Clinical Journal of Diabetes Care and Control

Chembio Publishers
Right Choice for Researchers

Review Article *Volume 1; Issue 2*

Minimal Effect but No Cure for Alzheimer's with Antidiabetic Drugs

Michael AB Naafs*

Department of Internal Medicine and Endocrinology, Naafs International Health Consultancy, Netherlands

***Corresponding author:** Dr. Michael AB Naafs, Department of Internal Medicine and Endocrinology, Naafs International Health Consultancy, Netherlands, Email: naafs.healthconsultancy@gmail.com

Received Date: June 27, 2018; **Published Date:** August 20, 2018

Abstract

In this mini-review the available evidence for a favorable effect of antidiabetic drugs in Alzheimer's disease (AD) is discussed. Beneficial effects are mostly seen in animal studies. Clinical studies are small, have many methodological flaws and show inconsistent results Oxidative stress inflammation, insulin resistance, advanced glycation end-products and obesity all play a pivotal role. However research relies heavily on the amyloid hypothesis. It is obvious that antidiabetic drugs are not the new cure after the failure of all amyloid-beta trials in the last decades. Dementia risks seem similar for type 2 and type1 diabetes but limited research has been performed in type 1 diabetes. Hypoglycemic episodes are not the culprit indementia and diabetes. Further research of Alzheimer's in type 1 DM is hampered by the low prevalence and the mixed nature of dementia in DM type 1.

Keywords: Antidiabetic; Oxidative stress; Insulin resistance; Glycation; Pivotal role; Amyloid hypothesis; Amyloid-beta

Abbreviations: AD: Alzheimer's Disease; IDE: Insulin Degrading Enzyme; ADDLs: Amyloid beta-Derived Diffusible Ligands; BBB: Blood Brain Barrier; GLUTs: Glucose Transporters; AGEs: Advanced Glycation End products; NFTs: Neurofibrillary Tangles; ROS: Reactive Oxygen Species; TNF: Tumor Necrosis Factor; MCI: Mild Cognitive Impairment; CRM: Caloric Restriction Mimetic; AMPK: Adenosine Mono Phosphate Kinase; PPAR: Peroxisome Proliferator Activated Receptor.

Introduction

As the population ages, dementia grows as a public health problem. In the absence of a cure primary prevention will have the largest effect on the reduction of dementia occurrence [1-10]. Diabetes mellitus is an established risk factor for dementia. Patients with diabetes have an increased risk for any dementia [2-5]. The exact mechanism of cognitive impairment in diabetic patient remains unknown. The main contributors to diabetes-associated cognitive decline include hyperglycemia decreased insulin secretion, obesity increased oxidative stress and inflammation. In addition patients with diabetes often have other co-morbidities such as high blood pressure and cardiovascular disease that may contribute to the development of dementia [4-8].

Several studies have examined the association of different antidiabetic medications and cognitive function as well in Alzheimer as in Parkinson's disease [9-11]. Central nervous insulin resistance in combination with inflammation and oxidative stress seem to contribute to the shared pathophysiological link. In this mini-review the

Citation: Michael AB Naafs. Minimal Effect but No Cure for Alzheimer's with Antidiabetic Drugs. Clin J Dia Care Control 2018, 1(2): 180006.

evidence on the mechanisms of action of antidiabetic drugs and their potential uses in Alzheimer's disease (AD) is discussed. The beneficial effects of antidiabetic drugs on cognition in Parkinson' disease is beyond the scope of this mini-review [10].

Diabetes and Alzheimer's Disease (AD)

Insulin signaling

Hyperinsulinemia and insulin resistance are two of the hallmarks of type2 DM, which have been shown to be important risk factors for elderly cognitive decline [12]. Indeed while an acute administration of insulin may improve memory domains dysfunctions in delayed memory processes can result from chronic administration [4,13]. Insulin signaling induces the brain to take up glucose and to produce insulin- degrading enzyme (IDE) in order to reduce its level. IDE is involved in both insulin and amyloid-beta (Abeta) degradation leading to amyloid accumulation [14]. Moreover in diabetes alteration of insulin signaling determines less IDE production resulting in reduction of Abeta (Amyloid-beta) degradation. This process definitely leads to abnormal beta accumulation. Therefore increasing insulin signaling in the brain might reduce Abeta accumulation in the brain. Insulin has also been reported to enhance Abeta clearance from the brain [15]. Furthermore soluble Abeta oligomers known as amyloid beta-derived diffusible ligands (ADDLs), contribute to insulin resistance in AD by modifying synapse confirmation. This altered shape confirmation is responsible for reduced affinity of synaptic insulin receptor for its ligand [13].

