HHS Public Access

Author manuscript

Eur Neuropsychopharmacol. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

Eur Neuropsychopharmacol. 2014 December ; 24(12): 1954–1960. doi:10.1016/j.euroneuro.2014.06.008.

Type 3 Diabetes is Sporadic Alzheimer's disease: Mini-Review

Suzanne M. de la Monte

Departments of Medicine, Pathology, Neurology, and Neurosurgery, Rhode Island Hospital and the Warren Alpert Medical School of Brown University, Providence, RI

Abstract

Alzheimer's disease (AD) is the most common cause of dementia in North America. Growing evidence supports the concept that AD is a metabolic disease mediated by impairments in brain insulin responsiveness, glucose utilization, and energy metabolism, which lead to increased oxidative stress, inflammation, and worsening of insulin resistance. In addition, metabolic derangements directly contribute to the structural, functional, molecular, and biochemical abnormalities that characterize AD, including neuronal loss, synaptic disconnection, tau hyperphosphorylation, and amyloid-beta accumulation. Because the fundamental abnormalities in AD represent effects of brain insulin resistance and deficiency, and the molecular and biochemical consequences overlap with Type 1 and Type 2 diabetes, we suggest the term 'Type 3 diabetes' to account for the underlying abnormalities associated with AD-type neurodegeneration. In light of the rapid increases in sporadic AD prevalence rates and vastly expanded use of nitrites and nitrates in foods and agricultural products over the past 30–40 years, the potential role of nitrosamine exposures as mediators of Type 3 diabetes is discussed.

Key terms

Insulin resistance; diabetes; glucose metabolism; Alzheimer's; nitrosamines

Alzheimer's disease and brain glucose starvation

Sporadic Alzheimer's disease (AD) is the most common cause of dementia in North America and its high incidence and prevalence rates now constitute an epidemic (de la Monte et al., 2009b). AD diagnosis is based on criteria set by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) and DSM-IV criteria (Cummings, 2007). Although neuroimaging and biomarker panels are beginning to facilitate its detection and severity (Gustaw-Rothenberg et al., 2010), a definitive diagnosis can only be rendered

Address correspondence to: Dr. S. M. de la Monte, Rhode Island Hospital, 55 Claverick Street, Room 419, Providence, RI. 02903 Telephone: 401-444-7364; Fax: 401-444-2939; Suzanne_DeLaMonte_MD@Brown.edu.

No conflict of interest to declare

by postmortem examination of the brain. AD presence and severity are gauged by the distribution and abundance of related and characteristic lesions, including neuronal loss, gliosis, insoluble aggregates of abnormally phosphorylated and ubiquitinated tau in the forms of neurofibrillary tangles, dystrophic neurites and neuropil threads, and neurotoxic amyloid-beta precursor protein peptides (AβPP-Aβ) as oligomers, fibrillar aggregates, or extracellular plaques. Secreted AβPP-Aβ oligomers are neurotoxic and inhibit synaptic plasticity (Walsh et al., 2002). Beyond these effects, AD is associated with degeneration and disconnection of synaptic terminals, disruption of the cortical laminar architecture, neuro-inflammation, and white matter fiber loss.

For decades, the dominant hypothesis was that neurodegeneration is caused by one or two of the specific lesions that characterize AD, e.g. AβPP-Aβ accumulation, pTau aggregation, or neuro-inflammation. However, a stream of human and experimental studies has provided convincing evidence that AD is a metabolic disease whereby the brain loses its capacity to efficiently utilize glucose for energy production and respond to critical trophic factor signals due to insulin as well as insulin-like growth factor (IGF) resistance (Baker et al., 2010; Craft, 2007; Hoyer, 2002, 2004b; Krikorian et al., 2010; Luchsinger, 2010; Neumann et al., 2008; Rivera et al., 2005; Schubert et al., 2004; Steen et al., 2005; Talbot et al., 2012; Watson and Craft, 2006). The molecular and biochemical consequences of insulin and IGF resistance in the brain are similar to those in other organs and tissues; however, in brain, insulin signaling impairments compromise neuronal survival, energy production, gene expression, plasticity and white matter integrity (de la Monte, 2011; de la Monte et al., 2009a). Since glucose is the primary fuel for the brain, deficits in glucose uptake and utilization cause the brain to “starve”. With the starvation comes oxidative stress, impairments in homeostasis, and increased cell death. Inhibition of insulin/IGF signaling mediates AD neurodegeneration due to increased: 1) activity of kinases that aberrantly phosphorylate tau; 2) accumulation of AβPP-Aβ; 3) oxidative and endoplasmic reticulum (ER) stress; 4) generation of reactive oxygen and reactive nitrogen species that damage proteins, RNA, DNA, and lipids; 5) mitochondrial dysfunction; and 6) signaling through pro-inflammatory and pro-apoptosis cascades (de la Monte, 2011, 2012; de la Monte et al., 2009a; de la Monte et al., 2012). In addition, insulin resistance down-regulates target genes needed for cholinergic function, further compromising neuronal plasticity, memory, and cognition (de la Monte, 2011; de la Monte et al., 2009a).

