ALZHEIMER'S DISEASE
AND TREATMENT

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Insulin Resistance in Alzheimer's Disease

Esra ATES BULUT MD[1]; Pinar SOYSAL MD[2]; Ahmet Turan ISIK MD[1]*

[1]*Department of Geriatric Medicine, DokuzEylul University, Turkey*

[2]*Geriatric Center, Kayseri Education and Research Hospital, Turkey*

Corresponding Author: Ahmet Turan ISIK,

Unit For Aging Brain and Dementia, Department of Geriatric Medicine, DokuzEylul University, Faculty of Medicine, Izmir, Turkey

Tel: +90 232 412 43 41, Email: atisik@yahoo.com

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Introduction

As the world population has aged, dementia has become a common diagnosis in aging populations and the numbers will increase in the forthcoming years. Globally, an estimated 47 million people are affected by dementia [1]. Alzheimer's Disease (AD) is the most common cause of dementia and one of the leading causes of morbidity and mortality in older adults.

While the pathogenesis of AD remains unclear, according to the evidence of epidemiologic studies, there are mainly three hypotheses that may explain the pathogenesis of Alzheimer's Disease [2]:

1. Extracellular amyloid plaques accumulation due to increased production of amyloid beta 42 (Aβ42), genetically high-risk individuals and reduced metabolism and removal among older individuals,

2. Vascular disease and also vascular risk factors such as diabetes, hypertension, hyperlipidemia, hyperhomocysteinemia are determinant of vascular dementia but also of increased amyloid deposition and neurodegeneration,

3. Dementia is due primarily to aging and neurodegeneration, independent of amyloid and vascular disease.

There is a long presymptomatic period between the onset of biochemical changes in the brain and the development of clinical symptoms of AD, suggesting that long-term epidemiologic studies are needed to show the gene-lifestyle environmental association of amyloid vascular disease and neurodegeneration. The mean age at diagnosis of dementia was 82 years, and clinical memory complaints in these patients began 16 years before diagnosis in the Rotterdam Study [3]. Therefore, it is important for clinicians to recognize early signs and symptoms of dementia and to figure out potentially modifiable risk factors and early disease markers.

AD is characterized by a series neuropathologic changes, including neuronal loss, formation of amyloid plaques, appearance of neurofibrillary tangles, and synaptic loss. Amyloid plaques and neurofibrillary tangles result from an aberration in deposition of the amyloid beta 42 peptide and the hyperphosphorylated tau protein, respectively, and these depositions lead to neuronal loss and neurotoxicity in the brain affected by AD. However, these changes in the brain are not found throughout the brain and preferentially affect specific brain areas in a manner that is essentially consistent from patient to patient [4]. Data obtained by electron microscopy, immunocytochemical and biochemical analysis on synaptic marker proteins in AD biopsies and autopsies indicate that synaptic loss in the hippocampus and neocortex is an early event and the major structural correlate of cognitive dysfunction. From all cortical areas analyzed, the hippocampus appears to be the most severely affected by the loss of synaptic proteins, while the occipital cortex

is affected least [5]. Furthermore, synaptic function is impaired in living neurons, as demonstrated by decrements in transcripts related to synaptic vesicle trafficking [6]. On the other hand, sporadic AD is associated with peripheral insulin abnormalities, which might influence cerebral glucose metabolism in the brain [7]. It was demonstrated the hypometabolism of hippocampal glucose in patients with AD compared to control individuals [8], and it was hypothesised that reduced glucose utilisation and energy metabolism may be two of the main causes of the impaired cognition observed in AD [9]. In addition, insulin dysregulation is one of the potential key factors in the pathogenesis of AD, which is associated with both age-related cognitive impairment and increased risk of AD. Conditions related to insulin dysregulation, such as obesity, diabetes mellitus, cardiovascular disease, and hypertension have increased in prevalence, raising concern about their potential deleterious effects on brain function [10]. Furthermore, epidemiological evidence has suggested that diabetes mellitus significantly increases the risk for AD, independent from vascular risk factors [11]. Higher fasting insulin levels and reduced cerebrospinal fluid-to-plasma insulin ratios, suggestive of Insulin Resistance (IR), have been observed in patients with AD apolipoprotein E epsilon 4 allele (ApoE-ε4) [12]. AD or vascular dementia could be a part of metabolic syndrome or even type-3 diabetes with some exaggerations [13,14]. However, the role of insulin and insulin resistance on cognition in non-diabetic patients is obscure, especially in older adults.

