# Alzheimer's Disease and Treatment

MEDDOCS
Open Access Publisher

# Impairment of Insulin Signalling Pathway Triggers a Series of Detrimental Effects in Alzheimer's disease

***Vidyasagar Naik Bukke[1]*; Moola Archana[2]***

*[1]Department of Clinical and Experimental Medicine, University of Foggia, Foggia 71122, Italy.*

*[2]Department of Medical and Surgical Sciences, University of Foggia, Foggia 71122, Italy.*

**Corresponding Author: Vidyasagar Naik Bukke**

Department of Clinical and Experimental Medicine, University of Foggia, Foggia 71122, Italy.
Tel: +39-32800-54297;
Email: vidyasagar.bukke@unifg.it

Published Online: Feb 15, 2021

eBook: Alzheimer's Disease & Treatment

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/



**Keywords:** Alzheimer's disease; Insulin resistance; Glycosylation; Glutamate; Oxidative stress; Mitochondrial dysfunction; Hormonal imbalance; ROS.

## Abstract

Alzheimer's disease (AD) is the most common cause of dementia and cognition impairment that interferes with the daily life. AD has no cure, but treatments are available to reduce the symptoms. Accumulating evidence reveals a connecting link between the impaired insulin signalling and AD. Alterations in insulin signalling remains to be a crucial factor that alters the glucose metabolism impacting the bioenergetics of the cell leading to mitochondrial dysfunction, Aβ accumulation, tau hyperphosphorylation, deviations in glycosylation, impairment of glutamatergic neurotransmission. Besides, mitochondrial abnormalities and oxidative stress play a primary role in AD pathogenesis through the generation of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), which contribute to energy failure. In addition, thyroid dysfunction is also implicated in reversible cognitive impairment and screening of thyroid stimulating hormone remained as a part of laboratory test for dementia. This text explores the insulin signalling dysfunction that impairs the bioenergetics and stimulates activation of devastating pathways that are associated with the enhancement of AD risk.

## Introduction

AD is an age-related neurodegenerative disorder and is associated with massive neuronal loss in the brain leading to severe deterioration of cognitive function. Worldwide, it is expected that the incidence of AD is going to increase from 56 million in 2020 to 88 million by 2050 [1]. AD is a pervasive disorder characterized by the deposition of amyloid-β (Aβ) senile plaques and Neurofibrillary Tangles (NFTs) of tau proteins [2]. Deposition of Aβ and tau protein impairs learning, memory, and suppress synaptic plasticity that impacts the behavioural and social skills, disrupting the person's ability to function independently. Aβ is a peptide produced from Amyloid Precursor Protein (APP), that undergoes cleavage by α-secretase, β-secretase, and γ-secretases into amyloidogenic and non-amyloidogenic pathways as shown in Figure 1. In the amyloidogenic pathway, Aβ, APP Intracellular Domain (AICD), and soluble APPβ (sAPPβ) are produced through sequential cleavage of APP by β-secretase and γ-secretase. While, non-amyloidogenic pathway produces P3 peptide, soluble APPα (sAPPα), and AICD through α-secretase and γ-secretase activity [3,4]. Soluble $A\beta_{1-42}$ is considered as the most toxic neurotoxic product formed after APP cleavage [5]. Aβ peptides form aggregates inducing synaptotoxicity leading to cognitive dysfunction. Low-Molecular-Weight (LMW) (dimers, trimers, and tetramers) and High-Molecular-Weight (HMW) oligomers of Aβ are found at synapse that alters the structure and functions of the neuronal synapses [6,7]. HMW oligomers dissociate into LMW species and LMW Aβ oligomers induce more cognitive dysfunction [8].

**Citation:** Bukke VN, Archana M, (2021). Impairment of Insulin Signalling Pathway Triggers a Series of Detrimental Effects in Alzheimer's Disease. Alzheimer's Disease and Treatment, MedDocs Publishers. Vol. 3, Chapter 2, pp. 13-20.

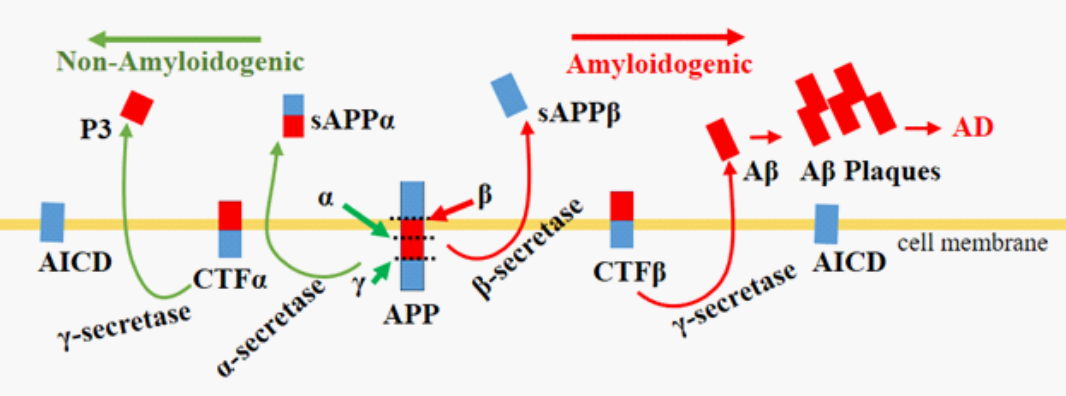


**Figure 1:** Non-amyloidogenic and amyloidogenic pathways of Amyloid Precursor Protein (APP) that is cleaved at different sites to yield different products. In the non-amyloidogenic pathway, P3 peptide, soluble APPα (sAPPα), and APP Intracellular Domain (AICD) are produced through the activity of α-secretase and γ-secretase. In the amyloidogenic pathway, Aβ, AICD, and soluble APPβ (sAPPβ) are produced through sequential cleavage of APP by β-secretase and γ-secretase. Accumulation of Aβ plaques increases Alzheimer's disease pathogenesis. CTFα- C-terminal fragment α; CTFβ- C-terminal fragment β.