Insulin and IGF Actions in the Brain

In the central nervous system (CNS), insulin and IGF signaling pathways play critical roles in cognitive function. Insulin, IGF-1 and IGF-2 polypeptide and receptor genes are expressed in neurons (de la Monte and Wands, 2005) and glial cells (Broughton et al., 2007; Freude et al., 2009; Zeger et al., 2007) throughout the brain; their highest levels are in structures that are heavily targeted by neurodegeneration, particularly AD (de la Monte et al., 2009a; de la Monte and Wands, 2005). Insulin and IGFs regulate a wide range of neuronal functions through ligand-receptor binding and activation of intrinsic receptor tyrosine kinases. Subsequent interactions between phosphorylated receptors and insulin receptor substrate molecules mediate transmission of signals downstream, and thereby inhibit apoptosis, and stimulate growth, survival, metabolism, and plasticity (de la Monte et

al., 2009a; de la Monte and Wands, 2005). The anti-apoptosis mechanisms that insulin/IGF-1 inhibit include BAD (inhibitor of Bcl-2), Forkhead Box O (FoxO), glycogen synthase kinase 3β (GSK-3β), and nuclear factor kappa B (NF-κB) (de la Monte et al., 2009a). GSK-3β regulates Wnt signaling by phosphorylating β-catenin, leading to its degradation via the ubiquitin-proteasome pathway (Cadigan and Liu, 2006; Foltz et al., 2002). Since Wnt mediates synaptic plasticity (Contestabile et al., 2013; Tabatadze et al., 2012; Varela-Nallar and Inestrosa, 2013), impairments in insulin/IGF signaling compromise cross-talk with various Wnt functions in the brain. In essence, insulin/IGF pathways support neuronal growth, survival, differentiation, migration, energy metabolism, gene expression, protein synthesis, cytoskeletal assembly, synapse formation, neurotransmitter function, and plasticity (Chesik et al., 2008; de la Monte and Wands, 2005; Gong et al., 2008; Liang et al., 2007). Correspondingly, impaired insulin/IGF signaling has dire effects on the CNS's structural and functional integrity.

Evidence of Type 3 Diabetes (Brain Insulin and IGF Resistance and Deficiency) in AD

The concept that AD represents a metabolic disease stemmed from studies showing that deficits cerebral glucose utilization were present very early in the course of disease (Caselli et al., 2008; Langbaum et al., 2010; Mosconi et al., 2009; Mosconi et al., 2008), either prior to, or coincident with the initial stages of cognitive dysfunction (Hoyer, 2004a; Iwangoff et al., 1980). Deficits in cerebral glucose utilization and energy metabolism worsen with progression of cognitive impairment (Hoyer et al., 1991). Furthermore, human postmortem studies revealed that brains from clinically well-characterized patients with pathologically proven AD have molecular and biochemical evidence of insulin and IGF resistance and deficiencies, as well as impairments in signal transduction (Rivera et al., 2005; Steen et al., 2005).

Brain insulin/IGF resistance is manifested by reduced levels of insulin/IGF receptor binding and decreased responsiveness to insulin/IGF stimulation (Rivera et al., 2005; Steen et al., 2005; Talbot et al., 2012), while insulin/IGF deficiencies are associated with altered expression of insulin and IGF polypeptides in brain and cerebrospinal fluid (Hoyer, 2004a, b; Rivera et al., 2005; Steen et al., 2005). These findings support the concept that chronic deficits in insulin signaling mediate the pathogenesis of AD (Steen et al., 2005). Moreover, AD could be regarded as a brain disorder that has composite features of Type 1 (insulin deficiency) and Type 2 (insulin resistance) diabetes. To consolidate this concept, we proposed that AD be referred to as, "Type 3 diabetes" (Rivera et al., 2005; Steen et al., 2005). As insulin stimulates brain glucose uptake and utilization (de la Monte and Wands, 2005), metabolism, memory, and cognition (Benedict et al., 2004; Craft et al., 2003; Krikorian et al., 2010; Reger et al., 2006; Reger et al., 2008), insulin resistance/deficiency associated impairments in glucose metabolism disrupt brain energy balance, increasing oxidative stress, reactive oxygen species (ROS) production, DNA damage, and mitochondrial dysfunction, all of which drive pro-apoptosis, pro-inflammatory, and pro-AβPP-Aβ cascades (de la Monte et al., 2009a; de la Monte and Wands, 2005). Correspondingly, experimental depletion or suppression of brain insulin receptor expression

and function causes cognitive impairment and molecular and biochemical abnormalities seen in AD (de la Monte et al., 2011; Grunblatt et al., 2007; Hoyer et al., 2000; Labak et al., 2010; Lester-Coll et al., 2006).

Role of Insulin/IGF resistance in Brain Metabolic Dysfunction and Oxidative Stress in AD

Insulin and IGF signaling regulate glucose utilization, metabolism, and ATP synthesis needed for both homeostasis and dynamic modulation of cellular functions (de la Monte and Wands, 2005; Frolich et al., 1998). Consequently, brain insulin/IGF resistance and deficiency are accompanied by impairments in glucose utilization and disruption of energy metabolism, with attendant increases in oxidative stress, ROS production, DNA damage, and mitochondrial dysfunction, all of which drive pro-apoptosis, pro-inflammatory, and pro-AβPP-Aβ cascades (de la Monte and Wands, 2006; Frolich et al., 1998; Hoyer, 2002, 2004b; Rivera et al., 2005; Steen et al., 2005). Moreover, as AD progresses, cerebral glucose utilization, responses to insulin signaling, and expression of insulin-responsive genes decline (Rivera et al., 2005; Talbot et al., 2012). Correspondingly, experimental depletion or suppression of brain insulin receptor expression and function causes cognitive impairment and AD-type neurodegeneration (de la Monte et al., 2011; Grunblatt et al., 2007; Hoyer et al., 2000; Labak et al., 2010; Lannert and Hoyer, 1998; Lester-Coll et al., 2006).

