Neurol Sci (2015) 36:1763–1769
DOI 10.1007/s10072-015-2352-5

REVIEW ARTICLE

Linking insulin with Alzheimer's disease: emergence as type III diabetes

Sara Ahmed[1] · Zahra Mahmood[1] · Saadia Zahid[1]

Received: 9 April 2015 / Accepted: 25 July 2015 / Published online: 7 August 2015

Abstract Alzheimer's disease (AD) has characteristic neuropathological abnormalities including regionalized neurodegeneration, neurofibrillary tangles, amyloid beta (Aβ) deposition, activation of pro-apoptotic genes, and oxidative stress. As the brain functions continue to disintegrate, there is a decline in person's cognitive abilities, memory, mood, spontaneity, and socializing behavior. A framework that sequentially interlinks all these phenomenons under one event is lacking. Accumulating evidence has indicated the role of insulin deficiency and insulin resistance as mediators of AD neurodegeneration. Herein, we reviewed the evidence stemming from the development of diabetes agent-induced AD animal model. Striking evidence has attributed loss of insulin receptor-bearing neurons to precede or accompany initial stage of AD. This state seems to progress with AD such that, in the terminal stages, it worsens and becomes global. Oxidative stress, tau hyperphosphorylation, APP-Aβ deposition, and impaired glucose and energy metabolism have all been linked to perturbation in insulin/IGF signaling. We conclude that AD could be referred to as "type 3 diabetes". Moreover, owing to common pathophysiology with diabetes common therapeutic regime could be effective for AD patients.

✉ Saadia Zahid
saadia.zahid@asab.nust.edu.pk; saadiazahid@hotmail.com

[1] Neurobiology Research Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan

Keywords Alzheimer's disease · Type 3 diabetes · Insulin signaling · Tau hyperphosphorylation · Acetylcholine · Anti-diabetics

Introduction

Alzheimer's disease (AD), an age-related, progressive neurodegenerative disorder, is the leading cause of dementia. It is characterized by two types of lesions; intracellular neurofibrillary tangles (NFT) and amyloid-β (Aβ) plaques [1]. These, together with elevated oxidative stress, synaptic loss, regionalized neuronal death, and brain atrophy have been observed in AD pathology [2]. In the past, efforts have been directed to interlink these abnormalities under a single primary pathogenic mechanism and several heavily debated hypotheses that exist trying to explain the underlying factor that trigger the development of AD brain pathology [3–5].

AD, often tagged as a heterogeneous disorder, implicates multiple aberrant signaling cascades in its pathogenesis. Insulin resistance is one such factor known to affect multiple cascades of known relevance to AD [6, 7]. De la Monte et al. reported cerebral insulin and Insulin-like growth factor (IGF) production. De la Monte et al. later observed that a common finding in AD was the impairments in energy metabolism and glucose utilization [8]. Insulin receptors (IRs), insulin, and IGF deficiency in AD brain further implicated insulin resistance in AD neuropathology [9, 10]. AD Braak stages have demonstrated an inversely proportional relationship to insulin expression. AD patients presented an 80 % decline in insulin receptors [8]. Insulin's ability to bind to its receptors was reportedly compromised. The decline in glucose processing was thought to coincide with, or even preceded, the early

stages of AD [11]. Moreover, Aβ pathology, impaired cholinergic system, tau hyperphosphorylation, pro-apoptotic and pro-inflammatory events have all also been attributed to impaired insulin signaling [12].

In a nut shell, evidence is growing to suggest impaired insulin signaling as the putative factor governing AD pathology hence favoring the conjecture of AD being a neuroendocrine disorder. Researchers thus concluded that perhaps Alzheimer's is a brain-specific type of diabetes which they termed as "type 3 diabetes" [8].

In the following review, we will provide a brief description about the role of insulin in brain and focus more closely on accumulating evidences implicating impaired insulin signaling in AD pathology. Finally we will discuss the potential of insulin targeting drugs in AD therapeutics.

Role of insulin in brain

The role of insulin in carbohydrate, lipid, and protein metabolism is already known [13]. Reflecting a major paradigm shift, hypothalamic actions of insulin in regulating energy homeostasis was reported [14]. This suggested insulin signaling in brain as well. IR localization in central nervous system (CNS), by ligand autoradiography was first documented by Havrankova et al. with later verification by immunohistochemistry and autoradiography [15]. Controversies still exist regarding the source of insulin in brain, where some claiming that insulin is of cerebral origin, it is however agreed upon that insulin plays a role in cerebral glucose utilization following its receptor-mediated transport across the blood brain barrier [16].