It is not surprising that a recent hypothesis suggested AD might be a neuro-endocrine disorder a so called "type 3 diabetes" [16,17]. Impaired insulin signaling has been critically involved in the development of both type2 DM and AD. However other abnormalities common to both pathologies include glucose dysmetabolism mitochondrial dysfunction, oxidative stress or deposition of amyloidogenic proteins [18].

Advanced glycation end products (AGEs)

Under physiological conditions glucose metabolism is critical for proper brain function and its neuronal connections. As neurons are unable to store and synthesize glucose, this is transported across the blood-brain barrier (BBB) via glucose transporters (GLUTs) with GLUT-1, GLUT-3 and GLUT-4 constituting the most abundant isoforms [19]. However under chronic glucose dysmetabolism as in type2 DM, brain damaging effects may arise with the formation and accumulation of advanced glycation end-products (AGEs) constituting one of the most deleterious ones [20]. AGEs are formed by a sequence of events originally identified as the end products of the Maillard reaction during which reducing sugars (e.g. glucose and fructose) react with amino groups from proteins that become auto-oxidized and form cross-linked complexes and unstable compounds [17]. Besides their massive formation in diabetic patients AGEs were also found in retinal vessels peripheral nerves, kidneys and CNS of aged patients without DM [21]. Moreover the extent of Abeta peptide glycation by AGEs has been correlated with its aggregation into senile plaques as well as with tau protein hyperphosphorylation and the subsequent formation of neurofibrillary tangles (NFTs) ultimately leading to the abnormal accumulation of both AD neuropathological hallmarks [17,18].

AGEs may also react with free radicals promoting oxidative damage and further cellular injury [22]. Therefore as type2 DM exacerbates the production of such deleterious molecules it is not surprising that AGEs production and eventually the vicious cycle of oxidative stress may create another putative biochemical link between type 2 DM and increased risk of AD.

Oxidative stress

Regarding oxidative stress mitochondria are one of the major sources and targets of reactive oxygen species (ROS) and have been increasingly demonstrated to have a pivotal role in AD and diabetes pathogenesis [23]. They are primarily responsible for several crucial cellular processes being also the main coordinators of energy metabolism by generating over 90% of cellular ATP [18]. Conversely given the mitochondria's high susceptibility to oxidative stress-mediated injury together with the neurons extreme sensitivity to alterations in their mitochondrial pool it is acceptable that the mitochondrial functional impairment can be correlated with AD and diabetes [24,25]. Over production of ROS and the general increase in oxidative stress are characteristic of DM. Oxidized protein accumulation has also been demonstrated in the hippocampus frontal and temporal lobes of mild cognitive impairment patients, suggesting an early impact of oxidative damage in AD development [24].

Inflammation

Both type2 DM and AD are largely related to inflammatory processes. Insulin resistance is associated with elevated levels of pro-inflammatory cytokines such as C-reactive protein tumor necrosis factor -alpha (TNF-alpha) interleukins (IL-1) and IL-6 [26]. All these cytokines are considered an indirect sign of the immunological dysfunction that leads to insulin resistance [27]. Likewise IL-6 and C-reactive protein are connected to Abeta plaque deposition and progression and on the other side a reduced AD incidence has been reported in

patients under chronic non-steroidal anti-inflammatory therapy [28]. Another relevant aspect is represented by the pro-inflammatory role of astrocytes and microglia surrounding Abeta plaques that are responsible of neuronal irreversible damage as a consequence of complement activation [29]. Interestingly insulin seems to have anti-inflammatory effects directly suppressing pro-inflammatory cytokines and inducing anti-inflammatory mediators as demonstrated in both preclinical and clinical studies [30].

Central obesity

Central obesity may result in the metabolic syndrome a well known risk factor for the development of insulin resistance. The role of obesity in AD has been explored in many studies and although the underlying mechanisms of this intervention are not yet known AD risk is correlated with insulin resistance, oxidative stress, AGEs and hyperglycemia [31]. Epidemiological data suggest that insulin resistance is associated with increased risk of cognitive impairment [32]. PET studies have demonstrated that greater insulin resistance is associated with an AD-like pattern of reduced cerebral glucose metabolism [33]. Thus it is not surprising that insulin could be an effective treatment for AD by increasing neuronal glucose uptake and cellular ATP levels [34].