Brain glucose uptake and utilization are mediated by glucose transporter (GLUT) proteins, whose expression and function are regulated by insulin. GLUT4 is abundantly expressed along with insulin receptors, in medial temporal structures, which are notable targets of AD. Insulin stimulates GLUT4 expression and protein trafficking from the cytosol to the plasma membrane to modulate glucose uptake and utilization (Gonzalez-Sanchez and Serrano-Rios, 2007). Therefore, insulin stimulation of GLUT4 is critical for regulating neuronal metabolism and energy production which are needed for memory and cognition. Despite evidence for brain insulin resistance and deficiency in AD, postmortem brain studies have not detected reduced levels of GLUT4 expression (Steen et al., 2005). Instead, the well-documented deficits in brain glucose utilization and energy metabolism vis-a-vis brain insulin/IGF resistance could be mediated by impairments in GLUT4 trafficking between the cytosol and plasma membrane (Winocur et al., 2005).

Deficiencies in energy metabolism caused by inhibition of insulin/IGF signaling promote oxidative stress, mitochondrial dysfunction, and pro-inflammatory cytokine activation (de la Monte and Wands, 2002; Hoyer and Lannert, 1999; Hoyer et al., 2000). Oxidative stress leads to the generation and accumulation of ROS and reactive nitrogen species, which attack subcellular organelles and cause chemical modifications of DNA, RNA, lipids, and proteins. For example, adducts formed with macromolecules can compromise the structural and functional integrity of neurons due to loss of membrane functions, disruption of the cytoskeleton, dystrophy of synaptic terminals, deficits in neurotransmitter functions and plasticity, and perturbation of signaling pathways for energy metabolism, homeostasis, and cell survival.

Impaired insulin/IGF signaling and tau pathology in AD

Neurofibrillary tangles and dystrophic neurites are the main neuronal cytoskeletal lesions that correlate with severity of dementia in AD (Duyckaerts et al., 2009; Takashima, 2009). Mechanistically, the microtubule-associated protein, tau, gets hyper-phosphorylated due to inappropriate activation of proline-directed kinases such as GSK-3β. Consequently, tau misfolds and self-aggregates into insoluble fibrillar structures (paired helical filaments and straight filaments) that form neurofibrillary tangles, dystrophic neurites, and neuropil threads (Iqbal et al., 2009). Intra-neuronal accumulations of fibrillar tau disrupt neuronal cytoskeletal networks and axonal transport, leading to synaptic disconnection and progressive neurodegeneration (Iqbal et al., 2009). Besides fibrillar tau, pre-fibrillar tau can aggregate, forming soluble tau oligomers or insoluble granular tau, which also contribute to neurodegeneration by causing synaptic disconnection and neuronal death (Takashima, 2010). The eventual ubiquitination of hyper-phosphorylated tau (Arnaud et al., 2006), combined with dysfunction of the ubiquitin-proteasome system (Oddo, 2008), cause further accumulations of insoluble fibrillar tau, oxidative stress, and ROS generation, leading to increased neuronal apoptosis, mitochondrial dysfunction, and necrosis in AD (Mandelkow et al., 2003).

Growing evidence suggests that many of the aforementioned cellular aspects of AD neurodegeneration can be mediated by brain insulin/IGF resistance (de la Monte et al., 2000; de la Monte et al., 2001; de la Monte and Wands, 2002; Rivera et al., 2005; Steen et al., 2005; Xu et al., 2003). Tau expression and phosphorylation are regulated by insulin and IGF (Schubert et al., 2003; Schubert et al., 2004). In AD, brain insulin and IGF resistance reduces signaling through phosphoinositol-3-kinase (PI3K), Akt (Schubert et al., 2003; Schubert et al., 2004), and Wnt/β-catenin (Doble and Woodgett, 2003), and increases activation of GSK-3β (De Ferrari and Inestrosa, 2000; Fraser et al., 2001; Grilli et al., 2003; Mudher et al., 2001; Nishimura et al., 1999). GSK-3β over-activation is partly responsible for the hyper-phosphorylation of tau, which promotes tau misfolding and fibril aggregation (Bhat et al., 2003). In addition, AD tau pathology is mediated by impaired tau gene expression due to reduced insulin and IGF signaling (de la Monte et al., 2003). Consequences include failure to generate sufficient quantities of normal soluble tau vis-a-vis accumulation of hyper-phosphorylated insoluble fibillar tau, and attendant exacerbation of cytoskeletal collapse, neurite retraction, and synaptic disconnection.