IR seems to be widely distributed with most of them concentrating the synapses of astrocytes and neurons. Cerebral regions such as hippocampus, amygdala, and septum have shown higher distribution of IR [17]. Intracellular pathways such as PI3K/AKT and ERK/MAP kinase pathways are reportedly activated via IR and IGF-1 receptors stimulation [17] thereby indicating broad impact of insulin signaling in the outside of the hypothalamus.

Hippocampus, with its abundant IR substrate (IRS) proteins regulates the acquisition and consolidation of memories thereby suggesting the role of insulin in memory potentiation [18]. In healthy adults, systemic infusion of insulin yielded a significant improvement in verbal memory and selective attention [19]. Insulin has been suggested to be neuroprotective and considered to have significant effects to enhance memory [20].

In accordance with this, AD patients have shown improvement in memory and performance following insulin administration [21]. Implication of causal impaired insulin signaling in stroke, AD, and Parkinson disease [22] has made it necessary to find the putative proteins that trigger these neurological disorders [23]. IRS-1, a putative target of known relevance to proper brain function, is found to be inhibited in AD brains [24].

Insulin-mediated AD pathology

Insulin receptor deficiency and aberrant insulin signaling in AD was first reported by Frolich and colleagues [25]. Their results were further strengthened when cerebrospinal fluid (CSF) of AD and mild cognitive impairment (MCI) patients showed reduced levels of insulin [4]. Reduced levels of insulin and IGF-1 polypeptide and receptor genes have been linked to advanced stage AD. It was observed that AD brains presented perturbed insulin and IGF-1-mediated neuronal development and mitochondrial dysfunction [26]. Evidence has suggested neurodegeneration of insulin and IGF-1 receptor-bearing neurons to precede or accompany initial stage of AD [11, 27]. This insulin-mediated neurodegeneration progresses with AD such that, in the later stages, it becomes global [26].

Role of insulin has also been suggested in the development of AD pathology markers [28]. The regulation of tau phosphorylation, one of the characteristic hallmarks of AD [29], is demonstrated to be governed by β-*N*-acetylglucosamine (GlcNAc)-mediated *O*-GlcNAcylation which inversely affects tau phosphorylation. Impaired glucose metabolism, one of the features of AD, has been linked with down regulation of *O*-GlcNAcylation consequently leading to tau hyperphosphorylation [30]. Furthermore, due to insulin deficiency, glycogen synthase kinase (GSK-3) remains inactivated (unphosphorylated), thereby leading to tau hyperphosphorylation, as shown in Fig. 1 [31]. Duration of diabetes has been demonstrated to positively correlate with neuritic plaques [32].

Acetylcholine deficiency has long been recognized as an early irregularity in AD [33] which has now also been linked to insulin resistance [12]. Acetylcholine transferase (ChAT), involved in Ach synthesis is expressed in insulin and IGF-I receptor-positive cortical neurons [34]. Insulin deficiency and resistance have been linked to decreased ACh level owing to underlying reduced ChAT expression [35]. Reduced ChAT co-localization has been documented in insulin receptor-bearing neurons of AD patients [26]. Hippocampi of non-diabetic AD patients have shown an increase in the levels of peripheral insulin resistance biomarkers [36]. This established a link between aberrant insulin signaling and dementia [34, 37]. In this regard anti-diabetic agents-mediated prevention of hypoglycemic events can be a potential strategy to reduce cognitive decline and dementia [38].

