# Genomic Linkage Between Alzheimer's Disease and Type 2 Diabetes

Taoufik Nedjadi[*,1,§], Absarul Haque[*,1,§], Qamre Alam[1], Siew H. Gan[2], Adeel G. Chaudhary[1], Adel M. Abuzenadah[1], Ghazi A. Damanhouri[1] and Mohammad A. Kamal[1]

[1]*King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia*

[2]*Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia*

**Abstract:** Alzheimer's disease (AD) is a major health concern that affects nearly every society worldwide. The disease is an irreversible, progressive and age-related neurodegenerative disorder. It is characterized by impaired cognitive function and the diffuse deposition of amyloid plaques and neurofibrillary tangles. The causes of AD and the underlying mechanisms that trigger the onset of the disease are still a matter of debate. Several epidemiological studies have shown that the development of AD is associated with type 2 diabetes mellitus (T2D). In this review, we provide evidence for the link between T2D and AD, highlighting the critical role of insulin in the pathogenesis of these diseases, and we provide information on the genes that might be involved in the interplay between these two disorders. New insight into the complex biology of AD is necessary for the early diagnosis of the disease, the development of novel drug therapies and the prevention of these health issues.

**Keywords:** Alzheimer's disease, type-2 diabetes, insulin, insulin resistance, genes.

## INTRODUCTION

In 1906, the German scientist Alois Alzheimer diagnosed the first case of Alzheimer's disease, which has since become a major health concern affecting nearly every society worldwide. The disease is the main cause of dementia and is characterized by a progressive impairment of cognitive function and behavioral deficits. It was reported that, in the year 2010, 36 million people were affected with dementia worldwide. These numbers are predicted to double every 20 years to 66 million by 2030 and 115 million by 2050 [1]. The disease has had a major impact on global healthcare and social services and has also become an economic burden. The estimated worldwide cost of dementia was over US $600 billion in the year 2010, which represents more than 1% of the global gross domestic product [2].

AD is clinically distinguished by a decline in cognitive functions associated with a progressive impairment in the daily living activities and behavioral disturbances [3]. Histologically, amyloid plaques and the deposition of neurofibrillary tangles constitute the main pathological features observed in Alzheimer's patients. These lesions are the result of aberrant protein processing and are characterized by the self-association and aggregation of β-amyloid (Aβ), which is derived from the amyloid precursor protein (APP) and results in neuritic plaques, and the microtubule associated protein tau, which forms neurofibrillary tangles [4]. Abnormal hyperphosphorylation

of tau, together with the accumulation of non-soluble β-amyloid, leads to neuron toxicity and induces apoptotic cell death [5].

Numerous multidisciplinary studies, such as epidemiological and clinical studies, have been undertaken in an attempt to identify the etiology, pathogenesis and risk factors associated with AD. These studies provide strong evidence that AD is associated with type 2 diabetes mellitus (T2D) and that both diseases share the same pathophysiology, suggesting that AD might be type 3 diabetes [6]. T2D is a non-insulin dependent metabolic disorder with increasing prevalence worldwide. The disease represents 90-95% of all diabetic cases [7]. It has been associated with the late onset of AD and with other neurodegenerative disorders, such as stroke [8] and, most likely, Parkinson's Disease [9, 10]. In a separate study, T2D was linked with a two-fold increased risk of developing mild cognitive impairment (MCI), which is an intermediate phase between normal behavior and AD, in elderly women [11]. Furthermore Ohara and colleagues reported that T2D was a significant risk factor for all types of dementia, including AD [12]. In an independent study using a transgenic mouse model, Jimenez-Palomares and colleagues provided experimental evidence that demonstrated that the increased production of aberrant Aβ triggered the onset of glucose intolerance and insulin resistance, which means that AD might lead to the development of T2D [13]. These diseases also share similar biochemical features characterized by amyloidosis, which presents as fibrillar amylin aggregates in the pancreatic islets of T2D patients and amyloid deposits in the brains of AD patients, suggesting that these diseases may have common pathogenic mechanisms [5]. Data gathered from animal mouse models support the epidemiological findings and highlight insulin as a mechanistic link between the two disorders [14]. Several mechanisms underlying this

*Address correspondence to this author at the Fundamental and Applied Biology Group, King Fahd Medical Research Centre, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia; Tel: +966-6401000 Ext 25673; Fax: + 15016368847; E-mails: absar99@gmail.com, ntaoufik@hotmail.com;

§These authors contributed equally to this work.

association have been proposed. These mechanisms include the presence of cerebrovascular disease commonly associated with T2D and the addition of the toxic effects of chronic hyperglycemia, hyperinsulinemia and insulin resistance [15].