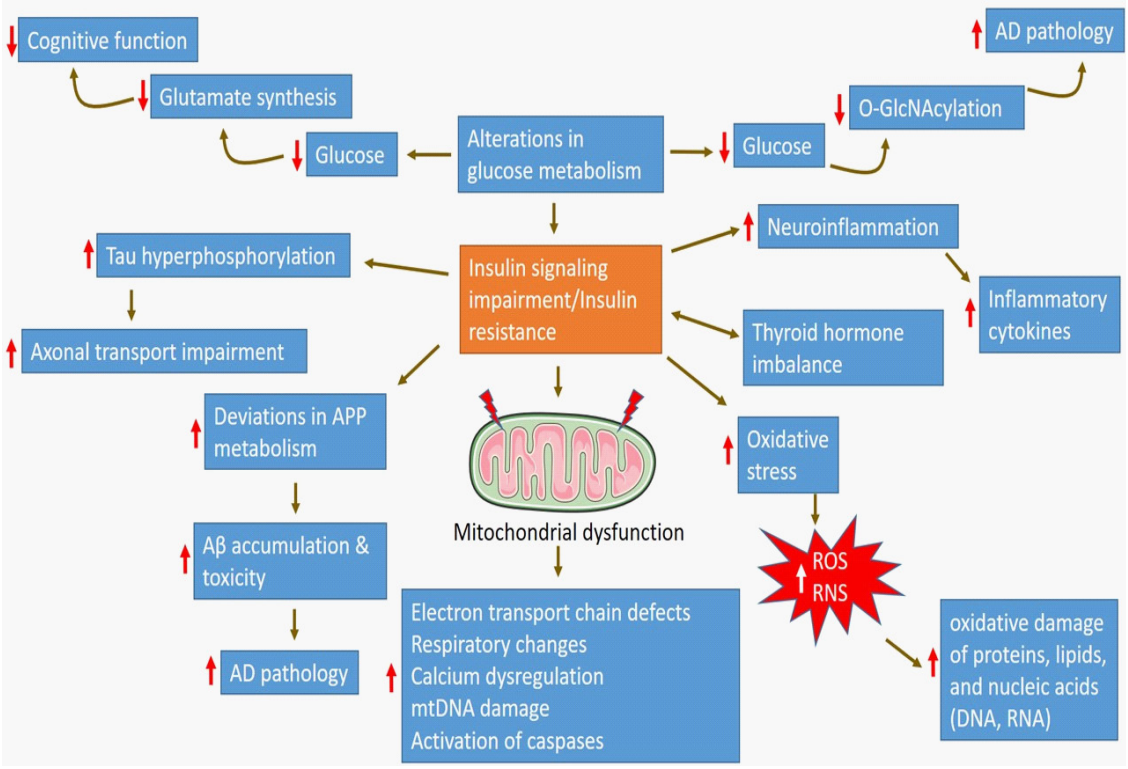


**Figure 2:** Molecular pathways linked to Alzheimer's disease with insulin resistance.

Tau is a Microtubule-Associated Protein (MAP), which maintains the stability of the microtubule and plays an important role in synaptic functions [9]. Tau protein undergoes phosphorylation by Proline-Directed Protein Kinases (PDPKs) or non-proline-directed protein kinases that are involved in the formation of NFTs, which is a major pathological hallmark of AD [10]. PDPKs comprise Cyclin-dependent kinase-5 (Cdk-5), extracellular Signal-Related Protein Kinase (ERK), and Glycogen Synthase Kinase-3 (GSK-3). While, non-PDPKs include Protein Kinase A (PKA), Casein Kinase 1 (CK1), and Casein Kinase 2 (CK2). Aberrant activities of these kinases and phosphatases act as an indicator in AD pathogenesis [10,11]. The irregular activity of Cdk-5 and GSK-3 causes tau phosphorylation leading to loss of dendritic spines and deterioration of synaptic plasticity [11]. GSK-3 mediated tau phosphorylation is regarded as the early-stage AD pathogenesis, while in the late-stage of AD, consistent inhibition is observed [12,13].

The complexity of the AD pathogenesis is increased by co-morbidities like stress, diabetes, depression, etc. Diabetes remains the most significant risk factor that is involved in increasing detrimental effects and AD progression [14-16]. Diabetes classified into two major forms, Type-1 Diabetes (T1D) and T2D, the latter case accounts for the majority (90%) of the diabetes cases. T1D is autoimmune destruction of pancreatic β-cells resulting in the deficiency of insulin production, while T2D is characterized by the inability of the insulin to stimulate glucose utilization due to insulin resistance [17,18]. Insulin resistance usually precedes the onset of T2D by several years and is closely associated with obesity. In addition, some studies suggest that even in non-diabetic populations, insulin resistance increases the risk of dementia in AD [19]. Diabetes is a complex metabolic disorder characterized by chronic hyperglycemia resulting in the damage and failure of the brain, eyes, kidneys, and heart. Diabetes has a severe impact and influence on brain morphol-

ogy, memory processing, and synaptic communications contributing multiple abnormalities to AD [20]. T2D individuals have a two-fold higher risk of developing AD when compared to non-diabetic individuals [21], and 80% of AD patients exhibit T2D or aberrations in blood glucose levels [22]. This work discusses the possible link of mechanisms underlying the enhancement of AD pathogenesis due to the alterations of insulin signalling pathways that influence glucose metabolism, and glutamate levels. Moreover, this text also highlights the mitochondrial dysfunction, oxidative stress, cognition and behavioural impairment, and hormonal deviations associated with AD as shown in Figure 2.