Insulin and cognition

Recent data, has pointed out the involvement of insulin in cognitive processes, and it is generally accepted that both insulin and Insulin-like Growth Factor I (IGF-I) are important modulators of brain function and also both have the modulatory effects on cognitive processes [15].

Insulin is transported into the Central Nervous System (CNS) across the Blood Brain Barrier (BBB) by a saturable receptor-mediated process. This transporter is not static but has been shown to alter the transport rate of insulin into the CNS under a variety of circumstances. For example, insulin transport is likely slower in Alzheimer's Disease than in normal aging. In adults, the transporter is partially saturated at euglycemic levels, suggesting that its role is not to signal hypoglycemic events to the brain [16]. Those insulin receptors, located in astrocytes and neuronal synapses, are highly concentrated in the hippocampus, entorhinal cortex, and frontal cortex is consistent with evidence that insulin influences memory [17]. Little amount or no insulin is produced in the CNS, so that CNS insulin is largely derived from peripheral insulin. As such, CNS insulin is dependent on the peripheral insulin.

It is possible that insulin plays a key role in learning and memory shown insulin receptors localization in the hippocampus, insulin receptors changes in the hippocampus secondary to spatial learning, and improvements in memory secondary to insulin administration in both animal models and human studies. Although it is not definite how insulin makes its action on cognition, several pathways are likely influenced [18].

In vitro experiments demonstrated that tau phosphorylation is regulated by insulin and IGF-1 [19,20]. In an experimental study, deterioration of the cerebral insulin-IGF action by Intracerebroventricular (ICV) Streptozotocin (STZ), a diabetogenic drug, leads to a deficit in energy metabolism and progressive cognitive impairment in rats [21]. Accordingly, Isik et al reported that Curcumin can be effective in ICV STZ-induced neurodegeneration by increasing IGF-1 levels, which may indicate neurogenesis [22]. It was also demonstrated that both the ICV injection of insulin in animals and the administration of insulin to healthy volunteers improves memory performance indicating a positive effect on cognition [23,24]. This improvement has also been observed in humans with intranasal insulin administration [25], after which insulin-like peptides follow perivascular channels and reach the brain within minutes. Insulin may facilitate memory through direct receptor-mediated effects, because of the special localization of these receptors as mentioned above [26]. Likely memory-related mechanisms include modulation of synaptic structure and function, long-term potentiation, and CNS levels of neurotransmitters such as acetylcholine, dopamine and norepinephrine that are known to influence cognitive function [17, 26]. Specific regional effects of insulin on glucose metabolism via insulin-sensitive glucose transporters 4 and 8 may also affect brain function [27].

Insulin receptor density is up-regulated in Alzheimer's Disease [28] indicating an impairment of the insulin signal transduction cascade similar to that seen in non-insulin-dependent diabetes mellitus. So, sporadic AD was speculated as the brain equivalent of non-insulin-dependent diabetes mellitus [13]. Therefore, it is not surprised that insulin/IGF-I function appears dysregulated in widely different neurodegenerative diseases such as AD [29].

In the Rotterdam study, it was pointed out that increased insulin levels may be associated with a cognitive decline in a prospective study but just in women patients. The results showed no significance when they made the analysis for whole group [30]. Similarly, Isik et al. did not find any statistical significant difference among 5 different cognitive status groups such as AD, vascular dementia, mixed dementia, mild cognitive impairment, and normal cognition group in a cross sectional study [31].