Still, there are no effective treatments to prevent, halt, or reverse AD, but emerging research from recently adopted genetic and transgenic mouse model approaches might provide new insight into the pathogenesis of AD and change this gloomy picture. These approaches focused on the molecular alterations and genetic susceptibility of individuals with AD and its linkage with others disorders, including T2D. In this article, we summarized the clinical and epidemiological features of AD in light of the current literature. We also reviewed the molecular mechanisms that possibly link the pathogenesis of AD and T2D, focusing on the potential involvement of insulin and the insulin signaling network in the progression of AD.

## CLINICAL FEATURES

AD is a progressive disorder; therefore, identifying the specific time of its initiation is often difficult. The disease is likely preceded by an intermediate phase referred to as mild cognitive impairment (MCI) [16]. This phase represents a transitional state and is characterized by memory complaints and objective memory deficits, but with preserved cognitive and functional abilities that can maintain the standard daily life activities [17]. Based on an epidemiological study performed by Gauthier and colleagues, the prevalence of MCI ranges from 3% to 19% in adults older than 65 years. Some of these adults will recover over time, whereas most of them will progress to dementia within 5 years [18]. In an independent study, Mitchell and Shiri-Freshki (2009) reported that 10–15% of MCI patients progress to dementia every year [19]. This observation was supported by other studies [20, 21]. Yet, after including the criteria for MCI, older persons have a ten-fold increased risk in developing AD [22]. For this reason, it is now generally accepted that studying the early phase of AD is more beneficial to understanding the biology of the disease. The progression of MCI to AD is associated with symptoms and signs of memory impairment, which is the most significant clinical feature. Memory decline represents the cardinal hallmark of AD. In this case, patients must exhibit other symptoms that reflect a severe decrease in their cognitive abilities and that jeopardize their daily life activities. These symptoms include the inability to generate coherent speech or to understand spoken or written language, the inability to recognize or identify objects and the inability to think abstractly and to make sound judgments [23]. Language impairment, visio-spatial dysfunction and behavioral and psychiatric symptoms are also common clinical features of AD. As the disease progresses, these signs become more prominent, eventually resulting in global aphasia, apathy and depression, which can occur in up to 50% of AD individuals [23, 24].

## EPIDEMIOLOGICAL EVIDENCE

### Risk Factors

Alzheimer's disease is a multi-factorial disease, and several factors have been implicated in its pathogenesis. The precise causes of AD are not yet known. However, epidemiological studies have been performed to identify risk factors that increase the likelihood of developing AD, and a number of risk factors have been identified. These include:

−   **Increasing age:** Population aging and increased life expectancy, especially in developed countries, has massively contributed to the increased prevalence of dementia, particularly AD. Dementia-related diseases will also increase in developing countries due to the increased total population, and this increasing population will be an enormous challenge to the global health care services [25]. A number of published reports have indicated that AD is the leading cause of neurodegeneration in elderly individuals, and therefore, the greatest risk factor for developing AD is advanced age [26]. It was reported that most people with AD are diagnosed at an age of 65 years and older, and the age-specific prevalence of AD almost doubles every 5 years after this point. It is expected that 50% of the population aged 85 and older may develop AD [27].

−   **Inherited predisposition:** The main genes that cause familial AD have not yet been identified (Tables **1** and **2**). However, early-onset AD has been associated autosomal dominant mutations in the APP, presenilin 1 and presenilin 2 genes [28]. This form of AD accounts for approximately 2–5% of all AD cases [29].

−   **Apolipoprotein Eε4:** The association between diabetes and AD is particularly strong among carriers of the APO-ε4 allele [30]. It has been postulated that early-onset AD and its risk of developing AD are attributed to the increased expression of the APO-ε4 isoform [31]. APO-ε4 contributes to the decreased clearance of plaques and is involved in the increased aggregation of the neurotoxic Aß. It has also been suggested that apoE-ε4 is less effective against oxidative stress and contributes to cholinergic dysfunction in AD [32].