**Insulin signalling**

Insulin is involved mainly in regulating glucose metabolism but also affects cognition, memory, and synaptic plasticity of the neurons through insulin signalling pathways [23]. Disturbances in insulin signalling have been found in T1D patients [24], Streptozotocin (STZ)-induced T1D model, that demonstrated that impaired cognitive performance is associated with a decrease in hippocampal activity [25]. BBZDR/Wor and BB/Wor rats of T2D and T1D models respectively showed neuronal loss, deviations in APP metabolism, tau protein hyperphosphorylation, impaired signalling of insulin and Insulin-like Growth Factor 1 (IGF-1) [26]. Of note, the T2D model with insulin resistance was associated with more severe alterations. Insulin resistance is the main characteristic feature shared among the people suffering from diabetes, obesity, and AD that leads to hyperinsulinemia, further resulting in saturation of Insulin-Degrading Enzyme (IDE). In addition, insulin resistance in the brain impairs the insulin signalling pathways altering the bioenergetics leading to defects in energy metabolism [27-29]. The insulin resistance is accompanied by an increase in insulin levels and reduces the activity of insulin that lowers the cerebrocortical glucose metabolism [30]. Lack of proper insulin response enhances the down-regulation of the insulin receptors, faulty activation of the insulin signalling cascade that consequently reduces the glucose uptake of neurons impairing neuronal plasticity, triggering inflammatory cascade, and neurotransmitter deficits [31].

**Altered glucose availability**

In AD pathology, brain glucose metabolism is severely impaired due to hypometabolism that precedes before the onset of cognitive symptoms [32]. Hypometabolism is mainly characterized by decreased consumption of brain glucose that is essential for neuronal survival. In the early stages of AD, hypometabolism is prominently found in posterior cingulate and parieto-temporal regions, while it spreads to other regions like the prefrontal cortex during the disease progression [33]. Neurons are unable to synthesize or store the glucose and are totally dependent on Glucose Transporters (GLUTs) across the Blood-Brain Barrier (BBB) [34]. In the brain, GLUT1 and GLUT3 isoforms are predominantly found, GLUT-1 located in cerebrovascular endothelial cells, astrocytes, oligodendrocytes, and neurons, while GLUT-3 is expressed specifically in neurons [35]. The post-mortem investigations revealed decreased protein levels of GLUT1 and GLUT3; especially a significant loss of GLUT3 in the cerebral cortex [36,37]. These shreds of evidences suggest that decrease in glucose availability leads to abnormal glucose metabolism due to disruption in glucose supply, in turn, associated with decrease in O-GlcNAcylation and hyperphosphorylation of tau proteins [38,39].

**Glycosylation imbalance**

Glycosylation is one of the important post-translational modification that acts as a cellular regulator of growth and proliferation. Dysregulation of the glycosylation pathway contributes to etiology of diseases, particularly diabetes and neurodegeneration [40,41]. The Hexosamine Biosynthetic Pathway (HBP) produces Uridine 5´-diphospho-N-acetylglucosamine (UDP-GlcNAc), a key substrate for protein glycosylation. 2 to 3% of cellular glucose is transformed into UDP-GlcNAc that acts as a substrate for O-GlcNAcylation, and dysregulation of O-GlcNAcylation occurs in AD [42]. Alteration in glucose metabolism lowers the availability of cellular glucose that seems to decrease the UDP-GlcNAc through HBP [43,44]. APP undergoes O-GlcNAcylation as a part of the post-translational modification to exert its function [38]. O-GlcNAcylation of APP enhances the non-amyloidogenic pathway that has a neuroprotective role [45]. Besides, the tau protein also undergoes O-GlcNAcylation that reduces the tau phosphorylation. Tau-O-GlcNAc plays neuroprotective role by preventing the formation of NFTs. However, due to aberrations in glucose availability in AD patients, imbalance in protein O-GlcNAcylation leads to increase the AD pathology by enhancing the amyloidogenic pathway of APP and tau hyperphosphorylation [38].

**Glucose/glutamate alterations**

Deviations in insulin signalling alter cerebral glucose metabolism, which affects the glutamatergic system by reducing the glutamate neurotransmitter in AD. In neurons and glial cells, glutamate is produced from precursors glucose and α-ketoglutarate [46]. However, these precursors are compromised in AD reducing the synthesis of glutamate. Therefore, impairment of glucose metabolism leads to memory-related aberrations in AD [47,48]. Glutamate is a nonessential amino acid and major excitatory neurotransmitter involved in 70% of all excitatory synapses of CNS [49]. Glutamate is released into synapse and excess amounts of glutamate is taken up by the astrocytes and is converted into glutamine by glutamine synthetase. This non-neuroactive glutamine is converted back into glutamate by the action of Phosphate-Activated Glutaminase (PAG) and this entire cycle is called the glutamate/glutamine cycle [50]. However, majority of the energy required for the conversion of glutamate to glutamine is produced from oxidation of the glucose in the form of ATP. In this regard, impairment of glucose metabolism and inability to produce sufficient ATP imbalances the glutamate synthesis leading to neuronal death [3]. These alterations in glutamate/glutamine cycle lead to excitotoxicity and toxic activation of extrasynaptic ionotropic receptors that increase the influx of $Ca^{2+}$, in turn triggering apoptotic pathways [51,52].

**Oxidative damage**

The imbalance between the production of oxidants and the defensive anti-oxidants results in oxidative stress. The damage done to the biomolecules during oxidative stress is referred to as oxidative damage. Oxidative damage is the result of insulin resistance that affects glucose metabolism in the brain that contributes significantly to the pathogenesis and progression of AD [53]. The brain is an energy-demanding organ and it depends heavily on glucose metabolism to utilize ATPs produced through glycolysis, TCA cycle, and oxidative phosphorylation [54]. But, glucose metabolism is severely depressed in the brains of AD patients. Ample research shows that inefficient glucose utilization and oxidative damage of proteins, lipids, and nucleic acids (DNA,RNA) are closely related [55]. ROS and RNS (Table 1) react with the biomolecules producing the biomarkers of oxidative

or nitrosative damage that are commonly measured during the oxidative damage of the brain. Of note, oxidative damage of mitochondrial DNA also contributes to the impairment in ATP production [56]. Moreover, redox proteomics of brain tissue in AD revealed the oxidative modifications of key glycolytic enzymes like aldolase, Triosephosphate Isomerase (TPI), Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH), Phosphoglycerate Mutase 1 (PGAM1), and α-enolase [57]. Besides, other vital enzymes like aconitase of TCA cycle, creatinine kinase that maintains ATP levels, and ATP synthase of brain mitochondria undergo oxidation reducing the production of ATP [58].