It is still not completely understood how insulin resistance affects the cognitive profile. Many of the important functions of insulin in the brain are disrupted in insulin-resistant conditions. Interestingly, prolonged peripheral hyperinsulinemia associated with IR reduces insulin transport across the BBB, subsequently lowering insulin levels and activity in the brain; this effect may be relevant to findings of reduced cerebrospinal fluid insulin and brain insulin-signaling markers in AD [17,32]. This CNS insulin deficiency may potentially cause to deterioration in memory, neuroprotective effects, synaptic transmission, as well as likely contributing to the development of neurodegenerative disease [33,34]. IR and hyperinsulinemia are implicated in a number of pathophysiological processes related to AD [17,35]. It was demonstrated that reduced brain insulin signaling is associated with increased tau phosphorylation and Aβ levels in a STZ induced model of diabetes mellitus [36], and also insulin promotes the release of intracellular Aβ in neuronal cultures and accelerates Aβ trafficking to the plasma membrane [37]. Similarly, intravenous insulin infusion also raised plasma Aβ42 levels in patients with Alzheimer's Disease but not in normal adults, an effect that was exaggerated in patients with Alzheimer's Disease with higher body mass indexes [38]. In addition, impaired insulin or IGF-1 signaling can result in the hyper-phosphorylation of tau, which can cause cell death mediated by apoptosis, mitochondrial dysfunction or necrosis [39,40] and promote oxidative stress, which contributes to the neurodegeneration cascade, and leads to dementia-associated behavioral and cognitive deficits [41]. For this reason, it seems that IR causes tau phosphorylation and neurofibrillary tangle formation and increased beta amyloid ag-

gregation in late onset AD [42].

In a recent study, Zhao and Townsend are demonstrated that IR and Aβ disrupt common signal transduction cascades including the insulin receptor family/Phosphoinositide 3-kinase/Akt/Glycogen synthase kinase-3 pathway. They reported that both disease processes contribute to overlapping pathology, thereby compounding disease symptoms and progression [17].

The age-associated decline in the metabolic rate and utilization of glucose by the frontal cortex imply that IR can cause executive dysfunctions in older people, not only global cognitive impairment [11,43,44]. IR may cause decreased cortical glucose utilization especially in hippocampus and entorhinal cortex and also increased oxidative stress with Advanced Glycation End-products (AGEs) [45,46]. AGEs bind the receptor for advanced glycation end products, and promote Nuclear factor kappa beta (NF-kB), which is a transcription factor and crucial mediator of inflammation [47]. It mediates inflammatory cascade and vascular injury leading to neurodegeneration. AGEs have been demonstrated in amyloid-containing senile plaques, tau-containing neurofibrillary tangles, neurons and glia [48].

In humans, raising plasma insulin levels through intravenous infusion increased cerebrospinal fluid levels of the Aβ 42 peptide; this effect was exacerbated by age [49]. That insulin may interfere with Aβ degradation via its regulation of the metalloprotease Insulin-Degrading Enzyme (IDE) may also be an important mechanism in Late-Onset Alzheimer's Disease (LOAD) that the Aβ clearance rather than Aβ production may be of special importance [50]. While the Aβ-degrading capacity of IDE in the AD brains is approximately 50% of that of controls, insulin degradation is decreased by about 30% [51]. Decreased IDE mRNA and IDE activity have been found in the hippocampus of LOAD [52]; however, in neurons adjacent to senile plaques, IDE is upregulated [53].

In our previous study, it was demonstrated that the IGF-1 levels decreased in parallel with impaired cognition and that Curcumin treatment improved both the IGF-1 levels and impaired cognition in the ICV STZ treated rat model. Besides the anti-inflammatory and antioxidative properties of Curcumin, the IGF levels in the ICV STZ models were also improved in this study. Improvements in the IGF-1 levels with Curcumin treatment may be a sign of the initiation of neurogenesis. It can be speculated that in addition to neuroprotection, neurogenesis is the main effect of Curcumin [22].