−   **Other risk factors:**

1.  Diabetes: A strong link between T2D and AD has been shown [33, 34] in a number of clinical and epidemiological studies. The detailed association between T2D and AD will be reviewed below.

2.  Diet: A variety of dietary factors are also associated with an increased risk of AD, all of which are amenable to intervention, such as increased red and processed meat consumption and a reduced intake of methionine [35] and folate from food sources [36].

3.  Cholesterol: Perturbed cholesterol levels have been proposed as an important factor contributing to the development of AD [37].

4.  Cardiovascular disorders: It was revealed that long-standing cardiovascular patients were susceptible to a decline in cognitive function and the development of AD [38]. Thus, controlling vascular risk factors, such as hypertension, obesity, coronary disease, and cholesterol level may contribute to the rescue of vulnerable patients [39].

**Table 1.    List of Genes Associated with Early-Onset AD and their Pathogenic Effects**

| Gene | Protein | Chromosome | Molecular Phenotype | References |
|------|---------|------------|---------------------|------------|
| PSEN1 | Presenilin 1 | 14q24 | Increased Aβ42/Aβ40 ratio | [144] |
| APP | Amyloid β [A4] protein precursor | 21q21 | Increased Aβ42/Aβ40 Increased Aβ production Increased Aβ aggregation ratio | [145] |
| PSEN2 | Presenilin 2 | 1q31 | Increased Aβ42/Aβ40 ratio | [146] |

**Table 2.    List of Genes Associated with Late-Onset AD and their Pathogenic Effects**

| Gene | Protein | Chromosome | Molecular Phenotype | References |
|------|---------|------------|---------------------|------------|
| ATXN1 | Ataxin 1 | 6p22.3 | Production of Aβ | [147] |
| CD33 | CD33 [Siglec 3] | 19q13.3 | Innate immunity, degradation of Aβ | [147] |
| CLU | Clusterin | 8p21.1 | Clearance of Aβ, innate immunity | [148] |
| CR1 | Complement component [3b/4b] receptor 1 | 1q32 | Clearance of Aβ, innate immunity | [148] |
| PICALM | Phosphatidylinositol binding clathrin assembly molecule | 11q14 | Production and clearance of Aβ, cellular signaling | [149] |
| BIN1 | Bridging integrator 1 | 2q14 | Production and clearance of Aβ, cellular signaling | [150] |
| ABCA7 | ATP-binding cassette subfamily A member 7 | 19p13.3 | Lipid metabolism; cellular signaling | [151] |
| CD2AP | CD2-associated protein | 6p12.3 | Cellular signaling | [151] |
| EPHA1 | EPH receptor A1 | 7q34 | Cellular signaling, innate immunity | [151] |
| MS4A6A/MS4A4E | Membrane-spanning 4-domains, subfamily A, members 6A and 4E | 11q12.1 | Cellular signaling | [152] |
| APOE | Apolipoprotein E | 19q13 | Clearance of Aβ, Lipid metabolism | [153] |

5.    Smoking: Ongoing studies are investigating the potential association between AD and tobacco smoking [40]. This association is still litigious and remains to be clarified.

6.    Gender: It has been reported that there is an increased incidence of AD in females compared to males [41].

7.    Level of education: It has been reported that AD is more prevalent in populations with low educational profiles [39].

**Prevalence and Incidence**

Alzheimer's disease is considered the sixth leading cause of death and the fifth leading cause of death in persons aged ≥65 years [42]. The prevalence and incidence rates of AD increase exponentially after the age of 70 [43]. Taking into consideration the regional distribution of high-risk populations, it has been noted that developed countries have a higher incidence rate compared to developing countries. Western European individuals aged 60 and above exhibited the highest prevalence of dementia (6.4%), and 4.4% of these individuals suffer from AD [44]. As for the North American population, the prevalence of AD has been reported to be approximately 9.7% for individuals above the age of 70 [45], followed by the populations from Latin America (4.9%) and China and its western-Pacific neighbors (4.0%). Data gathered from studies that were performed in

developing countries confirmed that the incidence of AD is generally lower than in North America and Europe [42]. For example, the incidence rate of AD among people aged 65 and older was 7.7 per 1000 persons/year in Brazil and 3.2 per 1000 persons/year in India [46]. Geographical discrepancy in the results may reflect the differences in study design and data analysis. Unfortunately, there have been very few studies on dementia in the Gulf region. In Saudi Arabia, the prevalence rate of AD was shown to be significantly lower than the rates reported in Western countries. The overall prevalence rate among the Saudi population was reported to be 0.22 per 1000 persons [47]. In Egypt, the prevalence ratio of people with dementia accounts for 2.26% of the population aged ≥50 years. This ratio increases to 4.5% in persons aged 60 and over, most of whom are affected by AD with an estimated ratio of 51.2% [48, 49].