**Table 1:** List of ROS and RNS.

| Type | ROS | RNS |
|---|---|---|
| Radical | Hydroxyl-OH$^{\bullet}$<br>Superoxide-$O_2^{\bullet-}$<br>Alkoxyl-RO$^{\bullet}$<br>Peroxyl-$RO_2^{\bullet}$<br>Hydroperoxyl-$HO_2^{\bullet}$<br>Lipid radical-L$^{\bullet}$<br>Lipid peroxyl-$LO_2^{\bullet}$ | Nitric oxide-NO$^{\bullet}$<br>Nitrogen dioxide-$NO_2^{\bullet}$<br>Nitrate-$NO_3^{\bullet}$ |
| Non-radical | Hydrogen peroxide-$H_2O_2$<br>Hypochlorous acid-HOCl<br>Peroxynitrite-$ONO_2^-$<br>Peroxynitrous acid-$ONO_2H$<br>Ozone-$O_3$ | Nitrous acid-$HNO_2$<br>Peroxynitrite-$ONO_2$<br>Peroxynitrous acid-$ONO_2H$<br>Nitrosyl cation-$NO^+$<br>Nitrosyl anion-$NO^-$<br>Dinitrogen trioxide-$N_2O_3$<br>Nitryl chloride-$NO_2Cl$ |

### Mitochondrial dysfunction

Mitochondria are regarded as the powerhouse of the cell, especially brain neurons require high metabolic energy for their proper function and hence synapses contain more number of mitochondria to meet their energy demand [59,60]. Brain mitochondria depend highly on glucose to produce ATP and also a major source of oxidative stress that happens due to unavoidable leakage of electrons, producing the superoxide anion that is responsible for endogenous ROS production [61,62]. In fact, low glucose metabolism is well documented in AD due to the impairment of mitochondrial function. In addition, mitochondrial dysfunction is not only efficient in producing less ATP, but also a major source for the oxidative imbalance. Besides, change in glucose metabolism and mitochondrial dysfunction alters cognition functionality that is regarded as an early feature of AD [63]. Mitochondrial Electron Transport Complex (ETC) contains cytochrome c-oxidase (Complex IV) that is more susceptible to modification through ROS/RNS, impairing the ETC cycle to produce hydrogen peroxide rather than water molecule [64]. It has been estimated that 1% of mitochondrial electron flow triggers the generation of ROS/RNS [65]. Thus, maintaining the mitochondrial homeostasis and bioenergetics in neurons is critical in the production of mitochondria-driven ATP that are generally accompanied by ROS as by-products. ROS are mainly produced from complex I and III of ETC, which react with electron acceptors generating free radicals [66,67].

Accumulating pieces of evidence also suggest that $Ca^{2+}$ dysregulation also plays a major role in AD pathogenesis. The $Ca^{2+}$ homeostasis alterations in neurons affect mitochondrial signalling that compromise neuron functions through debilitated mitochondrial function [68]. Mitochondria is a dynamic organelle in maintaining the intracellular $Ca^{2+}$ levels, generating ATP and scavenging free radicals. However, aged neurons are less efficient in handling the $Ca^{2+}$ related mechanisms that result in excess accumulation of intracellular $Ca^{2+}$ and activation of $Ca^{2+}$ dependent proteases leading to mitochondrial dysfunction and apoptosis [69]. Nonetheless, AD patients are observed with altered expression of $Ca^{2+}$ related genes in the brain [70]. Recombinant apolipoprotein E4 allele (ApoE4) cell line studies showed an increase in cytosolic $Ca^{2+}$ levels through the efflux of plasma membrane $Ca^{2+}$ channels [71,72]. Recent studies demonstrated that AD pathology alters $Ca^{2+}$ signalling, in turn triggering mitochondrial dysfunction. Post-mortem studies of AD patients demonstrate that Aβ accumulates into mitochondria and blocks the transport of mitochondrial proteins, damaging the mitochondria structurally, disrupting ETC, and causing synaptic damage leading to AD pathogenesis [73]. Of note, studies show that Aβ peptide in the presence of $Ca^{2+}$ opens the mitochondrial permeability transition pore (mtPTP) through the interaction of cyclophilin D (CypD), a mitochondrial protein that is present in the lumen of the inner mitochondrial membrane (IMM) [74]. While CypD knock-out mice displayed a stronger $Ca^{2+}$ threshold than wild-type [75]. Thus, Aβ42 oligomers alter the mitochondrial $Ca^{2+}$ signalling, promoting mtPTP opening, the release of cytochrome c, leading to apoptosis and cell death [76].

### Cognition and behavioural impairment

Aβ pathology and NFT formation are having a direct correlation with the onset of cognitive impairment in AD patients. In addition, mitochondria dysfunction and oxidative stress also play a critical role in cognitive impairment [77]. Mutations in mitochondrial DNA leads to disruption of certain mitochondrial genes, altering mitochondrial functions resulting in cognitive decline in neurodegenerative diseases, demonstrating the imperative role of mitochondrial dysfunction in the contribution of cognitive decline in AD [78]. Age-related memory impairments are associated with a decrease in brain and plasma antioxidant mechanism, indicating that an imbalance in oxidative stress triggers cognitive dysfunction in AD. Moreover, research suggests that melatonin helps in modulating the plasticity in hippocampal neurons. Thus, higher levels of melatonin content are associated with a lower prevalence of cognitive impairment through hippocampal neurogenesis [79,80].

Behavioural changes are also observed in AD patients when compared to healthy individuals. AD patients with mild cognitive impairment display aggressive and impulsive behaviour that worsens with the disease progression [81]. Besides, oxidative stress is also associated with aggression and intermittent explosive disorder. Expression of the MAO-A gene is decreased in oxidative stress and its low activity is implicated in violence and aggression [82,83]. In this regard, antioxidants could be helpful against aggression, impulsivity, and emotional stability [84].