Insulin/IGF resistance and Amyloid-beta (AβPP-Aβ) neurotoxicity

AD is associated with dysregulated expression and processing of amyloid precursor protein (AβPP), resulting in the accumulation of neurotoxic AβPP-Aβ oligomeric fibrils or insoluble larger aggregated fibrils (plaques). Increased AβPP gene expression, together with altered proteolysis, lead to accumulations of 40 or 42 amino acid length AβPP-Aβ peptides that can aggregate. In familial AD, mutations in the AβPP, presenilin 1 (PS1), or PS2 genes, and inheritance of the Apoliprotein E ε4 (ApoE- ε4) allele promote AβPP-Aβ accumulation in the brain. In sporadic AD, which accounts for 90% or more of the cases, the causes of AβPP-Aβ accumulation are not well understood. However, recent evidence points to brain insulin/IGF resistance as both causal and consequential factors.

Studies have shown that insulin stimulation promotes trafficking of AβPP-Aβ from the trans-Golgi network where it originates, to the plasma membrane for extracellular secretion (Watson et al., 2003). In addition, insulin inhibits AβPP-Aβ's intracellular accumulation and degradation by insulin-degrading enzyme (Gasparini et al., 2001; Gasparini et al., 2002). Impairments in insulin signaling disrupt AβPP processing and AβPP-Aβ clearance in the brain (Messier and Teutenberg, 2005). Accumulation of AβPP-Aβ further compromises insulin signaling by decreasing insulin's binding affinity to its own receptor, worsening effects of insulin resistance (Ling et al., 2002; Xie et al., 2002). Furthermore, AβPP-Aβ oligomers inhibit neuronal transmission of insulin-stimulated signals by desensitizing and reducing the surface expression of insulin receptors. Finally, intracellular AβPP-Aβ directly interferes with PI3 kinase activation of Akt, impairing neuronal survival and increasing GSK-3β activation and hyper-phosphorylation of tau. As discussed, hyper-phosphorylated tau is prone to misfold, aggregate, and become ubiquitinated, prompting the formation of dementia-associated paired-helical filament-containing neuronal cytoskeletal lesions.

Potential mechanisms of brain insulin/IGF resistance in neurodegeneration

Although aging is clearly the dominant risk factor for AD, growing evidence suggests that brain insulin/IGF resistance is a major factor contributing to mild cognitive impairment, dementia, and AD (Craft, 2005b, 2006; de la Monte et al., 2009a; Hoyer et al., 1991; Rivera et al., 2005). Within the past several years, this field of research has greatly expanded due to growing information about the causes and consequences of brain insulin resistance and deficiency in relation to cognitive impairment (Craft, 2005a, 2006, 2007; de la Monte et al., 2006; Lester-Coll et al., 2006; Rivera et al., 2005; Steen et al., 2005). A convincing argument could be made that AD, in its pure form, represents a brain form of diabetes mellitus (Craft, 2007; Hoyer, 2002; Hoyer et al., 1991; Rivera et al., 2005; Steen et al., 2005) since AD is often associated with progressive brain insulin resistance in the absence of Type 2 diabetes, obesity, or peripheral insulin resistance (de la Monte, 2011; de la Monte et al., 2009a; Rivera et al., 2005; Steen et al., 2005). Moreover, postmortem studies demonstrated that the molecular, biochemical, and signal transduction abnormalities in AD are virtually identical to those in Type 1 and Type 2 diabetes mellitus (Rivera et al., 2005; Steen et al., 2005; Talbot et al., 2012).

The strongest evidence favoring the concept that AD is Type 3 diabetes comes from experimental studies in which rats were administered intracerebroventricular injections of streptozotocin, a pro-diabetes drug. Streptozotocin treated rats develop cognitive impairment with deficits in spatial learning and memory, brain insulin resistance and insulin deficiency, and AD-type neurodegeneration (Hoyer et al., 1999; Lester-Coll et al., 2006; Weinstock and Shoham, 2004). Therefore, targeted exposure to a pro-diabetes drug can cause neurodegeneration with structural, molecular, biochemical and functional abnormalities that closely mimic the pathology of AD in humans.

This line of research was extended based upon the facts that streptozotocin is a nitrosamine-related compound, and over the past several decades, Western societies have been assaulted by continuous and escalated contacts with environmental, agricultural, and food source nitrates and nitrites that result in increased nitrosamine exposures (de la Monte et al.,

2009b). We found that experimental exposures to low, sub-mutagenic doses of the nitrosamines that can be found in processed and preserved foods, e.g. N-nitrosodiethylamine (NDEA), cause cognitive impairment, AD-type neurodegeneration, and brain insulin resistance (de la Monte et al., 2009c; Tong et al., 2010; Tong et al., 2009), similar to the effects of streptozotocin. Therefore, nitrosamine-related chemicals can cause Type 3 diabetes, mimicking the abnormalities seen in sporadic AD. We postulate that the rapid increases in prevalence rates of sporadic AD (Type 3 diabetes) are due to environmental exposures such as nitrosamines that contaminate highly processed and preserved foods and have become staples in our diets over the past 50 years (de la Monte and Tong, 2009). Further research is needed to better assess the impact of such exogenous mediators of neurodegeneration, and the spectrum of agents that can produce similar abnormalities leading to AD-type neurodegeneration.

Acknowledgments

Supported by AA11431 and AA12908 from the National Institutes of Health.