Recent studies have shown that the plasma and tissue activities of cholinesterase, which may potentiate both amyloid deposition and the toxicity of amyloid deposits [54], are elevated in patients with Alzheimer's Disease and IR [55]. Both IR and impaired cortical cholinergic function, however, have accelerated the amyloid deposition in the brain with Alzheimer's Disease [54-56]; Craft et al. have hypothesized that peripheral IR can affect CNS insulin levels, cognition and Aβ levels [57], and butyrylcholinesterase and acetylcholinesterase may be indirectly involved in the pathogenesis of IR in AD [58-60]. Different from this hypothesis, Hoyer has indicated that in LOAD, damage to the insulin signal transduction cascade may be an early and dramatic event and related with desensitization via the β-subunit of the insulin receptor in the neuronal insulin signal transduction cascade rather than peripheral IR [61]. A relationship between glucose metabolism and cholinergic transmission and β-amyloid has also been derived from animal experimental approaches suggesting functional links between cortical cholinergic activity and glucose metabolism in cholinoceptive target regions [62,63]. Besides, Randell et al. suggested that levels of serum butrylcholinesterase may be related to IR [58]. For these reasons, an investigation of whether there is a relation between inhibition of cholinesterases and IR in the patients with LOAD, is not a fishing expedition. It has been also thought that IR in the brain may be more important than peripheral IR in LOAD [31]. In our current study, it was demonstrated that inhibition of cholinesterase by galantamine did not affect IR indexes over the 18-month period although it improved the cognitive function in the patients with LOAD compared to their baseline values [64]. These results indicated that cholinergic deficit and IR may play a role in the pathogenesis of LOAD by different mechanisms. Due to the complexity of disease pathogenesis, it is too early to make general comments, and further longitudinal and long-term studies in the larger population on this issue are needed. Unlike the findings of other studies, in LOAD, intracerebral IR may be more important than is peripheral IR, and neuronal IR and cholinergic deficit may play a role in the pathogenesis of the disease by different mechanisms. Perhaps inhibition of butyrylcholinesterase as well as acetylcholinesterase should also be evaluated in order to determine the interaction between cholinesterase inhibition and IR in LOAD.

Treatment

Taking into consideration the interaction between the IR and AD, it has been suggested that treatment strategies aimed at improving insulin sensitivity may be effective to reduce the risk of developing the pathology associated with AD. It may be appropriate to combine antidiabetic drugs such as a analogues of the incretin Glucagon-Like Peptide-1 (GLP-1), Dipeptidyl Peptidase-4 (DPP-4) inhibitors, pioglitazone, intranasal insulin with NMDA receptor antagonists, such as memantine, and inhibitors of the Mammalian Target of Rapamycin (mTOR) activity, such as rapamycin and its derivatives (rapalogs) [65-68]. The thiazolidinediones, widely used in the treatment of type 2 diabetes, act as agonists at the nuclear receptor, Peroxisome Proliferator-Activated Receptor gamma (PPARγ), a ligand-inducible transcription factor that increases insulin sensitivity, decreases insulin resistance and regulates lipid metabolism and inflammation [69]. The increased occurrence of insulin resistance in dementia suggests improving insulin effectiveness may have therapeutic benefit for patients with AD and also for prevention of dementia with thiazolidinediones and other drugs that decrease insulin resistance [12,30,44,56]. PPARγ plays critical roles in energy metabolism due to its direct effects on mitochondrial function and ultimately ATP production. Mitochondria may be key players in the cerebral hypometabolism observed in AD, as this organelle plays critical roles in both energy metabolism as well as neuronal apoptosis [70]. It has postulated that these effects of PPARγ agonists responsible for their beneficial effects on memory and cognition in AD patients [71]. One study showed that infusion of insulin enhances the performance of cognitive functions in non-diabetic people [72]. In addition, DPP-4 enzyme modulates several natural substrates such as chemokines, cytokines, neuropeptides, circulating hormones, and bioactive peptides, which acts as regulatory role for peptide hormonal metabolism and amino acid transport [68]. DPP-4 inhibitors prolong lifespan of GLP-1 which is an important substrate of DPP-4. GLP-1 have been demonstrated for their protective action on synapses against toxic effects of amyloid in the hippocampus [73], and also chronic intraperitoneal injection of the Val(8)GLP-1 rescued synaptic plasticity by preventing synaptic degradation in AD mouse model [74]. It was also indicated that

6-month sitagliptin therapy was associated with increased cognitive functions in the elderly diabetic patients with and without AD [75]. In human studies, intranasal insulin increases insulin levels in CSF and acutely enhances memory [76]. Craft and coworkers reported that intranasal-administered insulin improves memory for adults with mild cognitive impairment and LOAD [77,78].