### Hormonal imbalance

Thyroid hormone improves the insulin sensitivity and reduces the activation of neurodegeneration pathway [85]. AD and other dementias are associated with the alterations in the endocrine system. Elevated cortisol, low estrogen, low testosterone, and imbalance in thyroid hormones have been implicated in the progression of AD [86]. Thyroid hormones are regarded as the powerful CNS neuro regulators that affect the neuronal cells during the early stages of CNS development [87]. Thyroid hormones are important in the maturation of neuronal cells [88,89], metabolic effects on mitochondrial ETC respiratory

complex activity [16], and expression of astrocyte structural proteins [90]. Indeed, thyroid dysfunction is associated with neurological abnormalities that result in memory impairment, cerebellar ataxia, depression, irritability, and psychosis [91]. It has been demonstrated that expression of APP mRNA, APP protein, and APP cleavage are influenced by the thyroid functioning status. *In vivo* studies done on female mice showed that the hypothyroid mouse brain increased the APP gene expression and hyperthyroid mice brain displayed opposite effects [86]. Thus hypothyroidism increases the vulnerability of Aβ deposition [92]. However, a cross-sectional study done on human patients concluded that subclinical hyperthyroidism has a consistent association with AD [93]. Nonetheless, depleted levels of Thyrotropin-Releasing Hormone (TRH), which suppresses the tau phosphorylation in hippocampal neurons have been found in AD brains [94]. A decrease in TRH gene expression is linked with elevated levels of tau and GSK-3β, which increases tau phosphorylation enhancing AD pathogenesis [95]. In this regard, administration of TRH resulted in the reduction of tau phosphorylation in hippocampal neurons [94,95].

Moreover, sex hormones like estrogen, progesterone, testosterone, and Luteinizing Hormone (LH) are involved in attenuating Aβ-induced AD pathogenesis [96]. Estrogen helps in elevating the soluble Aβ protein reducing cerebral Aβ levels. Besides, estrogen has anti-inflammatory properties and is involved in the inhibition of proinflammatory cytokines [97,98]. A low level of progesterone is also implicated with dementia and supplementation found to reduce tau levels [99]. In addition, testosterone is also found to attenuate the Aβ toxicity via estrogen-independent mechanism, and supplementation of testosterone stimulates the secretion of non-amyloidogenic APP and reduce neuronal secretion of Aβ peptides [100]. On the contrary, LH modulates Aβ processing and promote AD pathogenesis through amyloid-dependent mechanisms [101,102].

## Conclusions

AD is a neurodegenerative disorder characterized by progressive loss of memory and with ageing the prevalence of the disease increases exponentially. Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia and the individuals with T2D are believed to have two-fold higher risk of developing AD. Reports say that 80% of AD patients exhibit T2D or abnormal glucose levels, suggesting diabetes accelerates the onset of AD. Many studies reported the alterations of insulin signalling functions as a bridge between diabetes and AD. Malfunctioning of insulin signalling pathways leads to hypometabolism affecting the bioenergetics that leads to compromise in neural energy production. Moreover, decrease in glucose metabolism and insulin resistance leads to defects in APP processing leading to Aβ toxicity, increase in tau hyperphosphorylation impairing axonal transport, alterations in oxidative stress that changes mitochondrial functions, and energy metabolism leading to activation of the caspases. Besides, insulin resistance also changes the signal transduction in glial cells inducing the proinflammatory genes to produce the proinflammatory cytokines ultimately leading to neuronal death. Nevertheless, decrease in glucose availability in AD leads to aberrations in glycosylation, decline in glutamate neurotransmitter impairing the memory and cognition. Of note, thyroid and sex hormonal imbalance is also observed in AD. These complications are interlinked to one another, and currently there are no particular treatments established effectively to counteract the cognitive decline in AD.

## References


1. 2020 Alzheimer's disease facts and figures. Alzheimer's & dementia : The journal of the Alzheimer's Association. 2020.
2. Querfurth HW, LaFerla FM. Alzheimer's disease. The New England journal of medicine. 2010; 362: 329-344.
3. Bukke VN, Archana M, Villani R, Romano AD, Wawrzyniak A, et al. The Dual Role of Glutamatergic Neurotransmission in Alzheimer's Disease: From Pathophysiology to Pharmacotherapy. International journal of molecular sciences. 2020; 21.
4. Coronel R, Palmer C, Bernabeu-Zornoza A, Monteagudo M, Rosca A, et al. Physiological effects of amyloid precursor protein and its derivatives on neural stem cell biology and signaling pathways involved. Neural regeneration research. 2019; 14: 1661-1671.
5. Larson ME, Lesne SE. Soluble Abeta oligomer production and toxicity. Journal of neurochemistry. 2012; 120: 125-139.
6. Forner S, Baglietto-Vargas D, Martini AC, Trujillo-Estrada L, LaFerla FM. Synaptic Impairment in Alzheimer's Disease: A Dysregulated Symphony. Trends in neurosciences. 2017; 40: 347-357.
7. Koffie RM, Meyer-Luehmann M, Hashimoto T, Adams KW, Mielke ML, et al. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106: 4012-4017.
8. Yang T, Li S, Xu H, Walsh DM, Selkoe DJ. Large Soluble Oligomers of Amyloid beta-Protein from Alzheimer Brain Are Far Less Neuroactive Than the Smaller Oligomers to Which They Dissociate. The Journal of neuroscience : The official journal of the Society for Neuroscience. 2017; 37: 152-163.
9. Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, et al. Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. Cell. 2010; 142: 387-397.
10. Wang Y, Mandelkow E. Tau in physiology and pathology. Nature reviews Neuroscience. 2016; 17: 5-21.
11. Kimura T, Ishiguro K, Hisanaga S. Physiological and pathological phosphorylation of tau by Cdk5. Frontiers in molecular neuroscience. 2014; 7: 65.
12. Nicolia V, Ciraci V, Cavallaro RA, Ferrer I, Scarpa S, et al. GSK3beta 5'-flanking DNA Methylation and Expression in Alzheimer's Disease Patients. Current Alzheimer research. 2017; 14: 753-759.
13. Tramutola A, Triplett JC, Di Domenico F, Niedowicz DM, Murphy MP, et al. Alteration of mTOR signaling occurs early in the progression of Alzheimer Disease (AD): Analysis of brain from subjects with pre-clinical AD, amnestic mild cognitive impairment and late-stage AD. Journal of neurochemistry. 2015; 133: 739-749.
14. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Archives of neurology. 2004; 61: 661-666.
15. Barone E, Tramutola A, Triani F, Calcagnini S, Di Domenico F, et al. Biliverdin Reductase-A Mediates the Beneficial Effects of Intranasal Insulin in Alzheimer Disease. Molecular neurobiology. 2019; 56: 2922-2943.
16. Bedse G, Di Domenico F, Serviddio G, Cassano T. Aberrant insulin signaling in Alzheimer's disease: Current knowledge. Frontiers in neuroscience. 2015; 9: 204.
17. Allen KV, Frier BM, Strachan MW. The relationship between type 2 diabetes and cognitive dysfunction: Longitudinal studies and

their methodological limitations. European journal of pharmacology. 2004; 490: 169-175.