Literature Cited

Arnaud L, Robakis NK, Figueiredo-Pereira ME. It may take inflammation, phosphorylation and ubiquitination to ‘tangle’ in Alzheimer’s disease. Neurodegener Dis. 2006; 3:313–319. [PubMed: 16954650]

Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin Resistance and Alzheimer-like Reductions in Regional Cerebral Glucose Metabolism for Cognitively Normal Adults With Prediabetes or Early Type 2 Diabetes. Arch Neurol. 2010

Benedict C, Hallschmid M, Hatke A, Schultes B, Fehm HL, Born J, Kern W. Intranasal insulin improves memory in humans. Psychoneuroendocrinology. 2004; 29:1326–1334. [PubMed: 15288712]

Bhat R, Xue Y, Berg S, Hellberg S, Ormo M, Nilsson Y, Radesater AC, Jerning E, Markgren PO, Borgegard T, Nylof M, Gimenez-Cassina A, Hernandez F, Lucas JJ, Diaz-Nido J, Avila J. Structural insights and biological effects of glycogen synthase kinase 3-specific inhibitor AR-A014418. J Biol Chem. 2003; 278:45937–45945. [PubMed: 12928438]

Broughton SK, Chen H, Riddle A, Kuhn SE, Nagalla S, Roberts CT Jr, Back SA. Large-scale generation of highly enriched neural stem-cell-derived oligodendroglial cultures: maturation-dependent differences in insulin-like growth factor-mediated signal transduction. J Neurochem. 2007; 100:628–638. [PubMed: 17263792]

Cadigan KM, Liu YI. Wnt signaling: complexity at the surface. J Cell Sci. 2006; 119:395–402. [PubMed: 16443747]

Caselli RJ, Chen K, Lee W, Alexander GE, Reiman EM. Correlating cerebral hypometabolism with future memory decline in subsequent converters to amnestic pre-mild cognitive impairment. Arch Neurol. 2008; 65:1231–1236. [PubMed: 18779428]

Chesik D, De Keyser J, Wilczak N. Insulin-like growth factor system regulates oligodendroglial cell behavior: therapeutic potential in CNS. J Mol Neurosci. 2008; 35:81–90. [PubMed: 18299999]

Contestabile A, Greco B, Ghezzi D, Tucci V, Benfenati F, Gasparini L. Lithium rescues synaptic plasticity and memory in Down syndrome mice. The Journal of clinical investigation. 2013; 123:348–361. [PubMed: 23202733]

Craft S. Insulin resistance and cognitive impairment: a view through the prism of epidemiology. Arch Neurol. 2005a; 62:1043–1044. [PubMed: 16009754]

Craft S. Insulin resistance syndrome and Alzheimer’s disease: age- and obesity-related effects on memory, amyloid, and inflammation. Neurobiol Aging. 2005b; 26(Suppl 1):65–69. [PubMed: 16266773]

Craft S. Insulin resistance syndrome and Alzheimer disease: pathophysiologic mechanisms and therapeutic implications. Alzheimer Dis Assoc Disord. 2006; 20:298–301. [PubMed: 17132977]

Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr Alzheimer Res. 2007; 4:147–152. [PubMed: 17430239]

Craft S, Asthana S, Cook DG, Baker LD, Cherrier M, Purganan K, Wait C, Petrova A, Latendresse S, Watson GS, Newcomer JW, Schellenberg GD, Krohn AJ. Insulin dose-response effects on memory and plasma amyloid precursor protein in Alzheimer's disease: interactions with apolipoprotein E genotype. Psychoneuroendocrinology. 2003; 28:809–822. [PubMed: 12812866]

Cummings, JL. Definitions and diagnostic criteria. 3. Informa UK Limited; London: 2007.

De Ferrari GV, Inestrosa NC. Wnt signaling function in Alzheimer's disease. Brain Res Brain Res Rev. 2000; 33:1–12. [PubMed: 10967351]

de la Monte SM. Contributions of brain insulin resistance and deficiency in amyloid-related neurodegeneration in Alzheimer's disease. Drugs. 2011; 72:1–18.

de la Monte SM. Triangulated Mal-Signaling in Alzheimer's Disease: Roles of Neurotoxic Ceramides, ER Stress, and Insulin Resistance Reviewed. J Alzheimers Dis. 2012

de la Monte SM, Chen GJ, Rivera E, Wands JR. Neuronal thread protein regulation and interaction with microtubule-associated proteins in SH-Sy5y neuronal cells. Cell Mol Life Sci. 2003; 60:2679–2691. [PubMed: 14685691]

de la Monte SM, Ganju N, Banerjee K, Brown NV, Luong T, Wands JR. Partial rescue of ethanol-induced neuronal apoptosis by growth factor activation of phosphoinositol-3-kinase. Alcohol Clin Exp Res. 2000; 24:716–726. [PubMed: 10832914]

de la Monte SM, Longato L, Tong M, Wands JR. Insulin resistance and neurodegeneration: roles of obesity, type 2 diabetes mellitus and non-alcoholic steatohepatitis. Curr Opin Investig Drugs. 2009a; 10:1049–1060.