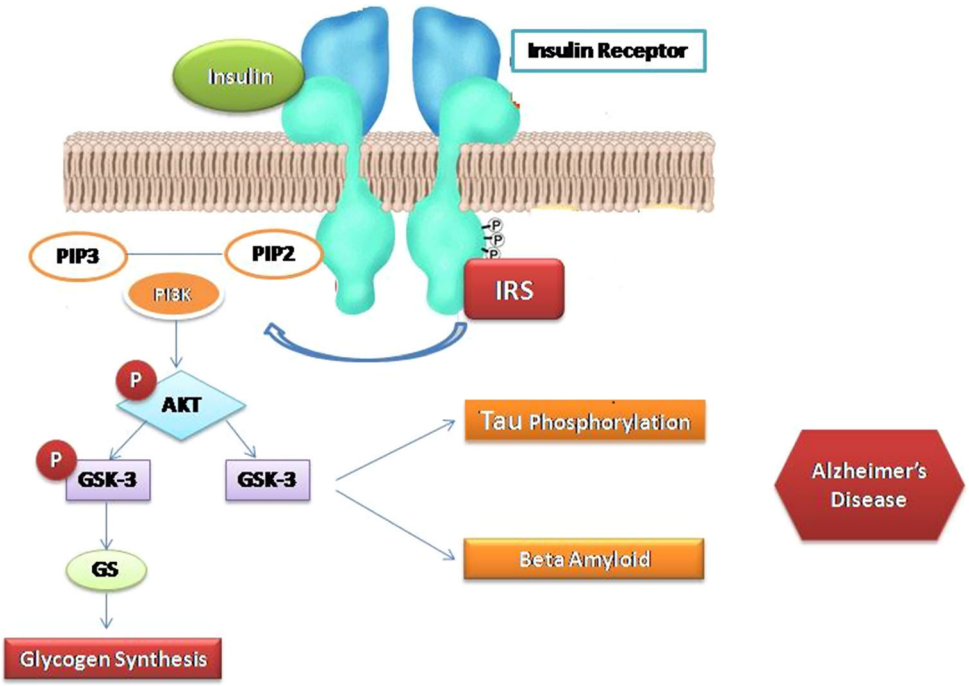

Fig. 1 Insulin receptor signaling. Insulin binds to and activates the membrane-bound insulin receptor (IR) tyrosine kinase, which consists of two α-subunits and two β-subunits forming an α2β2 heterotetramer. Receptor autophosphorylation and subsequent phosphorylation of IRS activates PI3K. PI3K further activates GSK-3 hence leading to glycogen synthesis. During conditions of insufficient insulin, GSK-3 remains inactivated. Unphosphorylated GSK-3 leads to tau phosphorylation and Aβ accumulation, the characteristic hallmarks of AD

Impairment in energy metabolism with attendant increased oxidative stress and cognitive deterioration may be due to perturbation in the insulin/IGF signaling [39] where progressive brain insulin/IGF resistance tends to increase the expression of cerebral inflammatory mediators in AD. Aberrant insulin/IGF signaling-mediated increased oxidative stress and mitochondrial dysfunction enhance the APP gene expression level while APP-Aβ deposition-mediated neurotoxicity further positively regulates oxidative stress-induced APP-Aβ deposition [8] (Fig. 2).

Evidences regarding underlying shared cascade that governs both AD and diabetes have extensively been reviewed [40, 41]. Impaired insulin signaling and inflammation appear to be shared processes in diabetes mellitus (DM) and AD. It was hence inferred that events analogous to those that result in peripheral insulin resistance in type 2 diabetes mellitus (T2DM) likely underlie aberrant insulin signaling in AD.

In T2DM, c-Jun N-terminal kinase (JNK) pathway is stimulated by TNF-α cascade [42] thereby initiating peripheral insulin resistance [43]. Likewise, in cultured hippocampal neurons and AD mouse models Aβ oligomers via activating the TNF-α/JNK pathway causes IRS-1 inhibition [44–46]. Following intracerebroventricular (i.c.v.) administration of Aβ oligomers, hippocampi of cynomolgus monkeys showed JNK activation and IRS-1 inhibition. Likewise, elevated IRS-1pSer and activated JNK levels have been reported in AD brains following postmortem analysis [36, 45]. Oligomer-mediated internalization of neuronal IRs [43] may facilitate IRS-1pSer following IR displacement from the cell surface. Insulin prevents both, Aβ oligomers-induced IR downregulation [47] and IRS-1pSer [45].

Insoluble Aβ fibrils, generated by self-association of Aβ in AD brains [48] were initially thought to cause neuronal loss (hence, memory loss). Overwhelming evidence in recent past has however indicated otherwise. Of clinical relevance, MCI-negative individuals presented brain Aβ deposition while, conversely, individuals displaying cognitive deterioration lacked Aβ load [49]. Moreover, it was suggested that synapse loss rather than amyloid burden, is the best correlate of the extent of dementia [50]. This led to the conclusion that a factor other than fibrillar Aβ mediates synapse and cognitive impairment.