18. Toth C, Schmidt AM, Tuor UI, Francis G, Foniok T, et al. Diabetes, leukoencephalopathy and rage. Neurobiology of disease. 2006; 23: 445-461.

19. Nguyen TT, Ta QTH, Nguyen TTD, Le TT, Vo VG. Role of Insulin Resistance in the Alzheimer's Disease Progression. Neurochemical research. 2020; 45: 1481-1491.

20. Correia SC, Santos RX, Carvalho C, Cardoso S, Candeias E, et al. Insulin signaling, glucose metabolism and mitochondria: Major players in Alzheimer's disease and diabetes interrelation. Brain research. 2012; 1441: 64-78.

21. Kroner Z. The relationship between Alzheimer's disease and diabetes: Type 3 diabetes? Alternative medicine review : A journal of clinical therapeutic. 2009; 14: 373-379.

22. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, et al. Increased risk of type 2 diabetes in Alzheimer disease. Diabetes. 2004; 53: 474-481.

23. Zhao WQ, Alkon DL. Role of insulin and insulin receptor in learning and memory. Molecular and cellular endocrinology. 2001; 177: 125-1234.

24. Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance: A meta-analysis. Diabetes care. 2005; 28: 726-735.

25. Biessels GJ, Kamal A, Urban IJ, Spruijt BM, Erkelens DW, et al. Water maze learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: Effects of insulin treatment. Brain research. 1998; 800: 125-135.

26. Li ZG, Zhang W, Sima AA. Alzheimer-like changes in rat models of spontaneous diabetes. Diabetes. 2007; 56: 1817-1824.

27. Gabbouj S, Ryhanen S, Marttinen M, Wittrahm R, Takalo M, et al. Altered Insulin Signaling in Alzheimer's Disease Brain-Special Emphasis on PI3K-Akt Pathway. Frontiers in neuroscience. 2019; 13: 629.

28. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, et al. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiological reviews. 2016; 96: 1169-1209.

29. Razay G, Vreugdenhil A, Wilcock G. Obesity, abdominal obesity and Alzheimer disease. Dementia and geriatric cognitive disorders. 2006; 22: 173-176.

30. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, et al. 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.

31. Ferreira LSS, Fernandes CS, Vieira MNN, De Felice FG. Insulin Resistance in Alzheimer's Disease. Frontiers in neuroscience. 2018; 12: 830.

32. Mosconi L, De Santi S, Li J, Tsui WH, Li Y, et al. Hippocampal hypometabolism predicts cognitive decline from normal aging. Neurobiology of aging. 2008; 29: 676-692.

33. Zhao WQ, Townsend M. Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. Biochimica et biophysica acta. 2009; 1792: 482-496.

34. Scheepers A, Joost HG, Schurmann A. The glucose transporter families SGLT and GLUT: Molecular basis of normal and aberrant function. JPEN Journal of parenteral and enteral nutrition. 2004; 28: 364-371.

35. Vannucci SJ, Maher F, Simpson IA. Glucose transporter proteins in brain: Delivery of glucose to neurons and glia. Glia. 1997; 21: 2-21.

36. Kalaria RN, Harik SI. Reduced glucose transporter at the blood-brain barrier and in cerebral cortex in Alzheimer disease. Journal of neurochemistry. 1989; 53: 1083-1088.

37. Simpson IA, Chundu KR, Davies-Hill T, Honer WG, Davies P. Decreased concentrations of GLUT1 and GLUT3 glucose transporters in the brains of patients with Alzheimer's disease. Annals of neurology. 1994; 35: 546-551.

38. Bukke VN, Villani R, Archana M, Wawrzyniak A, Balawender K, et al. The Glucose Metabolic Pathway as A Potential Target for Therapeutics: Crucial Role of Glycosylation in Alzheimer's Disease. International journal of molecular sciences. 2020; 21.

39. Liu Y, Liu F, Iqbal K, Grundke-Iqbal I, Gong CX. Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. FEBS letters. 2008; 582: 359-364.

40. McClain DA, Lubas WA, Cooksey RC, Hazel M, Parker GJ, et al. Altered glycan-dependent signaling induces insulin resistance and hyperleptinemia. Proceedings of the National Academy of Sciences of the United States of America. 2002; 99: 10695-10699.

41. Zachara NE, Hart GW. Cell signaling, the essential role of O-GlcNAc! Biochimica et biophysica acta. 2006; 1761: 599-617.

42. Ryan P, Xu M, Davey AK, Danon JJ, Mellick GD, et al. O-GlcNAc Modification Protects against Protein Misfolding and Aggregation in Neurodegenerative Disease. ACS chemical neuroscience. 2019; 10: 2209-2221.

43. Deng Y, Li B, Liu Y, Iqbal K, Grundke-Iqbal I, et al. Dysregulation of insulin signaling, glucose transporters, O-GlcNAcylation, and phosphorylation of tau and neurofilaments in the brain: Implication for Alzheimer's disease. The American journal of pathology. 2009; 175: 2089-2098.

44. Gong CX, Wang JZ, Iqbal K, Grundke-Iqbal I. Inhibition of protein phosphatase 2A induces phosphorylation and accumulation of neurofilaments in metabolically active rat brain slices. Neuroscience letters. 2003; 340: 107-110.

45. Wani WY, Chatham JC, Darley-Usmar V, McMahon LL, Zhang J. O-GlcNAcylation and neurodegeneration. Brain research bulletin. 2017; 133: 80-87.

46. Frisardi V, Panza F, Farooqui AA. Late-life depression and Alzheimer's disease: The glutamatergic system inside of this mirror relationship. Brain research reviews. 2011; 67: 344-355.

47. Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. European journal of pharmacology. 2004; 490: 115-125.

48. Iwangoff P, Armbruster R, Enz A, Meier-Ruge W. Glycolytic enzymes from human autoptic brain cortex: Normal aged and demented cases. Mechanisms of ageing and development. 1980; 14: 203-209.

49. Watkins JC, Evans RH. Excitatory amino acid transmitters. Annual review of pharmacology and toxicology. 1981; 21: 165-204.

50. Walton HS, Dodd PR. Glutamate-glutamine cycling in Alzheimer's disease. Neurochemistry international. 2007; 50: 1052-1066.

51. Jacob CP, Koutsilieri E, Bartl J, Neuen-Jacob E, Arzberger T, et al. Alterations in expression of glutamatergic transporters and receptors in sporadic Alzheimer's disease. Journal of Alzheimer's disease : JAD. 2007; 11: 97-116.

52. Li S, Mallory M, Alford M, Tanaka S, Masliah E. Glutamate transporter alterations in Alzheimer disease are possibly associated with abnormal APP expression. Journal of neuropathology and experimental neurology. 1997; 56: 901-911.

53. Maciejczyk M, Zebrowska E, Chabowski A. Insulin Resistance and Oxidative Stress in the Brain: What's New? International journal of molecular sciences. 2019; 20.

54. Mergenthaler P, Lindauer U, Dienel GA, Meisel A. Sugar for the brain: The role of glucose in physiological and pathological brain function. Trends in neurosciences. 2013; 36: 587-597.

55. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nature reviews Neuroscience. 2019; 20: 148-160.

56. Santos RX, Correia SC, Zhu X, Smith MA, Moreira PI, et al. Mitochondrial DNA oxidative damage and repair in aging and Alzheimer's disease. Antioxidants & redox signaling. 2013; 18: 2444-2457.

57. Di Domenico F, Tramutola A, Butterfield DA. Role of 4-hydroxy-2-nonenal (HNE) in the pathogenesis of alzheimer disease and other selected age-related neurodegenerative disorders. Free radical biology & medicine. 2017; 111: 253-261.

58. Sultana R, Reed T, Perluigi M, Coccia R, Pierce WM, et al. Proteomic identification of nitrated brain proteins in amnestic mild cognitive impairment: a regional study. Journal of cellular and molecular medicine. 2007; 11: 839-851.

59. Cai Q, Tammineni P. Mitochondrial Aspects of Synaptic Dysfunction in Alzheimer's Disease. Journal of Alzheimer's disease : JAD. 2017; 57: 1087-1103.

60. Du H, Guo L, Yan SS. Synaptic mitochondrial pathology in Alzheimer's disease. Antioxidants & redox signaling. 2012; 16: 1467-1475.

61. Kim GH, Kim JE, Rhie SJ, Yoon S. The Role of Oxidative Stress in Neurodegenerative Diseases. Experimental neurobiology. 2015; 24: 325-340.

62. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial Reactive Oxygen Species (ROS) and ROS-induced ROS release. Physiological reviews. 2014; 94: 909-950.

63. Wang X, Su B, Zheng L, Perry G, Smith MA, et al. The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. Journal of neurochemistry. 2009; 109: 153-159.

64. Zigdon H, Kogot-Levin A, Park JW, Goldschmidt R, Kelly S, et al. Ablation of ceramide synthase 2 causes chronic oxidative stress due to disruption of the mitochondrial respiratory chain. The Journal of biological chemistry. 2013; 288: 4947-456.

65. Klein JA, Ackerman SL. Oxidative stress, cell cycle, and neurodegeneration. The Journal of clinical investigation. 2003; 111: 785-793.

66. Chen Q, Vazquez EJ, Moghaddas S, Hoppel CL, Lesnefsky EJ. Production of reactive oxygen species by mitochondria: Central role of complex III. The Journal of biological chemistry. 2003; 278: 36027-36031.

67. Kushnareva Y, Murphy AN, Andreyev A. Complex I-mediated reactive oxygen species generation: Modulation by cytochrome c and NAD(P)+ oxidation-reduction state. The Biochemical journal. 2002; 368: 545-553.

68. Gleichmann M, Mattson MP. Neuronal calcium homeostasis and dysregulation. Antioxidants & redox signaling. 2011; 14: 1261-1273.

69. Supnet C, Bezprozvanny I. Neuronal calcium signaling, mitochondrial dysfunction, and Alzheimer's disease. Journal of Alzheimer's disease : JAD. 2010; 20 Suppl 2: S487-498.

70. Emilsson L, Saetre P, Jazin E. Alzheimer's disease: mRNA expression profiles of multiple patients show alterations of genes involved with calcium signaling. Neurobiology of disease. 2006; 21: 618-625.

71. Tolar M, Keller JN, Chan S, Mattson MP, Marques MA, et al. Truncated apolipoprotein E (ApoE) causes increased intracellular calcium and may mediate ApoE neurotoxicity. The Journal of neuroscience : The official journal of the Society for Neuroscience. 1999; 19: 7100-7110.

72. Veinbergs I, Everson A, Sagara Y, Masliah E. Neurotoxic effects of apolipoprotein E4 are mediated via dysregulation of calcium homeostasis. Journal of neuroscience research. 2002; 67: 379-387.

73. Tobore TO. On the central role of mitochondria dysfunction and oxidative stress in Alzheimer's disease. Neurological sciences : Official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2019; 40: 1527-1540.

74. Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: Implications for cognitive decline in aging and Alzheimer's disease. Trends in molecular medicine. 2008; 14: 45-53.

75. Du H, Guo L, Fang F, Chen D, Sosunov AA, et al. Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. Nature medicine. 2008; 14: 1097-1105.

76. Sanz-Blasco S, Valero RA, Rodriguez-Crespo I, Villalobos C, Nunez L. Mitochondrial Ca2+ overload underlies Abeta oligomers neurotoxicity providing an unexpected mechanism of neuroprotection by NSAIDs. PloS one. 2008; 3: e2718.