de la Monte SM, Neely TR, Cannon J, Wands JR. Ethanol impairs insulin-stimulated mitochondrial function in cerebellar granule neurons. Cell Mol Life Sci. 2001; 58:1950–1960. [PubMed: 11766890]

de la Monte SM, Neusner A, Chu J, Lawton M. Epidemiological Trends Strongly Suggest Exposures as Etiologic Agents in the Pathogenesis of Sporadic Alzheimer's Disease, Diabetes Mellitus, and Non-Alcoholic Steatohepatitis. J Alzheimers Dis. 2009b; 17:519–529. [PubMed: 19363256]

de la Monte SM, Re E, Longato L, Tong M. Dysfunctional Pro-Ceramide, ER Stress,and Insulin/IGF Signaling Networks with Progression of Alzheimer's Disease. J Alzheimers Dis. 2012

de la Monte SM, Tong M. Mechanisms of Nitrosamine-Mediated Neurodegeneration: Potential Relevance to Sporadic Alzheimer's Disease. J Alzheimers Dis. 2009

de la Monte SM, Tong M, Bowling N, Moskal P. si-RNA inhibition of brain insulin or insulin-like growth factor receptors causes developmental cerebellar abnormalities: relevance to fetal alcohol spectrum disorder. Mol Brain. 2011; 4:13. [PubMed: 21443795]

de la Monte SM, Tong M, Lawton M, Longato L. Nitrosamine exposure exacerbates high fat diet-mediated type 2 diabetes mellitus, non-alcoholic steatohepatitis, and neurodegeneration with cognitive impairment. Mol Neurodegener. 2009c; 4:54. [PubMed: 20034403]

de la Monte SM, Tong M, Lester-Coll N, Plater M Jr, Wands JR. Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. J Alzheimers Dis. 2006; 10:89–109. [PubMed: 16988486]

de la Monte SM, Wands JR. Chronic gestational exposure to ethanol impairs insulin-stimulated survival and mitochondrial function in cerebellar neurons. CMLS, Cell Mol Life Sci. 2002; 59:882–893.

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. [PubMed: 15750214]

de la Monte SM, Wands JR. Molecular indices of oxidative stress and mitochondrial dysfunction occur early and often progress with severity of Alzheimer's disease. J Alzheimers Dis. 2006; 9:167–181. [PubMed: 16873964]

Doble BW, Woodgett JR. GSK-3: tricks of the trade for a multi-tasking kinase. J Cell Sci. 2003; 116:1175–1186. [PubMed: 12615961]

Duyckaerts C, Delatour B, Potier MC. Classification and basic pathology of Alzheimer disease. Acta Neuropathol. 2009; 118:5–36. [PubMed: 19381658]

Foltz DR, Santiago MC, Berechid BE, Nye JS. Glycogen synthase kinase-3beta modulates notch signaling and stability. Curr Biol. 2002; 12:1006–1011. [PubMed: 12123574]

Fraser PE, Yu G, Levesque L, Nishimura M, Yang DS, Mount HT, Westaway D, St George-Hyslop PH. Presenilin function: connections to Alzheimer's disease and signal transduction. Biochem Soc Symp. 2001:89–100. [PubMed: 11447843]

Freude S, Schilbach K, Schubert M. The role of IGF-1 receptor and insulin receptor signaling for the pathogenesis of Alzheimer's disease: from model organisms to human disease. Curr Alzheimer Res. 2009; 6:213–223. [PubMed: 19519303]

Frolich L, Blum-Degen D, Bernstein HG, Engelsberger S, Humrich J, Laufer S, Muschner D, Thalheimer A, Turk A, Hoyer S, Zochling R, Boissl KW, Jellinger K, Riederer P. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neural Transm. 1998; 105:423–438. [PubMed: 9720972]

Gasparini L, Gouras GK, Wang R, Gross RS, Beal MF, Greengard P, Xu H. 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. [PubMed: 11306609]

Gasparini L, Netzer WJ, Greengard P, Xu H. Does insulin dysfunction play a role in Alzheimer's disease? Trends Pharmacol Sci. 2002; 23:288–293. [PubMed: 12084635]

Gong X, Xie Z, Zuo H. Invivo insulin deficiency as a potential etiology for demyelinating disease. Med Hypotheses. 2008; 71:399–403. [PubMed: 18621485]

Gonzalez-Sanchez JL, Serrano-Rios M. Molecular basis of insulin action. Drug News Perspect. 2007; 20:527–531. [PubMed: 18080040]

Grilli M, Ferrari Toninelli G, Uberti D, Spano P, Memo M. Alzheimer's disease linking neurodegeneration with neurodevelopment. Funct Neurol. 2003; 18:145–148. [PubMed: 14703895]

Grunblatt E, Salkovic-Petrisic M, Osmanovic J, Riederer P, Hoyer S. Brain insulin system dysfunction in streptozotocin intracerebroventricularly treated rats generates hyperphosphorylated tau protein. J Neurochem. 2007; 101:757–770. [PubMed: 17448147]

Gustaw-Rothenberg K, Lerner A, Bonda DJ, Lee HG, Zhu X, Perry G, Smith MA. Biomarkers in Alzheimer's disease: past, present and future. Biomarkers in medicine. 2010; 4:15–26. [PubMed: 20387301]

Hoyer S. The brain insulin signal transduction system and sporadic (type II) Alzheimer disease: an update. J Neural Transm. 2002; 109:341–360. [PubMed: 11956956]

Hoyer S. Causes and consequences of disturbances of cerebral glucose metabolism in sporadic Alzheimer disease: therapeutic implications. Adv Exp Med Biol. 2004a; 541:135–152. [PubMed: 14977212]

Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol. 2004b; 490:115–125. [PubMed: 15094078]

Hoyer S, Lannert H. Inhibition of the neuronal insulin receptor causes Alzheimer-like disturbances in oxidative/energy brain metabolism and in behavior in adult rats. Ann N Y Acad Sci. 1999; 893:301–303. [PubMed: 10672254]

Hoyer S, Lannert H, Noldner M, Chatterjee SS. Damaged neuronal energy metabolism and behavior are improved by Ginkgo biloba extract (EGb 761). J Neural Transm. 1999; 106:1171–1188. [PubMed: 10651112]

Hoyer S, Lee SK, Loffler T, Schliebs R. Inhibition of the neuronal insulin receptor. An in vivo model for sporadic Alzheimer disease? Ann N Y Acad Sci. 2000; 920:256–258. [PubMed: 11193160]

Hoyer S, Nitsch R, Oesterreich K. Predominant abnormality in cerebral glucose utilization in late-onset dementia of the Alzheimer type: a cross-sectional comparison against advanced late-onset and incipient early-onset cases. J Neural Transm Park Dis Dement Sect. 1991; 3:1–14. [PubMed: 1905936]

Iqbal K, Liu F, Gong CX, del Alonso AC, Grundke-Iqbal I. Mechanisms of tau-induced neurodegeneration. Acta Neuropathol. 2009; 118:53–69. [PubMed: 19184068]

Iwangoff P, Armbruster R, Enz A, Meier-Ruge W. Glycolytic enzymes from human autoptic brain cortex: normal aged and demented cases. Mech Ageing Dev. 1980; 14:203–209. [PubMed: 6259457]

Krikorian R, Eliassen JC, Boespflug EL, Nash TA, Shidler MD. Improved cognitive-cerebral function in older adults with chromium supplementation. Nutr Neurosci. 2010; 13:116–122. [PubMed: 20423560]

Labak M, Foniok T, Kirk D, Rushforth D, Tomanek B, Jasinski A, Grieb P. Metabolic changes in rat brain following intracerebroventricular injections of streptozotocin: a model of sporadic Alzheimer's disease. Acta Neurochir Suppl. 2010; 106:177–181. [PubMed: 19812944]

Langbaum JB, Chen K, Caselli RJ, Lee W, Reschke C, Bandy D, Alexander GE, Burns CM, Kaszniak AW, Reeder SA, Corneveaux JJ, Allen AN, Pruzin J, Huentelman MJ, Fleisher AS, Reiman EM. Hypometabolism in Alzheimer-affected brain regions in cognitively healthy Latino individuals carrying the apolipoprotein E epsilon4 allele. Arch Neurol. 2010; 67:462–468. [PubMed: 20385913]

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. [PubMed: 9829797]

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. [PubMed: 16627931]

Liang G, Cline GW, Macica CM. IGF-1 stimulates de novo fatty acid biosynthesis by Schwann cells during myelination. Glia. 2007; 55:632–641. [PubMed: 17299765]

Ling X, Martins RN, Racchi M, Craft S, Helmerhorst E. Amyloid beta antagonizes insulin promoted secretion of the amyloid beta protein precursor. J Alzheimers Dis. 2002; 4:369–374. [PubMed: 12446969]

Luchsinger JA. Type 2 diabetes, related conditions, in relation and dementia: an opportunity for prevention? J Alzheimers Dis. 2010; 20:723–736. [PubMed: 20413862]

Mandelkow EM, Stamer K, Vogel R, Thies E, Mandelkow E. Clogging of axons by tau, inhibition of axonal traffic and starvation of synapses. Neurobiol Aging. 2003; 24:1079–1085. [PubMed: 14643379]

Messier C, Teutenberg K. The role of insulin, insulin growth factor, and insulin-degrading enzyme in brain aging and Alzheimer's disease. Neural Plast. 2005; 12:311–328. [PubMed: 16444902]

Mosconi L, Mistur R, Switalski R, Tsui WH, Glodzik L, Li Y, Pirraglia E, De Santi S, Reisberg B, Wisniewski T, de Leon MJ. FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. Eur J Nucl Med Mol Imaging. 2009; 36:811–822. [PubMed: 19142633]

Mosconi L, Pupi A, De Leon MJ. Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease. Ann N Y Acad Sci. 2008; 1147:180–195. [PubMed: 19076441]

Mudher A, Chapman S, Richardson J, Asuni A, Gibb G, Pollard C, Killick R, Iqbal T, Raymond L, Varndell I, Sheppard P, Makoff A, Gower E, Soden PE, Lewis P, Murphy M, Golde TE, Rupniak HT, Anderton BH, Lovestone S. Dishevelled regulates the metabolism of amyloid precursor protein via protein kinase C/mitogen-activated protein kinase and c-Jun terminal kinase. J Neurosci. 2001; 21:4987–4995. [PubMed: 11438574]

Neumann KF, Rojo L, Navarrete LP, Farias G, Reyes P, Maccioni RB. Insulin resistance and Alzheimer's disease: molecular links & clinical implications. Curr Alzheimer Res. 2008; 5:438–447. [PubMed: 18855585]