Antidiabetic Drugs and Alzheimer's Disease (AD)

Insulin

Insulin resistance plays a crucial role in the development and progression of AD [35,36]. Several landmark studies have revealed reduced brain insulin receptor sensitivity and insulin expression in post-mortem AD [37-39]. In addition a recent meta-analysis of longitudinal population studies (n=1.746.777) revealed that the risk of AD is some 50% higher in diabetics as compared to the general population [40]. Extensive research has been performed to the specific pathways underlying this connection [41-44]. So there is enough indirect evidence to support insulin resistance as a primary feature of AD.

Animal studies have shown that insulin can be transferred along olfactory and trigeminal pathways by the intranasal route without compromising its biological properties [45-48]. For that reason intranasal insulin has been mostly studied in cognition research. The effects of acute and long-term administration of intranasal insulin on cognition were studied in young healthy adults. A single dose of nasal insulin was already sufficient to improve cognitive performance [49]. Novak et al. [50] showed that a single dose of intranasal insulin improved visiospatial memory and verbal fluency functions. If intranasal insulin influences tau metabolism and Abeta peptides turnover in healthy individuals is not known.

Studies on the plasma biomarker A beta42 are conflicting [51,52]. Therefore caution is needed to conclude that reduced plasma concentrations of Abeta 42 after intranasal insulin administration provide evidence for the putative neuroprotective effects of nasal insulin. Clinical trials for intranasal insulin in patients with amnestic MCI (mild cognitive impairment) and AD mostly show that both acute and chronic administration of various insulin formulations improve several aspects of cognition as verbal memory, memory savings and selective attention. There are unexplained APOE-related treatment differences in these trials as well as for results regarding AD biomarkers [53-59].

Nevertheless these studies indicate that AD is hallmarked by impaired brain insulin signaling. They also show that intranasal insulin reaches physiological concentrations in the brain. Intranasal insulin improves AD symptomatology but gender, genotype and formulation modify patient response. However most studies are small with less than 50 participants.

Metformin

The evidence for its use in AD is controversial. Preclinical data suggest that orally administered Metformin rapidly crosses the BBB and accumulates in different CNS regions [60]. In vitro studies showed that Metformin can resensitize insulin signaling and prevent the molecular and pathological changes observed in AD neurons [61]. Metformin reduced tau phosporylation in tau transgenic mice which is also a hallmark of AD [62]. The exact mechanisms of action of Metformin are not fully understood. It is also unsure what levels of Metformin are needed and in which brain region. Furthermore the bioavailability is poor (40-60%) and therefore pro-drug approaches have been tried to improve its oral absorption [63-65].

Metformin has been associated with reduced rates of dementia [66,67]. Metformin is also known as a caloric restriction mimetic (CRM) as its effect on AMPK (adenosinemono phosphate-kinase), which reduces gluconeogenesis in the live rafter activation, is similar to that produced by caloric restriction. Both caloric restriction and Metformin have been found to slow the aging process in animals and extend life span [68-70]. In addition caloric restriction has been shown to improve memory in older people [71]. Two clinical trials (MILES NCT02432287 and TAME are underway to investigate the effect of Metformin on aging and cognition in humans.

They should show if Metformin is beneficial as an effective prophylactic or as an early intervention for AD in older people who do not have diabetes.

However some evidence suggests that metformin can be detrimental to the cognitive health of older people with diabetes with one study finding an increased rate of AD and another finding lower cognitive function [72,73]. The study that identified lower cognitive function suggested that this could be due to vitamin B12 deficiency induced by Metformin [74,75]. The question if Metformin protects or harms cognitive health in older people has been unresolved until now [76].

Thiazolidinediones

These drugs are agonists of the peroxisome proliferator-activated-receptor-gamma (PPAR-gamma) [77]. Currently only pioglitazone is approved in DM therapy. Rosiglitazone has been withdrawn from the market due to a high incidence of cardiovascular events. Both drugs have been tested as potential treatment in AD with inconclusive results. PPAR-gamma has shown an increased expression in AD temporal cortex compared to controls [78]. In preclinical studies PPAR-gamma agonists have been shown to ameliorate AD-related pathology by reducing the expression of inflammatory genes and decreasing amyloid plaques [79].