Lambert and coworkers demonstrated that Aβ self-aggregation forms neurotoxic-soluble oligomers. These oligomers are not easily observed in pathological examination [51]. AD hippocampi analysis also revealed the presence of oligomers at the postsynapse [52]. Increased levels of Aβ oligomers were reported in CSF and AD brains [53, 54]. It was hypothesized that synapse failure and neuronal dysfunction are primarily mediated by Aβ oligomers [55, 56]. NMDA- and AMPA-type glutamate receptors, involved in synaptic plasticity [57, 58], upon oligomer exposure, are removed from the cell surface indicating a broad impact of oligomers on synapses. Oligomers; also implicated in AD-associated neuropathology, activates the signaling pathways that lead to abnormal tau phosphorylation [59] and oxidative stress [60]. Aβ oligomers, therefore, through altered neuronal IR function, mediates synaptic

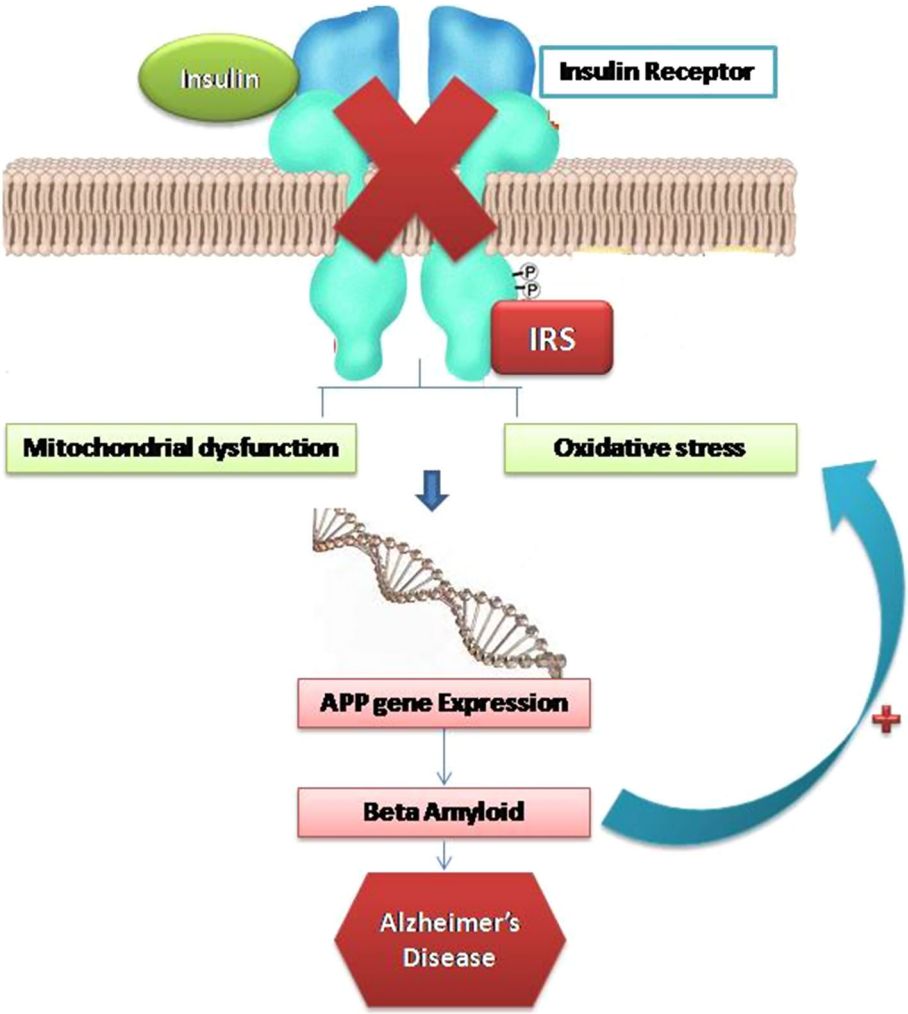

Fig. 2 Developmental profile of AD pathology. The schematic illustration depicts perturbed insulin signaling resulting in oxidative stress and mitochondrial dysfunction. Oxidative stress and attendant mitochondrial dysfunction further lead to APP gene expression and consequent APP-Aβ deposition. APP-Aβ deposition positively regulates the oxidative stress-mediated APP-Aβ deposition

dysfunction and neuronal pathology. This provides a basis for brain insulin resistance in AD and is likely connected to impaired learning and memory in disease.

Defective insulin signaling seems to be intimately linked to Aβ oligomers. The first evidence demonstrated that Aβ oligomers bind to hippocampal neurons thereby displacing IRs from the plasma membrane [43, 47]. This was subsequently verified in AD brains [9, 61]. Elevated IR levels in cell bodies of neurons with oligomers attached to their surface suggested a subcellular redistribution of IRs [62]. This redistribution and internalization of IRs mediates decreased responsiveness to insulin. The latter has been revealed by impaired insulin-induced receptor protein tyrosine kinase activity in oligomer-exposed cultured neurons [43].

