH, McCulloch DK, Von KorffM.,'Depression and advanced complications of diabetes: a prospective cohort study',*Diabetes Care*, 33 (2) (2010) 264–269.

4. Mooradian AD.,'Central nervous system complications of diabetes mellitus – a perspective from the blood-brain barrier',*Brain Res Brain Res Rev*, 23 (3) (1997) 210–218.

5. R.J. Schulingkamp, T.C. Pagano, D. Hung, R.B. Raffa, 'Insulin receptors and insulin action in the brain: review and clinical implications', *Neuroscience and Behavorial Reviews,* 24(8) (2000) 855-872.

6. Lin Li, Christian Hölscher, 'Common pathological processes in Alzheimer disease and type 2 diabetes: A review', *Brain Research Reviews*, 56(2) (2007) 384 - 402.

7. Kompoti, M., Mariolis, A., Alevizos, A., Kyrazis, I., Protopsaltis, I., Dimou, E., Lentzas, I., Levisianou, D., Gova, A., Melidonis, A.,'Elevated serum triglycerides is the strongest single indicator for the presence of metabolic syndrome in patients with type 2 diabetes',*Cardiovasc. Diabetol.*, 5, (21) (2006).

8. Gilmor ML, Erickson JD, Varoqui H, et al.,'Preservation of nucleus basalis neurons containing choline acetyltransferase and the vesicular acetylcholine transporter in the elderly with mild cognitive impairment and early Alzheimer's disease',*J Comp Neurol.,*411 (4) (1999) 693–704.

9. Brito GNO.,'Exercise and cognitive function: a hypothesis for the association of type II diabetes mellitus and Alzheimer's disease from an evolutionary perspective',*Diabetology& Metabolic Syndrome*,1 (1) (2009) 1–7.

10. Dixit M, Bhattacharya S, Mittal B.,'Association of CETP TaqI and APOE polymorphisms with type II diabetes mellitus in North Indians: a case control study', *BMC Endocrine Disorders,* 5 (7) (2005).

11. Landreth G, Jiang Q, Mandrekar S, Heneka M.,'PPARγ agonists as therapeutics for the treatment of Alzheimer's disease',*Neurotherapeutics*, 5 (3) (2008) 481–489.

12. Wahrle SE, Jiang H, Parsadanian M, et al.,'ABCA1 is required for normal central nervous system ApoE levels and for lipidation of astrocyte-secreted apoE',*J Biol Chem.,* 279 (39) (2004) 40987–40993.

13. Hirsch-Reinshagen V, Zhou S, Burgess BL, et al.,'Deficiency of ABCA1 impairs apolipoprotein E metabolism in brain',*J Biol Chem.*, 279 (39) (2004) 41197–41207.

14. Xu Q, Bernardo A, Walker D, et al.,'Profile and regulation of apolipoprotein E (ApoE) expression in the CNS in mice with targeting of green fluorescent protein gene to the ApoE locus',*J Neurosci.*, 26 (19) (2006) 4985–4994.

15. Horita K, Eto M, Makino I,'Apolipoprotein E2, renal failure and lipid abnormalities in non-insulin-dependent diabetes mellitus',*Atherosclerosis*,107 (2) (1994) 203-211.

16. Eto M, Saito M, Okada M, Kume Y, Kawasaki F, Matsuda M, Yoneda M, Matsuki M, Takigami S, Kaku K,'Apolipoprotein E genetic polymorphism,remnant lipoproteins, and nephropathy in type2 diabetic patients',*Am J Kidney Dis.*,40 (2) (2002) 243-251.

17. G. A. Dore & M. F. Elias & M. A. Robbins & P. K. Elias, Z. Nagy, 'Presence of the APOE ε4 allele modifies the relationshipbetween type 2 diabetes and cognitive performance:the Maine–Syracuse Study', *Diabetologia*, 52 (12) (2009) 2551–2560.

18. Martins IJ, Berger T, Sharman MJ, Verdile G, Fuller SJ, Martins RN.,'Cholesterol metabolism and transport in the pathogenesis of Alzheimer's disease',*J Neurochem*, 111 (6) (2009) 1275–1308.

19. Hirsch-ReinshagenV,Maia LF, Burgess BL, Blain JF, Naus KE, McIsaac SA, Parkinson PF, Chan JY, Tansley GH, Hayden MR, Poirier J, Van NostrandW,Wellington CL., 'The absence of ABCA1 decreases soluble ApoE levels but does not diminish amyloid deposition in two murine models of Alzheimer disease', *J BiolChem*,280 (52) (2005) 43243–43256.

20. Jie WANG, Yu-qian BAO, Cheng HU, Rong ZHANG, Cong-rong WANG, Jun-xi LU, Wei-ping JIA, Kun-san XIANG, 'Effects of ABCA1 on rosiglitazone monotherapy in newly diagnosed type 2 diabetes patients', *ActaPharmacol Sin.*, 29 (2) (2008) 252–258.