Galimberti and Scarpine performed a literature search for pioglitazone and AD trials. A phase 2 study in AD showed that pioglitazone is safe and well tolerated. So far two large phase 3 trials are ongoing but there are no preliminary results yet on a possible beneficial effect on cognition in patients with AD [80]. Heneka et al. [81] analyzed the data of a cohort (n=145.928) using pioglitazone and looked at the association of pioglitazone and the incidence of dementia. All subjects were > 60 years. Long-term pioglitazone use was associated with a lower dementia incidence. Relative to non-diabetics the cumulative long-term use of pioglitazone reduced the dementia risk by 47% (RR=0,53;p=0.029). If diabetic patients used pioglitazone <8 quarters the dementia risk was comparable to nondiabetics (RR=1,16; p=0,317) and diabetics without pioglitazone treatment had a 23% increase in dementia risk (RR=1,23;p<0,001). They concluded that prospective trials are needed to evaluate a possible neuroprotective effect.

GLP-1 receptor agonists

GLP-1(glucagon like peptide- 1) seems to have favorable effects within the CNS, where activation of GLP-1 receptors protects against apoptosis. Several preclinical studies in transgenic mice and rats showed favorable results [82,83]. Gejl *et al.* [84] performed a 6-month RCT with liraglutide in AD patients (n=38) and measured cerebral glucose metabolism as a parameter of AD progression. They concluded that in AD patients with longstanding disease 26 weeks of liraglutide treatment prevented the expected decline in cerebral glucose metabolism. They found no significant differences for this parameter between the liraglutide and the placebo group. A larger trial with liraglutide (ELAD) is ongoing and a trial with exanatide (n=60) showed some beneficial effects in motor symptoms in Parkinson patients treated for 60 months [10].

Type 1 DM and dementia

There has been a paucity of work in type 1diabetes and dementia because only recently have they been living longer and living long enough to be at risk for an age-related neurocognitive dysfunction. Whitmer et al. [85] evaluated dementia risk in older people with type 1 diabetes. They followed the health histories of 490. 344 people in the Kaiser Permanente Health system during 12 years. The patients were older than 60 with no prior dementia. The investigators identified 334 patients with type 1 diabetes n that group and 53 (6,5%) of these patients received diagnosis of dementia.

Patients in late life have an approximately increased risk of dementia compared with patients who do not have dementia. The risk appears similar to that for those with type 2 DM [85]. With a prevalence of 5% -10% type 1 DM is a rare disease for studying dementia in diabetes compared to type2 diabetes. Patients with type 1 DM are three times more likely to have had hypoglycemic episodes than type 2 DM patents [86]. Both hyperglycemic and hypoglycemic events increased dementia risk(139% Vs 47%)-(88). So hypoglycemiceisodes are not the culprit. Patients with type 1 DM have more microvascular risk factors than those with type 2 DM and have less adiposity and concomitant insulin resistance. In contrast patients with type 2 DM are more likely to have macrovascular risk factors such as end-stage renal disease or retinopathy and or a relatively high risk for stroke. Dementia in type 1 DM will be mostly mixed of nature, a combination of cerebrovascular disease and Alzheimer's [87]. This will complicate the study of Alzheimer's in type 1 DM due to the low prevalence in type 1 DM.

Conclusion

It may be obvious from this mini-review that following the failure of all Alzheimer amyloid trials antidiabetic drugs will not be the new cure for AD. Favorable results are usually present in animal studies, predominantly in transgenic mice a mankind created model. It is always

easier to fix a problem you created yourself. Clinical studies with antidiabetic drugs are small have many methodological flaws and show inconsistent and unexplained results probably related to differences in genotype gender and differences in drug formulations.

Research on antidiabetic drug in AD also relies heavily on the amyloid-beta-tau hypothesis. However it may be concluded that we don't understand this disease [88]. In an editorial in the New England Journal of Medicine Murphy wrote "the field is clearly in need of innovative ideas and we are very well be nearing the end of the amyloid hypothesis rope" [89].

References

1. Orkaby AR, Cho K, Cormack J, Gagnon DR, Driver JA (2017) Metformin vs sulfonylurea use and risk of dementia in US veterans aged> 65 years with diabetes. Neurology 89(18): 1877-1885.

2. Ahmed RM, MacMillan M, Bartley L, Halliday GM, Kiernan MC, et al. (2014) Systemic metabolism in frontotemporal dementia. Neurology 83(20): 1812-1818.

3. Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L (2004) Diabetes mellitus and risk of dementia in the Kungsholmenproject: a 6-year follow-up study. Neurology 63(7): 1181-1186.

4. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, et al. (1999) Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 53(9): 1937-1942.

5. Fink A, Haenisch B (2017) Oral antidiabetic drugs and dementia risk: Does treatment matter? Neurology 89(18): 1848-1849.

6. Engelhart MJ, Geerlings MI, Ruitenberg A, Van Swieten JC, Hofman A, et al. (2002) Diet and Risk of dementia.Does fat matter? Neurology 59(12): 1915-21.

7. Hörder H, Johansson L, Guo X, Grimby G, Kern S, et al. (2018) Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women. Neurology 90(15): e1298-e1305.

8. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, et al. (2018) Dementia in Latin America: Assessing the present and envisioning the future. Neurology 90(5): 222-231.

9. Markowicz-Piasecka M, Sikora J, Szydłowska A, Skupień A, Mikiciuk-Olasik E, et al. (2017) Metformin - a Future Therapy for Neurodegenerative Diseases : Theme: Drug Discovery, Development and Delivery in Alzheimer's Disease Guest Editor: Davide Brambilla. Pharm Res 34(12): 2614-2627.

10. König A, Vicente Miranda H, Outeiro TF (2018) Alpha-Synnuclein Glycation and the Action of Anti-Diabetic Agents in Parkinson's Disease. J Parkinsons Dis 8(1): 33-43.

11. Femminella GD, Bencivenga L, Petraglia L, Visaggi L, Gioia L, et al. (2017) Antidiabetic Drugs in Alzheimer's Disease: Mechanisms of Action and Future Perspectives. J Diab Res Art doi: 10.1155/2017/7420796.

12. Zhong Y, Miao Y, Jia WP, Yan H, Wang BY, et al. (2012) Hyperinsulinemia, insulin resistance and cognitive decline in older cohort. Biomed Environ Sci 25(1): 8-14.

13. Mittal K, Katare DP (2016) Shared links between type 2 diabetes mellitus and Alzheimer's disease: a review. Diabetes Metab Syndr 10(2 Suppl 1): S144-S149.

14. Edland SD (2004) Insulin-degrading enzyme, apolipoprotein E, and Alzheimer's disease. J Mol Neurosci 23(3): 213-217.

15. Vandal M, White PJ, Tremblay C, St-Amour I, Chevrier G, et al. (2014) Insulin reverses the high-fat-diet induced increase in brain Abeta and improves memory in an animal model of Alzheimer's disease. Diabetes. 63(12): 4291-4301.

16. Pasquier F, Boulogne A, Leys D, Fontaine P (2006) Diabetes mellitus and dementia. Diabetes Metab 32(5Pt 1): 403-414.

17. Kroner Z (2009) The relationship between Alzheimer's disease and diabetes: type 3 diabetes? Altern Med Rev 14(4): 373-379.

18. Correia SC, Santos RX, Carvalho C, Cardoso S, Candeias E, et al. (2012) Insulin signaling, glucose metabolism and mitochondria: major players in Alzheimer's disease and diabetes interrelation. Brain Res 1441: 64-78.

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

20. Biessels GJ, van der Heide LP, Kamal A, Bleys RL, Gispen WH (2002) Ageing and diabetes: implications for brain function. Eur J Pharmacol 441(1-2): 1-14.

21. Goh SY, Cooper ME (2008) Clinical review: the role of advanced glycation end products in progression and complications of diabetes. J Clin Endocrinol Metab 93(4):1143-1152.

22. Roriz-Filho SJ, Sa-Roriz TM, Rosset I, Camozzato AL, Santos AC, et al. (2009) (Pre) diabetes, brain aging and cogniton. Biochim Biophys Acta 1792(5): 432-443.

23. Moreiro PI, Carvalho C, Zhu X, Smith MA, Perry G (2010) Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. Biochim Biophys Acta 1802(1): 2-10.

24. Sims-Robinson C, Kim B, Rosko A, Feldman EL (2010) How does diabetes accelerate Alzheimers disease pathology? Nat Rev Neurol 6(10):551-559.

25. Sebastiao I, Candeias E, Santos MS, De Oliveira CR, Moreira PI, et al. (2014) Insulin as a bridge between type 2 diabetes and Alzheimer disease-how anti-diabetics could be a solution for dementia. Front Endocrinol (Lausanne) 5: 110.