Glycogen syntase-3 is also a potential target for central nervous system therapies [79]. The problem is which patients will benefit from the drugs and who will be the nonresponders. Also there are studies on the agents that target the cardiovascular and cerebrovascular risk factors such as hypertension, hyperlipidemia, and insulin resistance, which have sufficient epidemiological and preclinical evidence to warrant further investigation. AD is a catabolic state in advanced cases and this may also effect the role of insulin resistance in severe cases. Gauthier clearly emphasizes that initiating treatment early in AD is important and reinforces the necessity to assess behavior and activities of daily living [80].

Conclusion

AD pathophysiology has been studied for decades. Several types of studies indicate a relationship between obesity, insulin resistance, type 2 diabetes and neurodegeneration. Besides, current data supports that insulin resistance may play key role in the pathogenesis of the AD, and insulin sensitizer agents such as thiazolidinediones, DPP 4 inhibitors may have therapeutic benefit for patients with Alzheimer's type dementia and also for prevention of the disease. Therefore, we highlight that insulin resistance should be taken into account in both explaining the pathophysiological mechanisms and the managing of the AD.

References

1. World Alzheimer Report: The Global Impact of Dementia. 2015. http://www.alz.co.uk/research/world-report-2015 (Accessed on October 30, 2015)
2. Kuller LH, Lopez OL. Dementia and Alzheimer's disease: a new direction. The 2010 Jay L. Foster Memorial Lecture. Alzheimers Dement. 2011; 7: 540-550.
3. Verlinden VJA, van der Geest JN, de Bruijn RFAG, Hofman A, Koudstaal PJ, Ikram MA. Trajectories of decline in cognition and daily functioning in preclinical dementia. Alzheimers Dement. 2016; 12: 144-153.
4. Isik AT. Late onset Alzheimer's disease in older people. Clin Interv Aging. 2010; 5: 307-311.
5. Arendt T. Synaptic degeneration in Alzheimer's disease. Acta Neuropathol. 2009; 118: 167-179.
6. Coleman PD, Yao PJ. Synaptic slaughter in Alzheimer's disease. Neurobiol Aging. 2003; 24: 1023-1027.
7. Lester-Coll N, Rivera EJ, Soscia SJ, Doiron K, Wands JR, de la Monte SM. Intracerebral streptozotocin model of type 3 diabetes: relevance to sporadic Alzheimer's disease. J Alzheimers Dis. 2006; 9: 13-33.
8. De Santi S. Hippocampal formation glucose metabolism and volume losses in MCI and AD. Neurobiol Aging. 2001; 22: 529-539.
9. Rivera EJ. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimers Dis. 2005; 8: 247-268.
10. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr Alzheimer Res. 2007; 4: 147-152.
11. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. Jama. 2004; 292: 2237-2242.
12. Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. CNS Drugs. 2003; 17: 27-45.
13. Hoyer S. Is sporadic Alzheimer disease the brain type of non-insulin dependent diabetes mellitus? A challenging hypothesis. J Neural Transm (Vienna). 1998; 105: 415-422.
14. Pilcher H. Alzheimer's disease could be "type 3 diabetes". Lancet Neurol. 2006; 5: 388-389.
15. Craft S, Asthana S, Schellenberg G, Baker L, Cherrier M, Boyt AA, et al. Insulin effects on glucose metabolism, memory, and plasma amyloid precursor protein in Alzheimer's disease differ according to apolipoprotein-E genotype. Ann N Y Acad Sci. 2000; 903: 222-228.
16. Banks WA. The source of cerebral insulin. Eur J Pharmacol. 2004; 490: 5-12.
17. 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: 482-496.
18. Neth BJ, Craft S. Insulin Resistance and Alzheimer's Disease: Bioenergetic Linkages. Front Aging Neurosci. 2017; 9: 345.
19. Pei JJ, Grundke-Iqbal I, Iqbal K, Bogdanovic N, Winblad B, Cowburn RF. Accumulation of cyclin-dependent kinase 5 (cdk5) in neurons with early stages of Alzheimer's disease neurofibrillary degeneration. Brain Res. 1998; 797: 267-277.
20. Hong M, Lee VM. Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. J Biol Chem. 1997; 272: 19547-19553.
21. Lannert H, Hoyer S. Intracerebroventricular administration of streptozotocin causes long-term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. Behav Neurosci. 1998; 112: 1199-1208.
22. Isik AT, Celik T, Ulusoy G, Ongoru O, Elibol B, Doruk H, et al. Curcumin ameliorates impaired insulin/IGF signalling and memory deficit in a streptozotocin-treated rat model. 2009; 31: 39-49.
23. Park CR, Seeley RJ, Craft S, Woods SC. Intracerebroventricular insulin enhances memory in a passive-avoidance task. Physiol Behav. 2000; 68: 509-514.
24. Kern W, Peters A, Fruehwald-Schultes B, Deininger E, Born J, Fehm HL. Improving influence of insulin on cognitive functions in humans. Neuroendocrinology. 2001; 74: 270-