77. Finsterer J. Cognitive dysfunction in mitochondrial disorders. Acta neurologica Scandinavica. 2012; 126: 1-11.

78. Petschner P, Gonda X, Baksa D, Eszlari N, Trivaks M, et al. Genes Linking Mitochondrial Function, Cognitive Impairment and Depression are Associated with Endophenotypes Serving Precision Medicine. Neuroscience. 2018; 370: 207-217.

79. Manda K, Reiter RJ. Melatonin maintains adult hippocampal neurogenesis and cognitive functions after irradiation. Progress in neurobiology. 2010; 90: 60-68.

80. Ramirez-Rodriguez G, Klempin F, Babu H, Benitez-King G, Kempermann G. Melatonin modulates cell survival of new neurons in the hippocampus of adult mice. Neuropsychopharmacology : Official publication of the American College of Neuropsychopharmacology. 2009; 34: 2180-2191.

81. Bidzan L, Bidzan M, Pachalska M. Aggressive and impulsive behavior in Alzheimer's disease and progression of dementia. Medical science monitor : International medical journal of experimental and clinical research. 2012; 18: CR182-189.

82. El-Terras A, Soliman MM, Alkhedaide A, Attia HF, Alharthy A, et al. Carbonated soft drinks induce oxidative stress and alter the expression of certain genes in the brains of Wistar rats. Molecular medicine reports. 2016; 13: 3147-3154.

83. McDermott R, Tingley D, Cowden J, Frazzetto G, Johnson DD. Monoamine oxidase A gene (MAOA) predicts behavioral aggression following provocation. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106: 2118-2123.

84. Hira S, Saleem U, Anwar F, Ahmad B. Antioxidants Attenuate Isolation- and L-DOPA-Induced Aggression in Mice. Frontiers in

pharmacology. 2017; 8: 945.

85. Prieto-Almeida F, Panveloski-Costa AC, Crunfli F, da Silva Teixeira S, Nunes MT, et al. Thyroid hormone improves insulin signaling and reduces the activation of neurodegenerative pathway in the hippocampus of diabetic adult male rats. Life sciences. 2018; 192: 253-258.

86. Tan ZS, Vasan RS. Thyroid function and Alzheimer's disease. Journal of Alzheimer's disease : JAD. 2009; 16: 503-507.

87. Bernal J, Pekonen F. Ontogenesis of the nuclear 3,5,3'-triiodothyronine receptor in the human fetal brain. Endocrinology. 1984; 114: 677-679.

88. Garza R, Puymirat J, Dussault JH. Influence of soluble environmental factors on the development of fetal brain acetylcholinesterase-positive neurons cultured in a chemically defined medium: Comparison with the effects of L-triiodothyronine (L-T3). Brain research Developmental brain research. 1990; 56: 160-168.

89. Honegger P, Lenoir D. Triodothyronine enhancement of neuronal differentiation in aggregating fetal rat brain cells cultured in a chemically defined medium. Brain research. 1980; 199: 425-434.

90. Siegrist-Kaiser CA, Juge-Aubry C, Tranter MP, Ekenbarger DM, Leonard JL. Thyroxine-dependent modulation of actin polymerization in cultured astrocytes. A novel, extranuclear action of thyroid hormone. The Journal of biological chemistry. 1990; 265: 5296-5302.

91. Smith JW, Evans AT, Costall B, Smythe JW. Thyroid hormones, brain function and cognition: A brief review. Neuroscience and biobehavioral reviews. 2002; 26: 45-60.

92. Ghenimi N, Alfos S, Redonnet A, Higueret P, Pallet V, et al. Adult-onset hypothyroidism induces the amyloidogenic pathway of amyloid precursor protein processing in the rat hippocampus. Journal of neuroendocrinology. 2010; 22: 951-959.

93. Agarwal R, Kushwaha S, Chhillar N, Kumar A, Dubey DK, et al. A cross-sectional study on thyroid status in North Indian elderly outpatients with dementia. Annals of Indian Academy of Neurology. 2013; 16: 333-337.

94. Luo L, Yano N, Mao Q, Jackson IM, Stopa EG. Thyrotropin Releasing Hormone (TRH) in the hippocampus of Alzheimer patients. Journal of Alzheimer's disease : JAD. 2002; 4: 97-103.

95. Luo L, Stopa EG. Thyrotropin releasing hormone inhibits tau phosphorylation by dual signaling pathways in hippocampal neurons. Journal of Alzheimer's disease : JAD. 2004; 6: 527-536.

96. Grimm A, Biliouris EE, Lang UE, Gotz J, Mensah-Nyagan AG, et al. Sex hormone-related neurosteroids differentially rescue bioenergetic deficits induced by amyloid-beta or hyperphosphorylated tau protein. Cellular and molecular life sciences : CMLS. 2016; 73: 201-215.

97. Brown CM, Mulcahey TA, Filipek NC, Wise PM. Production of proinflammatory cytokines and chemokines during neuroinflammation: Novel roles for estrogen receptors alpha and beta. Endocrinology. 2010; 151: 4916-4925.

98. Villa A, Vegeto E, Poletti A, Maggi A. Estrogens, Neuroinflammation, and Neurodegeneration. Endocrine reviews. 2016; 37: 372-402.

99. Dang TN, Dobson-Stone C, Glaros EN, Kim WS, Hallupp M, et al. Endogenous progesterone levels and frontotemporal dementia: Modulation of TDP-43 and Tau levels in vitro and treatment of the A315T TARDBP mouse model. Disease models & mechanisms. 2013; 6: 1198-1204.

100. Gouras GK, Xu H, Gross RS, Greenfield JP, Hai B, et al. Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides. Proceedings of the National Academy of Sciences of the United States of America. 2000; 97: 1202-1205.

101. Verdile G, Asih PR, Barron AM, Wahjoepramono EJ, Ittner LM, et al. The impact of luteinizing hormone and testosterone on beta amyloid (Abeta) accumulation: Animal and human clinical studies. Hormones and behavior. 2015; 76: 81-90.

102. Webber KM, Perry G, Smith MA, Casadesus G. The contribution of luteinizing hormone to Alzheimer disease pathogenesis. Clinical medicine & research. 2007; 5: 177-183.