26. Wieser V, Moschen AR, Tilg H (2013) Inflammation, cytokines and insulin resistance: a clinical perspective. Arch Immunol Ther Exp(Warsz) 61(2): 119-125.

27. Patel PS, Buras ED, Balasubramanyam A (2013) The role of the immune system in obesity and insulin resistance. J Obes doi: 10.1155/2013/616193.

28. Akter K, Lnza 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.

29. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, et al. (2000) Inflammation and Alzheimer's disease. Neurobiol Aging 21(3): 383-421.

30. Sun Q, Li J, Gao F (2014) New insights into insulin: the anti-inflammatory effect and its clinical relevance. World J Diabetes 5(2): 89-96.

31. Kim B, Feldman EL (2015) Insulin resistance as a key link for the increased risk of cognitive impairment i the metabolic syndrome. Exp Mol Med 47: e149.

32. Tan ZS, Beiser AS, Fox CS, Au R, Himali JJ, et al. (2011) Association of metabolic dysregulation with volumetric brain magnetic resonance imaging and cognitive markers of subclinical brain aging in middle-aged adults: the Framingham Offspring Study. Diabetes Care 34(8):1766-1770.

33. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, et al. (2011) Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol 68(1): 51-57.

34. Jauch-Chara K, Friedrich A, Rezmer M, Melchert UH, Scholand-Engler GH, et al. (2012) Intranasal insulin suppresses food intake via enhancement of brain energy levels in humans. Diabetes 61(9): 2261-2268.

35. Mu QL, Yang ER, Roserto OJ (2009) Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega -3-fatty acids and curcumin. J Neurosci 29(28): 9078-9089.

36. De Felice FG, Vieira MN, Bomfim TR, Decker H, Velasco PT, et al. (2009) Protection of synapses against Alzheimer's linked toxins; insulin signaling prevents the pathogenic binding of Abeta oligomers. Proc Natl Acad Sci USA 106(6): 1971-1976.

37. Steen E, Terry BM, Rivera JL, Cannon JL, Neely TR, et al. (2005) Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease -is this type 3 diabetes? J Alzheimers Dis 7(1): 63-80.

38. Moleoney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R, et al. (2010) Defects in IGF-1 receptor, insulin receptor and IRS-1.2 in Alzheimer's indicate possible resistance to IGF-1 and insulin signaling. Neurobiol Aging 31(2): 224-243.

39. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, et al. (2012) Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation and cognitive decline. J Clin Invest 122(4): 1316-1338.

40. Zhang J, Chen C, Hua S, Liao H, Wang M, et al. (2017) An updated meta-analysis of cohort studies: diabetes and risk of Alzheimer's disease. Diabetes Res Clin Pract 124: 41-47.

41. Ferreira ST, Clarke JR, Bomfim TR, De Felice FG (2014) Inflammation, defective insulin signaling and neuronal dysfunction in Alzheimer's disease. Alzheimers Dement 10 (1 Suppl): S76-S83.

42. Biessels GJ, Reagan LP (2015) Hippocampal insulin resistance and cognitive dysfunction. Nat Rev Neurosci 16(11): 660-671.

43. Vieira MNN, Lima-Filho RAS, De Felice FG (2018) Connecting Alzheimer's disease to diabetes: underlying mechanisms and potential therapeutic targets. Neuropharmacology 136 (Pt B): 160-171.

44. Bloom GS, Lazo JS, Narambueno A (2018) Reduced brain insulin signaling: a seminal process in Alzheimer's disease pathogenesis. Neuropharmacology 136(Pt B): 192-195.

45. Lochhead JJ, Thorne RG (2012) Intranasal delivery of biologics in the central nervous system. Adv Drug Deliv Rev 64(7): 614-628.

46. Dhuria SV, Fine JM, Bingham D, Svitak AL, Burns RB, et al. (2016) Food consumption and activity levels increase in rats following intranasal Hypocretin-1. Neurosci Lett 627: 155-159.

47. Renner DB, Svitak AL, Gallas NJ, Ericson ME, Frey WH, et al. (2012) Intranasal delivery of insulin via the olfactory nerve pathway. J Pharm Pharmacol 64(12): 1709-1714.

48. Chapman CD, Schiöth HB, Grillo CA, Benedict C (2018) Intranasal insulin in Alzheimer's disease: Food for thought. Neuropharmacology 136 (Pt B) : 196-201.