280.

25. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 2008; 294: 15-26.

26. Reaven G. Why a cluster is truly a cluster: insulin resistance and cardiovascular disease. Clin Chem. 2008; 54: 785-787.

27. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. Arch Neurol. 2009; 66: 300-305.

28. Frölich L, Blum-Degen D, Bernstein HG, Engelsberger S, Humrich J, Laufer S, et al. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neural Transm (Vienna). 1998; 105: 423-438.

29. Carro E, Torres-Aleman I. The role of insulin and insulin-like growth factor I in the molecular and cellular mechanisms underlying the pathology of Alzheimer's disease. Eur J Pharmacol. 2004; 490: 127-133.

30. Stolk RP, Breteler MM, Ott A, Pols HA, Lamberts SW, Grobbee DE, et al. Insulin and cognitive function in an elderly population. The Rotterdam Study. Diabetes Care. 1997; 20: 792-795.

31. Isik AT, Cankurtaran M, Bozoglu E, Comert B, Doruk H, Mas MR. Is there any relation between insulin resistance and cognitive function in the elderly? Int Psychogeriatr. 2007; 19: 745-756.

32. Craft S, Peskind E, Schwartz MW, Schellenberg GD, Raskind M, Porte D Jr. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype. Neurology. 1998; 50: 164-168.

33. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes. 2014; 63: 2262-2272.

34. De Felice FG, Lourenco MV. Brain metabolic stress and neuroinflammation at the basis of cognitive impairment in Alzheimer's disease. Front Aging Neurosci. 2015; 7: 94.

35. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol. 2004; 3: 169-178.

36. Jolivalt CG, Lee CA, Beiswenger KK, Smith JL, Orlov M, Torrance MA, at al. Defective insulin signaling pathway and increased glycogen synthase kinase-3 activity in the brain of diabetic mice: parallels with Alzheimer's disease and correction by insulin. J Neurosci Res. 2008; 86: 3265-3274.

37. Gasparini L, Gouras GK, Wang R, Gross RS, Beal MF, Greengard P, et al. Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. J Neurosci. 2001; 21: 2561-2570.

38. Kulstad JJ, Green PS, Cook DG, Watson GS, Reger MA, Baker LD, et al. Differential modulation of plasma beta-amyloid by insulin in patients with Alzheimer disease. Neurology. 2006; 66: 1506-1510.

39. Schubert M, Brazil DP, Burks DJ, Kushner JA, Ye J, Flint CL, et al. Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation. J Neurosci. 2003; 23: 7084-7092.

40. Schubert M, Gautam D, Surjo D, Ueki K, Baudler S, Schubert D, et al. Role for neuronal insulin resistance in neurodegenerative diseases. Proc Natl Acad Sci USA. 2004; 101: 3100-3105.

41. de la Monte SM, Wands JR. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. J Alzheimers Dis. 2005; 7: 45-61.