Evidence of insulin resistance in AD

From the past couple of decades, evidence is being gathered by producing diabetes agent-induced experimental AD animal models. In spite of several factors known to trigger AD, overwhelming evidence suggests involvement of cerebral insulin/IGF resistance in MCI, dementia, and AD [37, 63–65]. Cerebral insulin, agreed to be of pancreatic origin, is known to modulate synaptic plasticity that regulates learning and memory. It has been shown to induce memory consolidation, retrieval and extinction of contextual memory via phosphatidylinositol 3-kinase (PI3K) pathway [31]. AD association with increasing brain insulin resistance in the absence of T2DM, indicates primary impaired insulin signaling [9, 37, 64].

Cognitive impairment in rats following i.c.v. injections of streptozotocin (STZ), with deficits in spatial memory, insulin resistance, and insulin deficiency further consolidates the hypothesis of AD being a type 3 diabetes [66]. AD hallmarks, including tau hyperphosphorylation, APP-Aβ deposition, and decreased neuronal survival have been recapitulated by STZ. Downstream effects of STZ-induced impaired insulin and IGF signaling in the CNS could be responsible for this. Craft et al. have suggested that progressive insulin resistance, accompanied by reduced cerebral glucose metabolism and subtle cognitive impairments

at initial AD stages, may serve as a marker of AD even before the onset of MCI [6].

Results from i.c.v. injection of STZ have demonstrated reduced glucose metabolism, oxidative stress, IR dysfunction, and cognitive impairment [67]. Reduced expression of insulin and IR encoding genes has been linked to STZ. Striking evidence of STZ-induced brain atrophy, increased tau phosphorylation, and APP-Aβ deposition was demonstrated by De la Monta et al. [68].

Moreover, low-dose nitrosamines exposure has been shown to induce cognitive impairment, AD-type neurodegeneration, and brain insulin resistance [69], similar to the effects of STZ. This may account for progressive increase in sporadic AD (Type 3 diabetes) prevalence rates, since environmental exposures such as nitrosamines that contaminate highly processed and preserved foods and have become staples in our diets [65]. Studies on Tg2576 have linked increased APP-Aβ aggregation to diet-induced insulin resistance [70]. This increased APP production coincides with increased amyloid load and poor performance in spatial water maize task [71]. These findings establish that cerebral insulin signaling is perturbed in rodent and non-human primate AD models, by mechanisms similar to those, governing insulin resistance in DM.

Anti-diabetics—a promising solution for AD patients

Alzheimer's disease pathology, recapitulated by treatment with diabetes agents led to the hypothesis that AD pathology and cognitive deterioration could be reduced by treatment regime involving anti-diabetic agents such as peroxisome proliferator-activated receptor (PPAR) agonists [68]. PPARγ, a neuromodulator, has been implicated in the pathogenesis of both DM and AD. PPARγ agonists, thiazolidinediones, have been shown to improve insulin resistance. Treatment with rosiglitazone yielded positive relation between insulin levels and cognition as compared with placebo. This was proved by the fact that IR expression and binding were significantly enhanced by the PPAR-agonist treatment [72].

Intranasal insulin administration exhibited improvement in memory [73] and attention on the 21st day of treatment. Likewise, Exendin-4 has been documented to activate pathways common to insulin signaling via glucagon-like peptide 1 (GLP-1) receptor simulation. This in turn has shown to block insulin signaling impairment in hippocampal cultures [45]. Exendin-4 in transgenic (Tg) mice thus reverses insulin-mediated AD pathology and cognitive improvement [74]. These results reflect paradigm shift regarding AD pathogenesis, i.e., AD is mediated by perturbed insulin signaling owing to underlying insulin resistance and insulin deficiency in the brain.

Conclusion

Initially thought to be an independent disorder, DM and AD, seemingly have shared pathophysiological mechanisms. Positive results stemming from the results of (a) development of animal model with diabetes agent-induced insulin-resistant brain state accompanied by cognitive impairment, (b) anti-diabetes agent-induced reversal of insulin signaling-associated neurodegenerative effects suggest AD to be a neuroendocrine disorder.