In an attempt to investigate the etiology of AD, a number of risk factors have been nominated that may trigger or facilitate the development of AD. Strong evidence from epidemiologic research has emerged that supports the hypothesis that T2D is associated with an increased risk of AD [42] and that controlling diabetes could have a major impact on the prevention of the disease [50]. The evidence is based on the fact that both diseases are age-related. The evidence takes also into consideration the total number of both T2D and AD patients, which is expected to increase from 171 million in 2000 to 366 million in 2030 for T2D

[51] and from 36 million people in 2010 to 66 million by 2030 for AD [43]. The Rotterdam study showed that the risk of developing AD increased almost two-fold in diabetic patients compared with normal individuals, and insulin treatment was associated with a more than four-fold increase in AD incidence. In contrast, in a different study led by Curb *et al*. (1999), there was no association between T2D or impaired glucose tolerance and AD episodes in Japanese American men living in Hawaii [52]. A number of other cross-sectional studies linked the increased risk of AD to hyperinsulinemia and not directly to T2D [53]. Similarly, another longitudinal study from the American continents found that the risk of AD was higher in persons with hyperinsulinemia, indicating that insulin might directly influence the risk of AD [54]. A recent report from the Alzheimer's Association (2012) revealed that 29% of AD patients showed signs of coexisting diabetes conditions. In a recent meta-analysis, which included 10 longitudinal studies assessing the association between T2D and AD, stated that T2D increased the risk of AD by 54% [55].

Epidemiological and clinical data provide evidence of the overlap between T2D and AD, suggesting that these two diseases possess a natural, parallel history and may share a similar genetic signature and homologous underlying mechanisms.

**Molecular Linkage Between T2D and AD**

Various mechanisms of how T2D influences the development of AD have been suggested. Because the common features of T2D disease are hyperglycemia, hyperinsulinemia, and insulin resistance, which in turn lead to impaired downstream signaling pathways [56], most of the previous studies have focused on insulin as a core molecule mediating the cognitive impairment in AD. Furthermore, the observation that insulin sensitizer therapy enhanced the cognitive performance in an experimental model [57] also lent support to the concept that insulin is an important molecule in the pathogenesis of AD [58]. It has been suggested that insulin resistance contributes to the neuropathy that frequently occurs in patients with impaired glucose tolerance [59]. It was also revealed that insulin resistance was detected in the majority of elderly people and contributes to the development of AD [60]. Insulin is a major metabolic hormone that regulates glucose metabolism. Diabetic patients can no longer control their blood sugar levels, resulting in hyperglycemia. Chronic overload with sugars leads to chronic hyperinsulinemia, which eventually triggers insulin resistance. This condition is mediated, to a certain extent, by a defect in the insulin receptor, leading to an impaired downstream insulin signaling cascade [61]. A broad distribution of insulin receptors in the brain, particularly in the hippocampus, makes the brain more vulnerable to a glucose level imbalance. This will have a direct effect on the activity of the brain, including cognitive processes [58]. Thus, glucose imbalances lead to the progressive impairment of the brain's capacity to utilize glucose and respond to insulin and insulin-like growth factors (IGF), which regulate neuronal survival, energy metabolism, and plasticity and are required for learning and memory [62, 63]. Hence, endogenous brain-specific impairments in insulin and IGF signaling account for the