42. Xie L, Helmerhorst E, Taddei K, Plewright B, Van Bronswijk W, Martins R. Alzheimer's beta-amyloid peptides compete for insulin binding to the insulin receptor. J Neurosci. 2002; 22: 221.

43. Razay G, Wilcock GK. Hyperinsulinaemia and Alzheimer's disease. Age Ageing. 1994; 23: 396-399.

44. Taubes G. Neuroscience. Insulin insults may spur Alzheimer's disease. Science. 2003; 301: 40-41.

45. Abbatecola AM, Paolisso G, Lamponi M, Bandinelli S, Lauretani F, Launer L, et al. Insulin resistance and executive dysfunction in older persons. J Am Geriatr Soc. 2004; 52: 1713-1718.

46. Rasgon N, Jarvik L. Insulin resistance, affective disorders, and Alzheimer's disease: review and hypothesis. J Gerontol A Biol Sci Med Sci. 2004; 59: 178-183.

47. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation. 2006; 114: 597-605.

48. Lüth HJ, Ogunlade V, Kuhla B, Kientsch-Engel R, Stahl P, Webster J, et al. Age- and stage-dependent accumulation of advanced glycation end products in intracellular deposits in normal and Alzheimer's disease brains. Cereb Cortex. 2005; 15: 211-220.

49. Watson GS, Peskind ER, Asthana S, Purganan K, Wait C, Chapman D, et al. Insulin increases CSF Abeta42 levels in normal older adults. Neurology. 2003; 60: 1899-1903.

50. Qiu WQ, Ye Z, Kholodenko D, Seubert P, Selkoe DJ. Degradation of amyloid beta-protein by a metalloprotease secreted by microglia and other neural and non-neural cells. J Biol Chem. 1997; 272: 6641-6646.

51. Pérez A, Morelli L, Cresto JC, Castaño EM. Degradation of soluble amyloid beta-peptides 1-40, 1-42, and the Dutch variant 1-40Q by insulin degrading enzyme from Alzheimer disease and control brains. Neurochem Res. 2000; 25: 247-255.

52. Cook DG, Leverenz JB, McMillan PJ, Kulstad JJ, Ericksen S, Roth RA, at al. Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's disease is associated with the apolipoprotein E-epsilon4 allele. Am J Pathol. 2003; 162: 313-319.

53. Bernstein HG, Ansorge S, Riederer P, Reiser M, Frölich L, Bogerts B. Insulin-degrading enzyme in the Alzheimer's disease brain: prominent localization in neurons and senile plaques. Neurosci Lett. 1999; 263: 161-164.

54. Reyes AE, Chacón MA, Dinamarca MC, Cerpa W, Morgan C, Inestrosa NC. Acetylcholinesterase-Abeta complexes are more toxic than Abeta fibrils in rat hippocampus: effect on rat beta-amyloid aggregation, laminin expression, reactive astrocytosis, and neuronal cell loss. Am J Pathol. 2004; 164: 2163-2174.

55. Das UN. Acetylcholinesterase and butyrylcholinesterase as possible markers of low-grade systemic inflammation. Med Sci Monit. 2007; 13: 214-221.

56. Ho L, Qin W, Pompl PN, Xiang Z, Wang J, Zhao Z, et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. Faseb j. 2004; 18: 902-904.

57. Craft S, Reger MA, Baker LD. Insulin resistance in Alzheimer's disease: a novel therapeutic target. In: Gauthier S, Scheltens P, Cummings JL, editors. Alzheimer's disease and related disorders Annual 5, London, Taylor and Francis. 2006l; 111-133.

58. Randell EW, Mathews MS, Zhang H, Seraj JS, Sun G. Relationship between serum butyrylcholinesterase and the metabolic syndrome. Clin Biochem. 2005; 38: 799-805.

59. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature. 2006; 440: 944-948.

60. Sharma P, Senthilkumar RD, Brahmachari V, Sundaramoorthy E, Mahajan A, Sharma A, et al. Mining literature for a comprehensive pathway analysis: a case study for retrieval of homocysteine related genes for genetic and epigenetic studies. Lipids Health Dis. 2006; 5: 1.

61. Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol. 2004; 490: 115-125.

62. 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.

63. Mehlhorn G, Löffler T, Apelt J, Rossner S, Urabe T, Hattori N, et al. Glucose metabolism in cholinoceptive cortical rat brain regions after basal forebrain cholinergic lesion. Int J Dev Neurosci. 1998; 16: 675-690.

64. Isik AT, Bozoglu E. Acetylcholinesterase inhibition and insulin resistance in late onset Alzheimer's disease. Int Psychogeriatr. 2009; 21: 1127-1133.

65. Galimberti D, Scarpini E. Pioglitazone for the treatment of Alzheimer's disease. Expert Opin Investig Drugs. 2017; 26: 97-101.

66. Holscher C. Drugs developed for treatment of diabetes show protective effects in Alzheimer's and Parkinson's diseases. Sheng Li Xue Bao. 2014; 66: 497-510.

67. Tramutola A, Lanzillotta C, Di Domenico F. Targeting mTOR to reduce Alzheimer-related cognitive decline: from current hits to future therapies. Expert Rev Neurother. 2017; 17: 33-45.

68. Chalichem NSS, Gonugunta C, Krishnamurthy PT, Duraiswamy B. DPP4 Inhibitors Can Be a Drug of Choice for Type 3 Diabetes: A Mini Review. Am J Alzheimers Dis Other Demen. 2017; 32: 444-451.

69. Escribano L, Simón AM, Pérez-Mediavilla A, Salazar-Colocho P, Del Río J, Frechilla D. Rosiglitazone reverses memory decline and hippocampal glucocorticoid receptor down-regulation in an Alzheimer's disease mouse model. Biochem Biophys Res Commun. 2009; 379: 406-410.

70. Landreth G, Jiang Q, Mandrekar S, Heneka M. PPARgamma agonists as therapeutics for the treatment of Alzheimer's disease. Neurotherapeutics. 2008; 5: 481-489.

71. Roses AD, Saunders AM, Huang Y, Strum J, Weisgraber KH, Mahley RW. Complex disease-associated pharmacogenetics: drug efficacy, drug safety, and confirmation of a pathogenetic hypothesis (Alzheimer's disease). Pharmacogenomics J. 2007; 7: 10-28.

72. Rasgon NL, Kenna HA. Insulin resistance in depressive disorders and Alzheimer's disease: revisiting the missing link hypothesis. Neurobiol Aging. 2005; 26: 103-107.

73. Gault VA, Holscher C. GLP-1 agonists facilitate hippocampal LTP and reverse the impairment of LTP induced by beta-amyloid. Eur J Pharmacol. 2008; 587: 112-117.

74. Gengler S, McClean PL, McCurtin R, Gault VA, Hölscher C. Val(8)GLP-1 rescues synaptic plasticity and reduces dense core plaques in APP/PS1 mice. Neurobiol Aging. 2012; 33: 265-276.

75. Isik AT, Soysal P, Yay A, Usarel C. The effects of sitagliptin, a DPP-4 inhibitor, on cognitive functions in elderly diabetic patients with or without Alzheimer's disease. Diabetes Res Clin Pract. 2017; 123: 192-198.

76. Reger MA, Watson GS, Green PS, Baker LD, Cholerton B, Fishel MA, et al. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. J Alzheimers Dis. 2008; 13: 323-331.

77. Craft S, Claxton A, Baker LD, Hanson AJ, Cholerton B, Trittschuh EH, et al. Effects of Regular and Long-Acting Insulin on Cognition and Alzheimer's Disease Biomarkers: A Pilot Clinical Trial. J Alzheimers Dis. 2017; 57: 1325-1334.

78. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol. 2012; 69: 29-38.

79. Bhat RV, Budd Haeberlein SL, Avila J. Glycogen synthase kinase 3: a drug target for CNS therapies. J Neurochem. 2004; 89: 1313-1317.

80. Gauthier SG. Alzheimer's disease: the benefits of early treatment. Eur J Neurol. 2005; 12: 11-16.