21. Messier C., 'Diabetes, Alzheimer's disease and apolipoprotein genotype',*ExpGerontol.*, 38 (9) (2003) 941–946.

22. Peila R, Rodriguez BL, Launer LJ., 'Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study',*Diabetes*, 51 (4) (2002) 1256–1262.

23. van Harten B, Oosterman JM, van Loon BP, Scheltens P, Weinstein HC, 'Brain lesions on MRI in elderly patients with Type 2 diabetes mellitus',*EurNeurol*, 57 (2) (2007)70–74.

24. Alafuzoff I, Aho L, Helisalmi S, Mannermaa A, Soininen H,'β-Amyloid deposition in brains of subjects with diabetes',*NeuropatholApplNeurobiol*, 35 (1) (2009) 60–68.

25. Nagy Z, EsiriMM, JobstKA, Johnston C et al., 'Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease',*Neuroscience*, 69 (3) (1995) 757–761.

26. Drewes G.,'MARKing tau for tangles and toxicity',*Trends BiochemSci*, 29 (10) (2004) 548–555.

27. Doble BW,Woodgett JR.,'Role of glycogen synthase kinase-3 in cell fate and epithelial-mesenchymal transitions',*Cells Tissues Organs*, 185 (1-3) (2007) 73–84.

28. Phiel CJ, Wilson CA, Lee VM, Klein PS.,'GSK-3alpha regulates production of Alzheimer's disease amyloid-beta peptides',*Nature*, 423(6938) (2003) 435–439.

29. Sivaprakasam P, Xie A, Doerksen RJ.,'Probing the physicochemical and structural requirements for glycogen synthase kinase-3alpha inhibition: 2D-QSAR for 3-anilino-4-phenylmaleimides',*Bioorg Med Chem*, 14 (24) (2006) 8210–8218.

30. Bhat RV, Budd Haeberlein SL, Avila J.,'Glycogen synthase kinase 3: a drug target for CNS therapies',*J Neurochem*, 89(6) (2004) 1313–1317.

31. Cole AR, Astell A, Green C, Sutherland C.,'Molecular connexions between dementia and diabetes',*NeurosciBiobehav Rev*, 31 (7) (2007) 1046–1063.

32. Kummer MP, Heneka MT.,'PPARs in Alzheimer's disease',*PPAR Res*, (2008) 1-8.

33. Akiyama H, Barger S, Barnum S, et al.,'Inflammation and Alzheimer's disease',*Neurobiology of Aging*, 21(3) (2000) 383–421.

34. Evans JL, GoldfineID,Maddux BA, Grodsky GM.,'Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes',*Endocr Rev*, 23 (5) (2002) 599–622.

35. Schmeichel AM, Schmelzer JD, Low PA.,'Oxidative injury andapoptosis of dorsal root ganglion neurons in chronicexperimental diabetic neuropathy',*Diabetes*, 52 (1) (2003)165–71.

36. Swerdlow RH, Khan SM. A, 'Mitochondrial cascade hypothesis for sporadic Alzheimer's disease', *Med Hypotheses*, 63 (1) (2004) 8–20.

37. Münch G, Schinzel R, Loske C, Wong A, Durany N, et al.,'Alzheimer's disease–synergistic effects of glucose deficit, oxidative stress and advanced glycationendproducts',*J Neural Transm*, 105(4–5) (1998) 439–461.

38. Smith MA, Harris PLR, Sayre LM, Perry G,'Iron accumulation in Alzheimerdisease is a source of redox-generated free radicals', *ProcNatlAcadSci USA*, 94 (18) (1997) 9866–9868.

39. Smith MA, Sayre LM, Perry G., 'Diabetes mellitus and Alzheimer's disease: glycation as a biochemical link', *Diabetologia*, 39 (2) (1996) 247.

40. Luca Mascitelli, Francesca Pezzetta, Mark R. Goldstein, 'Iron, type 2 diabetes mellitus, and Alzheimer's disease', *Cell Mol Life Sci.*, 66(17) (2009) 2943.

41. Swaminathan S, Fonseca VA, AlamMG, Shah SV, 'The roleof iron in diabetes and its complications',*Diabetes Care*, 30 (7) (2007) 1926–1933.

42. Zecca L, Youdim MB, Riederer P, Connor JR, Crichton RR, 'Iron, brain ageing and neurodegenerative disorders',*Nat Rev Neurosci*, 5 (11) (2004) 863–873.

43. Landreth G.,'Therapeutic use of agonists of the nuclear receptor PPARγ inAlzheimer's disease',*Curr Alzheimer Res*, 4 (2) (2007) 159–164.

44. Hanyu H, Sato T, Kiuchi A, Sakurai H, Iwamoto T., Pioglitazone improved cognition in a pilot study on patients with Alzheimer's diseaseand mild cognitive impairment with diabetes mellitus, *J Am Geriatr Soc.*, 57(1) (2009) 177-179.