majority of AD-associated abnormalities, which are pathologically characterized by the occurrence of intracellular neurofibrillary tangles rich in tau protein and extracellular plaques containing amyloid peptide [64]. It has been documented that too much insulin in the brain can contribute to β -amyloid production and subsequent accumulation of amyloid plaques [65]. Hence, T2D leads to the destructive deposition of amyloid (Aβ), and the accumulation of Aβ in the brain results in Alzheimer's. Insulin resistance and hyperinsulinemia trigger inflammation, and T2D has been associated with elevated levels of inflammatory markers that increase the risk of AD [66-68]. Patients with AD have elevated concentrations of the inflammatory cytokine interleukin (IL) 6 and the lipid peroxidation marker F2- isoprostane in their cerebrospinal fluid (CSF) [69, 70]. Furthermore, *in vitro* and animal studies suggest that inflammation interferes with the processing and deposition of amyloid (Aβ), a key peptide linked to AD pathogenesis [67]. Insulin may also contribute to the inflammation of the central nervous system (CNS), partially through its effects on Aβ [71]. Insulin promotes the release of Aβ from intracellular neuronal compartments and inhibits its degradation by the metalloprotease insulin-degrading enzyme [72, 73]. However, a second major mechanism of cognitive impairment has been linked to obesity and T2D. Human and experimental animal studies revealed that neurodegeneration associated with peripheral insulin resistance is likely mediate by a liver brain axis whereby toxic lipids, including ceramides, cross the blood brain barrier, resulting in brain insulin resistance, oxidative stress, neuro-inflammation, and cell death. In essence, there are two mechanisms of brain insulin resistance that can lead to AD-like neurodegeneration: one is mediated by endogenous, CNS factors, whereas the other is caused by peripheral insulin resistance with excess cytotoxic ceramide production [74].

The similarities between T2D and AD include the aging-related nature, degeneration, high cholesterol levels, peripheral and CNS insulin resistance, dysfunctional IR and IR-mediated signaling pathways, and decreased glucose transport and metabolism, despite the higher levels of non-metabolized glucose in the cerebral blood [75-77]. Of note, the imbalance between low and high glucose levels in T2D patients may be responsible for vascular damage in the brain and neurodegeneration, thus facilitating the onset of AD.

**Insulin Function in the Brain**

The biological basis of T2D is a systemic and chronic impairment in glucose metabolism and utilization. Glucose metabolism is vital to the brain because glucose is nearly the exclusive energy source required to fuel the high-energy machinery of its cells (neurons) [78, 79]. Surprisingly, the brain represents only 2% of the body weight but consumes 18–30% of the total body glucose [80]. However, it is now well established that the consumption of glucose is critical for the brain, and the uptake of glucose into the neurons is mediated through insulin, an important component of brain glucose metabolism [79]. If the uptake of glucose into the neurons is diminished, energy metabolism is hindered with significant consequences on the brain's capacity to generate connections that are vital to memory and learning [81].

Experimental diabetes in animal models showed a clear association between abnormal glucose metabolism and impaired memory and synaptic plasticity [82-84]. Furthermore, it has been shown that insulin and IGF play a role in modulating neuronal survival, energy metabolism, synapse formation and plasticity, which are required for learning and memory [85]. Additionally, insulin/IGF also regulate the growth, survival and myelin production/maintenance in oligodendrocytes [86]. Therefore, the impairment of the insulin/IGF receptor signal adversely affects glucose homeostasis, energy metabolism and the structure and function of white matter fiber, which are directly associated with a wide range of neuronal and glial functions. Insulin binds to receptors at the synapse, a key communication locus between neurons in the brain. Synaptic junctures between the neurons are where the cell-to-cell brain circuitry is facilitated. Insulin is now known to serve as a vital element for the maintenance of the synapse structure and function and subsequently for the strength of the connections between neurons [82-84]. This insulin/synaptic axis and the formation of new circuits in the brain are key contributors to "brain plasticity". Brain plasticity refers to the brain's capacity for adaptive changes. Thus, disruptions in glucose supply, transport, and utilization can lead to neuronal damage and directly affect cognitive function. Furthermore, there is now evidence that demonstrates that insulin and its receptors in the brain are key elements in memory formation and learning beyond their function in glucose uptake [81].