Insulin and IGF signaling impairment, with attendant inflammatory mediators, oxidative stress, and impaired mitochondrial function contribute to AD-associated neurodegeneration. Owing to common underlying pathological cascade governing AD and DM, AD could be rightfully referred to as Type 3 diabetes thereby indicating that common therapeutic intervention could be effective. Currently a number of clinical trials based on testing effectiveness of anti-diabetic drugs against Alzheimer's are being conducted. The results, if positive, would pave ways for potential new pharmacotherapy for AD patients.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest pertaining to this review.

References

1. Selkoe DJ (2001) Alzheimer's disease: genes, proteins, and therapy. Physiol Rev 81:741–766
2. Ashe KH, Zahs KR (2010) Probing the biology of Alzheimer's disease in mice. Neuron 66:631–645
3. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 29:353–356
4. Gil-Bea FJ, Solas M, Solomon A, Mugueta C, Winblad B, Kivipelto M et al (2010) Insulin levels are decreased in the cerebrospinal fluid of women with prodomal Alzheimers disease. J Alzheimers Dis 22:405–413
5. Markesbery WR (1997) Oxidative stress hypothesis in Alzheimer's disease. Free Radic Biol Med 23:134–147
6. Craft S, Cholerton B, Baker LD (2013) Insulin and Alzheimer's disease: untangling the web. J Alzheimers Dis 33:S263–S275
7. Zhu X, Perry G, Smith MA (2005) Insulin signaling, diabetes mellitus and risk of Alzheimer disease. J Alzheimers Dis 7:81–84
8. de la Monte SM, Wands JR (2005) 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 7:45–61
9. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R 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 7:63–80
10. Craft S (2012) Alzheimer disease: insulin resistance and AD—extending the translational path. Nat Rev Neurol 8:360–362
11. Iwangoff P, Armbruster R, Enz A, Meier-Ruge W (1980) Glycolytic enzymes from human autoptic brain cortex: normal aged and demented cases. Mech Ageing Dev 14:203–209