49. Benedict C, Kern W, Schultes B, Born J, Hallschmid M (2008) Differential sensitivity of men and women to anorexigenic and memory-improving effects of intranasal insulin. J Clin Endocrinol Metab 93(4): 1339-1344.

50. Novak V, Milberg W, Hao Y, Munshi M, Novak P, et al. (2014) Enhancement of vasoreactivity and cognition by intranasal insulin in type 2 diabetes. Diabetes Care 37(3): 751-759.

51. Lue LF, Sabbagh MN, Chiu MJ, Jing N, Snyder NL, et al. (2017) Plasma levels of Aβ 42 and tau identified probable Alzheimer's dementia: findings in two cohorts. Front Ageing Neurosci 9: 226.

52. Lui JK, Laws M, Li QX (2010) Plasma amyloid -beta as a marker in Alzheimer's disease; the ATBL study of aging. J Alzheimer Dis 20(4): 1233-42.

53. Reger MA, Watson GS, Frey WH, Baker LD, Cholerton B, et al. (2006) Effects of intranasal insulin on cognition in memory -impaired older adults. Modulation by APOE genotype. Neurobiol Aging 27(3): 451-458.

54. Reger MA, Watson GS, Green PS, Baker LD, Cholerton B, et al. (2008) Intranasal administration dose depently modulates verbal memory and plasma amyloid-beta in memory impaired older adults. J Alzheimers Dis 13(3): 323-331.

55. Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, et al. (2008) Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology 70(6): 440-448.

56. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, et al. (2012) Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment; a pilot clinical trial. Arch Neurol 69(1): 29-38.

57. Craft S, Claxton A, Baker LD, Hanson AJ, Cholerton B, et al. (2017) Effects of regular and long-acting insulin on cognition and Alzheimer's disease biomarkers: a pilot clinical trial. J Alzheimer Dis 57(4): 1325-1334.

58. Claxton A, Baker LD, Wilkinson CW, Trittschuh EH, Chapman D, et al. (2013) Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or Alzheimer's disease. J Alzheimer Dis 35(4): 789-797.

59. Claxton A, Baker LD, Hanson A, Trittschuh EH, Cholerton B, et al. (2015) Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. J Alzheimers Dis 44(3): 897-906.

60. Łabuzek K, Suchy D, Gabryel B, Bielecka A, Liber S, et al. (2010) Quantification of metformin by the HPLC method in brain regions, cerebrospinal fluid and plasma of rats treated with lipopolysaccharide. Pharmacol Rep 62(5): 956-965.

61. Gupta A, Bishr B, Dey CS (2011) Peripheral insulin-sensitizer drug metformin ameliorates neuronal insulin resistance and Alzheimer's like changes. Neuropharmacology 60(6): 910-920.

62. Kickstein E, Krauss S, Thornhill P, Rutschow D, Zeller R, et al. (2010) Biguanide metformin acts on tau phosphorylation via mTor/protein phosphatase 2A (PP2A) signaling. Proc Natl Acad Sci USA 107(50): 21830-21835.

63. Huttunen KM, Mannila A, Laine K, Kemppainen E, Leppanen J, et al. (2009) The first bioreversible prodrug of metformin with improved lipophilicity and enhanced intestinal absorption. J Med Chem 52(14): 4142-4148.

64. Huttunen KM, Leppanen J, Laine K, Vepsalainen J, Rautio J (2013) Convenient microwave-assisted synthesis of lipophillc sulfonamide prodrugs of metformin. Eur J Pharm Sci 49(4): 624-628.

65. Exalto LG, Whitmer RA, Kappele LJ, Biessels GJ (2012) An update on type 2 diabetes, vascular dementia and Alzheimer's disease. Exp Gerontol 47(11): 858-864.

66. Cheng C, Lin CH, Tsai YW, Tsai CJ, Chou PH, et al. (2014) Type 2 diabetes and Antidiabetic medications in relation to dementia diagnosis. J Gerontol A Biol Sci Med Sci 69(10): 1299-1305.

67. Hsu CC, Wahlqvist ML, Lee MS, Tsai HN (2011) Incidence of dementia s increased in type 2 diabetes and reduced by the use of sulfonylurea's and metformin. J Alzheimer Dis 24(3): 485-493.