## Insulin Receptors Function in the Brain

Until approximately 30 years ago, there was speculation that neurons do not require insulin for glucose transport; therefore, the brain was considered a non-insulin targeting organ. However, this misconception was changed when widespread distribution of insulin receptor (IR) was detected in the brain [87, 88]. A growing body of experimental evidence, such as the specific regional expression of IR mRNA by *in situ* hybridization [89, 90] and insulin binding with autoradiography [91], revealed that IR is distributed in discrete areas, including the olfactory bulb, pyriform cortex, hippocampus, amygdala, and hypothalamus. Surprisingly, the most elevated IR mRNA expression was found in the choroid plexus and the cerebellum [92-94]. Interestingly, while the cerebellum has high levels of IR mRNA, only low levels of protein are detectable [91, 95], presumably due to the high protein turnover rate of the receptor. IRs are present at the synapses and are highly expressed in highly plastic areas of rich synaptic density, such as the cortex and hippocampus [95], suggesting a possible relationship between insulin signaling and synaptic plasticity. It has been demonstrated that there is an alteration in insulin and IR gene expression in the brains of advanced AD patients. Moreover, IR expression is upregulated in the rat hippocampus during spatial memory tasks, such as the Morris- Water Maze [95]. IR is a membrane receptor tyrosine kinase that is activated by tyrosine autophosphorylation of the β subunit upon insulin binding to the α subunit, which is exposed to the extracellular surface [96, 97]. The phosphorylated receptor subsequently activates several downstream signaling cascades primarily through the insulin receptor substrates 1–6 (IRS1-6). Activation of the insulin receptors results in the downstream activation of the phosphatidylinositide 3 kinase (PI3)/Akt kinase (Akt) pathway [98, 99], an important signaling pathway for synaptic plasticity [100]. Akt inactivates glycogen synthase kinase-3 (GSK-3) by phosphorylating the protein on serine 9 [100]. It has recently been reported that GSK-3 co-immunoprecipitates with GluR1/2 AMPA receptor subunits [101] and that GSK-3 activity is essential for determining the direction of synaptic plasticity, as its inactivation is crucial for the induction of long-term potentiation [102-104]. The brain forms new connections and "rewires" itself to integrate new information during the learning process, or it "rewires" itself to replace the damaged pathways that were lost in a stroke. If the function of insulin is disrupted in the brain, synapse function and density are diminished, and the neural pathways that optimize and reflect learning and memory formation are hindered. Therefore, dysfunction of insulin and insulin signaling at the synapse is largely to blame for the decreased synaptic density and brain plasticity that are central features of the brains of AD patients.

## Insulin Resistance and Amyloidogenesis as Common Molecular Features of Both T2D and AD

Insulin resistance may be caused by abnormalities in insulin signal transduction at any level of the signaling pathways in the target cells. This process is initiated through various mechanisms, such as the binding of IR to its ligands, the activation of IR kinases and the activation of individual molecules in specific signaling pathways or, ultimately, at the level of the effector systems, such as the glucose transport system or glycogen synthesis. Approximately 20% of the neurodegenerative diseases that affect the general population worldwide are associated with diabetes mellitus, increased insulin resistance, obesity, disturbed insulin sensitivity and excessive or impaired insulin secretion [105]. T2D is becoming widely recognized as a risk factor for the development of AD and clinical features such as insulin signaling defects. Possible contributors to this relationship may include Aβ accumulation and the hyperphosphorylation of tau protein [106]. As we have previously mentioned, insulin resistance develops as a result of the reduced ability of the IR to respond to insulin stimulation [107]. Under this condition, the islet β -cells in the pancreas secrete higher levels of insulin to compensate for the declined receptor function, making hyperinsulinemia a common characteristic of T2D patients. Therefore, numerous lines of evidence clearly dictate that insulin deficiency or insulin resistance is a feature of T2D, which in turn plays an important role in AD pathogenesis.

## COMMON MOLECULAR LINKAGES IN T2D AND AD

### Role of Insulin Signaling Deregulation in AD Pathogenesis

The understanding of IR physiology in AD will contribute to the development of more adequate preventive and therapeutic strategies to decrease the burden of complications related to insulin resistance. Although IRs in the brain have structures and functions that are distinct from their peripheral counterparts [108], evidence indicates that excessive insulin levels are associated with a functional decline in the CNS. Studies conducted with elderly subjects

demonstrated that the elderly men with the highest insulin levels made 25% more errors on the Mini-Mental State Examination than men with the lowest insulin levels [109-111]. In their study using postmortem brain tissues, Frolich and colleagues first reported an increase in the insulin binding activity in the brain regions of sporadic AD [112]. It is important to note that despite the increased insulin binding, insulin receptor activity was reduced in the AD brain [113], which was consistent with insulin insensitivity.