12. Schiöth HB, Craft S, Brooks SJ, Frey WH II, Benedict C (2012) Brain insulin signaling and Alzheimer's disease: current evidence and future directions. Mol Neurobiol 46:4–10
13. Havel PJ (2004) Update on adipocyte hormones regulation of energy balance and carbohydrate/lipid metabolism. Diabetes 53:S143–S151
14. Schwartz MW, Figlewicz DP, Baskin DG, Woods SC, Porte D Jr (1992) Insulin in the brain: a hormonal regulator of energy balance. Endocr Rev 13:387–414
15. Havrankova J, Roth J, Brownstein M (1978) Insulin receptors are widely distributed in the central nervous system of the rat. Nature 272:827–829
16. Margolis RU, Altszuler N (1967) Insulin in the cerebrospinal fluid. Nature 215:1375–1376
17. Boura-Halfon S, Zick Y (2009) Phosphorylation of IRS proteins, insulin action, and insulin resistance. Am J Physiol Endocrinol Metab 296:E581–E591
18. Zhao W-Q, Alkon DL (2001) Role of insulin and insulin receptor in learning and memory. Mol Cell Endocrinol 177:125–134
19. Kern W, Peters A, Fruehwald-Schultes B, Deininger E, Born J, Fehm HL (2001) Improving influence of insulin on cognitive functions in humans. Neuroendocrinology 74:270–280
20. Nelson TJ, Sun M-K, Hongpaisan J, Alkon DL (2008) Insulin, PKC signaling pathways and synaptic remodeling during memory storage and neuronal repair. Eur J Pharmacol 585:76–87
21. Benedict C, Hallschmid M, Schmitz K, Schultes B, Ratter F, Fehm HL et al (2006) Intranasal insulin improves memory in humans: superiority of insulin aspart. Neuropsychopharmacology 32:239–243
22. Prolla TA, Mattson MP (2001) Molecular mechanisms of brain aging and neurodegenerative disorders: lessons from dietary restriction. Trends Neurosci 24:21–31
23. Schubert M, Gautam D, Surjo D, Ueki K, Baudler S, Schubert D et al (2004) Role for neuronal insulin resistance in neurodegenerative diseases. Proc Natl Acad Sci USA 101:3100–3105
24. Watson G, Craft S (2004) Modulation of memory by insulin and glucose: neuropsychological observations in Alzheimer's disease. Eur J Pharmacol 490:97–113
25. Frölich L, Blum-Degen D, Bernstein H-G, Engelsberger S, Humrich J, Laufer S et al (1998) Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neural Transm 105:423–438
26. Suzanne M, Wands JR (2008) Alzheimer's disease is type 3 diabetes—evidence reviewed. J Diabetes Sci Technol 2:1101–1113
27. Hoyer S (2004) Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol 490:115–125
28. Cole GM, Frautschy SA (2007) The role of insulin and neurotrophic factor signaling in brain aging and Alzheimer's Disease. Exp Gerontol 42:10–21
29. Liu X, Erikson C, Brun A (1996) Cortical synaptic changes and gliosis in normal aging, Alzheimer's disease and frontal lobe degeneration. Dementia 7:128–134
30. Liu F, Iqbal K, Grundke-Iqbal I, Hart GW, Gong C-X (2004) O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease. Proc Natl Acad Sci USA 101:10804–10809
31. Watson GS, Craft S (2003) The role of insulin resistance in the pathogenesis of Alzheimer's disease. CNS Drugs 17:27–45
32. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC (2004) Increased risk of type 2 diabetes in Alzheimer disease. Diabetes 53:474–481
33. Tabet N (2006) Acetylcholinesterase inhibitors for Alzheimer's disease: anti-inflammatories in acetylcholine clothing! Age Ageing 35:336–338
34. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB (2011) Diabetes mellitus and Alzheimer's disease: shared pathology and treatment? Br J Clin Pharmacol 71:365–376
35. De la Monte S, Chen G, Rivera E, Wands J (2003) Neuronal thread protein regulation and interaction with microtubule-associated proteins in SH-Sy5y neuronal cells. Cell Mol Life Sci 60:2679–2691
36. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A 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 122:1316–1338
37. Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM (2005) 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 8:247–268
38. Alagiakrishnan K, Sankaralingam S, Ghosh M, Mereu L, Senior P (2013) Antidiabetic drugs and their potential role in treating mild cognitive impairment and Alzheimer's disease. Discov Med 16:277–286
39. Correia SC, Santos RX, Perry G, Zhu X, Moreira PI, Smith MA (2011) Insulin-resistant brain state: the culprit in sporadic Alzheimer's disease? Ageing Res Rev 10:264–273
40. Li L, Hölscher C (2007) Common pathological processes in Alzheimer disease and type 2 diabetes: a review. Brain Res Rev 56:384–402
41. Valente T, Gella A, Fernàndez-Busquets X, Unzeta M, Durany N (2010) Immunohistochemical analysis of human brain suggests pathological synergism of Alzheimer's disease and diabetes mellitus. Neurobiol Dis 37:67–76
42. Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, Maeda K et al (2002) A central role for JNK in obesity and insulin resistance. Nature 420:333–336
43. Zhao W-Q, De Felice FG, Fernandez S, Chen H, Lambert MP, Quon MJ et al (2008) Amyloid beta oligomers induce impairment of neuronal insulin receptors. FASEB J 22:246–260
44. Ma Q-L, Yang F, Rosario ER, Ubeda OJ, Beech W, Gant DJ et al (2009) β-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 29:9078–9089
45. Bomfim TR, Forny-Germano L, Sathler LB, Brito-Moreira J, Houzel J-C, Decker H et al (2012) An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease–associated Aβ oligomers. J Clin Invest 122:1339–1353
46. Lourenco MV, Clarke JR, Frozza RL, Bomfim TR, Forny-Germano L, Batista AF et al (2013) TNF-α mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's β-amyloid oligomers in mice and monkeys. Cell Metab 18:831–843
47. De Felice FG, Vieira MN, Bomfim TR, Decker H, Velasco PT, Lambert MP et al (2009) Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Aβ oligomers. Proc Natl Acad Sci 106:1971–1976
48. Walsh DM, Selkoe DJ (2007) Aβ oligomers—a decade of discovery. J Neurochem 101:1172–1184
49. Negash S, Bennett DA, Wilson RS, Schneider JA, Arnold SE (2011) Cognition and neuropathology in aging: multidimensional perspectives from the Rush Religious Orders Study and Rush Memory and Aging Project. Curr Alzheimer Res 8:336
50. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R et al (1991) Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 30:572–580

51. Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, Liosatos M et al (1998) Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. Proc Natl Acad Sci USA 95:6448–6453
52. Bjorklund NL, Reese LC, Sadagoparamanujam V, Ghirardi V, Woltjer RL, Taglialatela G (2012) Absence of amyloid beta oligomers at the postsynapse and regulated synaptic Zn^{2+} in cognitively intact aged individuals with Alzheimer's disease neuropathology. Mol Neurodegener 7:23
53. Gong Y, Chang L, Viola KL, Lacor PN, Lambert MP, Finch CE et al (2003) Alzheimer's disease-affected brain: presence of oligomeric Aβ ligands (ADDLs) suggests a molecular basis for reversible memory loss. Proc Natl Acad Sci 100:10417–10422
54. Fukumoto H, Tokuda T, Kasai T, Ishigami N, Hidaka H, Kondo M et al (2010) High-molecular-weight beta-amyloid oligomers are elevated in cerebrospinal fluid of Alzheimer patients. FASEB J 24:2716–2726
55. Ferreira ST, Vieira MN, De Felice FG (2007) Soluble protein oligomers as emerging toxins in Alzheimer's and other amyloid diseases. IUBMB Life 59:332–345
56. Haass C, Selkoe DJ (2007) Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. Nat Rev Mol Cell Biol 8:101–112
57. Lacor PN, Buniel MC, Furlow PW, Clemente AS, Velasco PT, Wood M et al (2007) Aβ oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. J Neurosci 27:796–807
58. Jurgensen S, Antonio LL, Mussi GE, Brito-Moreira J, Bomfim TR, De Felice FG et al (2011) Activation of D1/D5 dopamine receptors protects neurons from synapse dysfunction induced by amyloid-beta oligomers. J Biol Chem 286:3270–3276
59. De Felice FG, Wu D, Lambert MP, Fernandez SJ, Velasco PT, Lacor PN et al (2008) Alzheimer's disease-type neuronal tau hyperphosphorylation induced by Aβ oligomers. Neurobiol Aging 29:1334–1347
60. De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST et al (2007) Aβ oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. J Biol Chem 282:11590–11601
61. Moloney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R, O'Neill C (2010) Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. Neurobiol Aging 31:224–243
62. Klein WL, Krafft GA, Zhao W-Q (2011) Compositions and methods for the enhancement of soluble amyloid beta oligomer (ADDL) uptake and clearance. Google Patents
63. Craft S (2006) Insulin resistance syndrome and Alzheimer disease: pathophysiologic mechanisms and therapeutic implications. Alzheimer Dis Assoc Disord 20:298–301
64. de la Monte SM, Longato L, Tong M, Wands JR (2009) Insulin resistance and neurodegeneration: roles of obesity, type 2 diabetes mellitus and non-alcoholic steatohepatitis. Curr Opin Investig Drugs 10:1049–1060
65. de la Monte SM, Tong M (2009) Mechanisms of nitrosamine-mediated neurodegeneration: potential relevance to sporadic Alzheimer's disease. J Alzheimers Dis 17:817–825
66. Lester-Coll N, Rivera EJ, Soscia SJ, Doiron K, Wands JR, de la Monte SM (2006) Intracerebral streptozotocin model of type 3 diabetes: relevance to sporadic Alzheimer's disease. J Alzheimers Dis 9:13–33
67. Duelli R, Schröck H, Kuschinsky W, Hoyer S (1994) Intracerebroventricular injection of streptozotocin induces discrete local changes in cerebral glucose utilization in rats. Int J Dev Neurosci 12:737–743
68. de la Monte SM, Tong M, Lester-Coll N, Plater J, Michael Wands JR (2006) Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. J Alzheimers Dis 10:89–109
69. Tong M, Longato L, de la Monte SM (2010) Early limited nitrosamine exposures exacerbate high fat diet-mediated type 2 diabetes and neurodegeneration. BMC Endocr Disord 10:4
70. Ho L, Qin W, Pompl PN, Xiang Z, Wang J, Zhao Z et al (2004) Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. FASEB J 18:902–904
71. Gallagher J, Minogue A, Lynch M (2012) Impaired performance of female APP/PS1 mice in the Morris water maze is coupled with increased Aβ accumulation and microglial activation. Neurodegener Dis 11:33–41
72. Watson G, Bernhardt T, Reger MA, Cholerton BA, Baker LD, Peskind ER et al (2006) Insulin effects on CSF norepinephrine and cognition in Alzheimer's disease. Neurobiol Aging 27:38–41
73. Reger M, Watson G, Green P, Wilkinson C, Baker L, Cholerton B et al (2008) Intranasal insulin improves cognition and modulates β-amyloid in early AD. Neurology 70:440–448
74. Li Y, Duffy KB, Ottinger MA, Ray B, Bailey JA, Holloway HW et al (2010) GLP-1 receptor stimulation reduces amyloid-β peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer's disease. J Alzheimers Dis 19:1205–1219