45. Pedersen WA, McMillan PJ, Kulstad JJ, Leverenz JB, Craft S, Haynatzki GR., 'Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice', *Exp Neurol.*, 199(2) (2006) 265-273.

46. Watson GS et al., 'Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study', *Am J Geriatr Psychiatry.*, 13(11) (2005) 950-958.

47. Craft S et al, 'Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease',*Pharmacogenomics J.*, 6(4) (2006) 246-254.

48. Patrick Imfeld, Michael Bodmer, Susan S. Jick,Christoph R. Meier, 'Metformin, Other Antidiabetic Drugs, and Risk of Alzheimer'sDisease: A Population-Based Case–Control Study', *Journal of American Geriatrics Society*, 60 (5) (2012)916-921

49. Kickstein E, Krauss S, Thornhill P et al.,'Biguanide metformin acts on tau phosphorylation via mTOR/protein phosphatase 2A (PP2A) signaling',*ProcNatlAcadSci U S A*, 107 (50) (2010) 21830–21835.

50. Amit Gupta, Bharti Bisht, ChinmoySankarDey, 'Peripheral insulin-sensitizer drug metformin ameliorates neuronalinsulin resistance and Alzheimer's-like changes', *Neuropharmacology*, 60 (6) (2011) 910-920.

51. El-Mir, M.Y., Detaille, D., G, R.V., Delgado-Esteban, M., Guigas, B., Attia, S.,Fontaine, E., Almeida, A., Leverve, X., 'Neuroprotective role of antidiabeticdrug metformin against apoptotic cell death in primary cortical neurons',*J. Mol. Neurosci.*, 34 (1) (2008) 77-87.

52. Correia, S., Carvalho, C., Santos, M.S., Proenca, T., Nunes, E., Duarte, A.I., Monteiro, P.,Seica, R., Oliveira, C.R., Moreira, P.I., 'Metformin protects the brain againstthe

oxidative imbalance promoted by type 2 diabetes',*Med. Chem.,* 4 (4) (2008) 358-364.

53. Mielke, J.G., Taghibiglou, C., Wang, Y.T., 'Endogenous insulin signaling protectscultured neurons from oxygen-glucose deprivation-induced cell death', *Neuroscience*, 143 (1) (2006)165-173.

54. Rosengarten B, Paulsen S, Molnar S, Kaschel R, Gallhofer B, Kaps M.,'Acetylcholine esterase inhibitor donepezil improves dynamic cerebrovascular regulation in Alzheimer patients',*J Neurol.*, 253 (1) (2006) 58–64.

55. Jones RW, Soininen H, Hager K, Aarsland D, Passmore P, Murthy A, Zhang R, Bahra R., 'A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease', *Int J Geriatr Psychiatry*, 19(1) (2004) 58-67.

56. Robin D. J. Harry and Konstantine K. Zakzanis, 'A comparison of donepezil and galantamine in thetreatment of cognitive symptoms of Alzheimer's disease: a meta-analysis', *Hum PsychopharmacolClinExp*, 20 (3) (2005) 183-187.

57. Suzanne Craft, Laura D. Baker, Thomas J. Montine, Satoshi Minoshima, G. Stennis Watson, Amy Claxton, Matthew Arbuckle, Maureen Callaghan, Elaine Tsai, Stephen R. Plymate, Pattie S. Green, James Leverenz, Donna Cross, Brooke Gerton, 'Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment', *Arch Neurol.,* 69(1) (2012) 29.

58. Francis GJ, Martinez JA, Liu WQ, et al., 'Intranasal insulin prevents cognitive decline, cerebral atrophy and white matter changes in murine type I diabetic encephalopathy', *Brain*, 131 (pt 12) (2008) 3311-3334

59. Reger MA, Watson GS, Green PS, et al., 'Intranasal insulin improves cognition and modulates beta amyloid in early AD', *Neurology*, 70(6) (2008) 440-448.

60. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC, 'Increased risk of type 2 diabetes in Alzheimerdisease',*Diabetes*, 53 (2) (2004) 474–81.

61. Rivera EJ, Goldin A, Fulmer N, Tavares R,Wands JR,de la Monte SM.,'Insulin and insulin-like growth factor expression and function deteriorate with progression ofAlzheimer's disease: link to brain reductions inacetylcholine',*J Alzheimers Dis*, 8 (3) (2005) 247–268.

62. Miklossy J, Qing H, Radenovic A, Kis A, Vileno B, Laszlo F,Miller L,MartinsRN,Waeber G, Mooser V, Bosman F,Khalili K, DarbinianN,McGeer PL,'Beta amyloid andhyperphosphorylated tau deposits in the pancreas in type2 diabetes',*Neurobiol Aging*, 31 (9) (2010) 1503–15.