Nishimura M, Yu G, Levesque G, Zhang DM, Ruel L, Chen F, Milman P, Holmes E, Liang Y, Kawarai T, Jo E, Supala A, Rogaeva E, Xu DM, Janus C, Levesque L, Bi Q, Duthie M, Rozmahel R, Mattila K, Lannfelt L, Westaway D, Mount HT, Woodgett J, St George-Hyslop P, et al. Presenilin mutations associated with Alzheimer disease cause defective intracellular trafficking of beta-catenin, a component of the presenilin protein complex. Nat Med. 1999; 5:164–169. [PubMed: 9930863]

Oddo S. The ubiquitin-proteasome system in Alzheimer's disease. Journal of cellular and molecular medicine. 2008; 12:363–373. [PubMed: 18266959]

Reger MA, Watson GS, Frey WH 2nd, Baker LD, Cholerton B, Keeling ML, Belongia DA, Fishel MA, Plymate SR, Schellenberg GD, Cherrier MM, Craft S. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. Neurobiol Aging. 2006; 27:451–458. [PubMed: 15964100]

Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton B, Fishel MA, Plymate SR, Breitner JC, Degroodt W, Mehta P, Craft S. Intranasal insulin improves cognition and modulates {beta}-amyloid in early AD. Neurology. 2008; 70:440–448. [PubMed: 17942819]

Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimers Dis. 2005; 8:247–268. [PubMed: 16340083]

Schubert M, Brazil DP, Burks DJ, Kushner JA, Ye J, Flint CL, Farhang-Fallah J, Dikkes P, Warot XM, Rio C, Corfas G, White MF. Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation. J Neurosci. 2003; 23:7084–7092. [PubMed: 12904469]

Schubert M, Gautam D, Surjo D, Ueki K, Baudler S, Schubert D, Kondo T, Alber J, Galldiks N, Kustermann E, Arndt S, Jacobs AH, Krone W, Kahn CR, Bruning JC. Role for neuronal insulin resistance in neurodegenerative diseases. Proc Natl Acad Sci U S A. 2004; 101:3100–3105. [PubMed: 14981233]

Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR, de la Monte SM. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? J Alzheimers Dis. 2005; 7:63–80. [PubMed: 15750215]

Tabatadze N, Tomas C, McGonigal R, Lin B, Schook A, Routtenberg A. Wnt transmembrane signaling and long-term spatial memory. Hippocampus. 2012; 22:1228–1241. [PubMed: 22180023]

Takashima A. Amyloid-beta, tau, and dementia. J Alzheimers Dis. 2009; 17:729–736. [PubMed: 19542626]

Takashima A. Drug development for tauopathy and Alzheimer's disease. Nihon Shinkei Seishin Yakurigaku Zasshi. 2010; 30:177–180. [PubMed: 20857696]

Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, Arvanitakis Z, Schneider JA, Wolf BA, Bennett DA, Trojanowski JQ, Arnold SE. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. The Journal of clinical investigation. 2012; 122:1316–1338. [PubMed: 22476197]

Tong M, Longato L, de la Monte SM. Early limited nitrosamine exposures exacerbate high fat diet-mediated type 2 diabetes and neurodegeneration. BMC Endocr Disord. 2010; 10:4. [PubMed: 20302640]

Tong M, Neusner A, Longato L, Lawton M, Wands JR, de la Monte SM. Nitrosamine Exposure Causes Insulin Resistance Diseases: Relevance to Type 2 Diabetes Mellitus, Non-Alcoholic Steatohepatitis, and Alzheimer's Disease. J Alzheimers Dis. 2009

Varela-Nallar L, Inestrosa NC. Wnt signaling in the regulation of adult hippocampal neurogenesis. Frontiers in cellular neuroscience. 2013; 7:100. [PubMed: 23805076]

Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature. 2002; 416:535–539. [PubMed: 11932745]

Watson GS, Craft S. Insulin resistance, inflammation, and cognition in Alzheimer's Disease: lessons for multiple sclerosis. J Neurol Sci. 2006; 245:21–33. [PubMed: 16631207]

Watson GS, Peskind ER, Asthana S, Purganan K, Wait C, Chapman D, Schwartz MW, Plymate S, Craft S. Insulin increases CSF Abeta42 levels in normal older adults. Neurology. 2003; 60:1899–1903. [PubMed: 12821730]

Weinstock M, Shoham S. Rat models of dementia based on reductions in regional glucose metabolism, cerebral blood flow and cytochrome oxidase activity. J Neural Transm. 2004; 111:347–366. [PubMed: 14991459]

Winocur G, Greenwood CE, Piroli GG, Grillo CA, Reznikov LR, Reagan LP, McEwen BS. Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. Behav Neurosci. 2005; 119:1389–1395. [PubMed: 16300445]

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:RC221. [PubMed: 12006603]

Xu J, Eun Yeon J, Chang H, Tison G, Jun Chen G, Wands JR, De La Monte SM. Ethanol impairs insulin-stimulated neuronal survival in the developing brain: Role of PTEN phosphatase. J Biol Chem. 2003; 278:26929–26937. [PubMed: 12700235]

Zeger M, Popken G, Zhang J, Xuan S, Lu QR, Schwab MH, Nave KA, Rowitch D, D'Ercole AJ, Ye P. Insulin-like growth factor type 1 receptor signaling in the cells of oligodendrocyte lineage is required for normal in vivo oligodendrocyte development and myelination. Glia. 2007; 55:400–411. [PubMed: 17186502]