68. Handschin C (2016) Caloric restriction and exercise "mimetics": Ready for prime time? Pharmacol Res 103: 158-166.

69. Anisimov VN, Berstein LM, Egormin PA, Piskunova TS, Popovich IG, et al. (2005) Effect of metformin on life span and on the development of spontaneous mammary tumors in HER-2/neu transgenic mice. Exp Gerontol 40(8-9): 685-693.

70. Anderson BM, Shanmuganayagam D, Weindruck R (2009) Caloric restriction and aging; studies in mice and monkeys. Toxicol Pathol 37(1): 47-51.

71. Witte AV, Fobker M, Gellner R, Knecht S, Floel A (2009) Caloric restriction improves memory in elderly humans. Proc Natl Acad Sci USA 106(4): 1255-1260.

72. Imfeld P, Bodmer M, Jick SS, Meier CR (2012) Metformin, other Antidiabetic drugs and risk of Alzheimer's disease: a population-based case-control study. J Am Geriatr Soc 60(5): 916-921.

73. Moore EM, Mander AG, Ames D, Kotowicz MA, Carne RP, et al. (2013) Increased risk of cognitive impairment in patients with diabetes is associated with metformin. Diabetes Care 36(10): 2981-2987.

74. Obeid R (2014) Metformin causing vitamin B12 deficiency: a guilty verdict without sufficient evidence. Diabetes Care 37(2): e22-e23.

75. Moore E, Mander A, Ames D, Carne R, Sanders K, et al. (2012) Cognitive impairment and vitamin B12: a review. Int Psychogeriatr 24(4): 541-556.

76. Ye F, Luo YJ, Xiao J, Yu NW, Yi G (2016) Impact of Insulin Sensitizers on the Incidence of Dementia: A Meta-Analysis. Dement Geriatr Cogn Disord 41(5-6): 251-260.

77. Naafs Michael AB (2017) Pharmocodynamc Evaluation: Endocrinology Drug Discovery and Evaluation. In: Hock FJ & Gralinski MR (Eds.), Methods in Clinical Pharmacology. (2nd edn), Springer Verlag Berlin, Heidelberg, New York.

78. Kitamuraab Y, Shun S, Koikea H, Jun-ichi K, Yasuji M, et al. (1999) Increased expression of cyclooxygenase and peroxisome proliferators-activated-receptor gamma in Alzheimer's disease brains. Biochemical and Biophysical Research Communications 254(3): 582-586.

79. Jiang Q, Heneka M, Landreth GE (2008) The role of peroxisome proliferative-activated-receptor-gamma (PPRA-gamma) in Alzheimer's disease: therapeutic implications. CNS Drugs 22(1): 1-14.

80. Galimberti D, Scarpini E (2017) Proglitazone for the treatment of Alzheimer's disease. Exp Opin Invest Drugs 26(1): 97-101.

81. Heneka MT, Fink A, Doblhammer G (2015) Effect of pioglitazone medication on the incidence of dementia. Ann Neurol 78(2): 284-294.

82. Colsolara V, Edison P (2015) Novel GLP-1 (glucagon-like -peptide-1) analogues and insulin in the treatment for Alzheimer's disease and Other Neurodegenerative Diseases. CNS Drugs 29(12): 1023-1039.

83. Holscher C (2014) Central effects of GLP-1: new opportunities for treatments of neurodegenerative diseases. J Endocrinol 221(1): T31-T41.

84. Gejl M, Gjedde A, Egefjord L, Møller A, Hansen SB, et al. (2016) In Alzheimer's Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial. Front Aging Neurosci 8: 108.

85. M Dedge (2015) Type 1 Diabetes increases Dementia Risk. Neurology Reviews 23(9): 25.

86. Liora G Rodill, Paola Gilsanz, Charles P Quesenberry Jr, Alexander Dean, Geert Jan Biessels, et al. (2017) Acute Glycemic Events and Risk of Dementia in Older Patients with Type1 Diabetes. Alzheimer's & Dementia 13(7): P564.

87. Nilton Custodio, Rosa Montesinos, David Lira, Eder Herrera-Pérez, Yadira Bardales, et al. (2017) Mixed dementia: A review of the evidence. Dement Neuropsychol 11(4): 364-370.

88. Shurkin J (2018) Alzheimer's Drug Trials Keep Failing-It May Be Because We Don't Undrstand the Disease. Inside Science.

89. Murphy MP (2018) Amyloid-Beta Solubility in the Treatment of Alzheimer's Disease. N Engl J Med 378(4): 391-392.