Impaired insulin signaling negatively affects several functions of brain cells, such as glucose homeostasis, energy metabolism, white matter fiber structure and function [114]. Like other hormones, insulin exerts its effects by binding to its specific cell surface receptor, causing the pleiotropic hormone to activate multiple signaling pathways. This binding initiates a cascade of intracellular signaling pathways, which ultimately lead to changes in glucose transport, glycogen and lipid synthesis and specific gene expression [115]. The IRs and the insulin-like growth factor receptor belong to the receptor tyrosine kinase super-family. However, signal transduction by these receptors [116] mainly occurs *via* the insulin receptor substrate (IRS) adapter proteins (IRS-1–4) [117]. These adapter proteins bind to the transphosphorylated activated receptors at the tyrosine docking sites. Tyrosine phosphorylated (TP) IRSs transmit intracellular signals that mediate growth, metabolism, and viability by interacting with downstream SH2 domain-containing molecules [118], including the p85 regulatory subunit of phosphatidylinositol-3 kinase (PI3K) [119]. IRS proteins are involved in an important regulatory step in IR activation. The degree of serine/threonine phosphorylation determines the positive or negative signal transmission *via* the IRS proteins [116]. During insulin stimulation, PI3K becomes activated *via* IRS association, as well as the Ras–MAPK pathway, leading to glucose transport activation through GLUT-4 and other metabolic actions [115]. However, this processes relies on the tyrosine phosphorylation of IRS after it is bound to the juxta-membrane region of the activated IR [120]. Experimental data indicate that increased serine/threonine phosphorylation of IRS could affect the action of insulin. This hyperphosphorylation of the serine/threonine residues could explain why tyrosine phosphorylation of IRS does not occur in the presence of insulin and leads to insulin resistance. Thus, PI3k is a key molecule in signal transduction that stimulates glucose transport [121] and inhibits apoptosis by activating Akt/Protein kinase B and inhibiting glycogen synthase kinase-3β (GSK-3β) [122]. Positive stimulation through the PI3K/Akt pathway preserves mitochondrial membrane integrity [123] and inhibits the production of free radicals that causes mitochondrial DNA damage, mitochondrial dysfunction, and the initiation of pro-apoptotic mechanisms [124]. Hence, impairments in insulin and IGF signaling due to insulin/IGF resistance and/or trophic factor withdrawal lead to decreased energy metabolism due to reduced glucose uptake and ATP production [125]. Reduced ATP adversely affects cellular homeostasis, membrane permeability, and fundamental processes required for synaptic maintenance and remodeling, which are needed for learning and establishing new memory.

## Role of Insulin Degrading Enzyme (IDE) in AD Pathogenesis

Apart from the insulin signaling deregulation in AD, elevated insulin poses another problem. Insulin regulates Aβ levels by modulating Aβ production through the actions of APP cleaving enzyme (BACE) and/or γ-secretase on the β-site, as well as by modulating Aβ degradation *via* insulin-degrading enzyme [126-129]. It is conceivable that the actions of insulin or the lack of action may be a link between T2D and AD. IDE is a metalloprotease enzyme that catalyzes the degradation of insulin in the brain following internalization of insulin and its receptor [130]. IDE also degrades soluble Aβ, thereby regulating its extracellular levels by reducing aggregation and toxic amyloid plaque formation that occurs during AD pathogenesis [130]. It is believed that the net production of Aβ is directly related to the processing of APP and Aβ degradation, as well as its clearance; these factors are crucial determinants for the aggregation and formation of neurotoxic amyloid plaques in the brains of AD patients. It has been demonstrated that Aβ-degrading proteases could regulate the cerebral levels of the peptide: thus, IDE is considered an Aβ-degrading protease [131]. Among the IDE substrates, insulin and amylin are significant as they are involved in the pathogenesis of T2D and in AD pathology [132-136]. These substrates compete with each other to be degraded by IDE *in vivo*. If the insulin level increases in the brain, it would hinder the ability of IDE to effectively degrade Aβ. IDE catalyzes insulin degradation and negatively regulates its signaling. However, the affinity of IDE for insulin is much greater than Aβ [133], but, surprisingly, it has been demonstrated that the C-terminal cleavage products of APP, inhibit insulin binding and insulin receptor autophosphorylation by reducing the affinity of insulin for its own receptor [137]. Because APP-Aβ competes with insulin for receptor binding, the inefficient degradation of soluble APP-Aβ could represent an important factor mediating brain insulin resistance in AD patients. Interestingly, when IDE is overexpressed in transgenic mice, the mutant IDE mice exhibits hyperinsulinemia, glucose intolerance, and increased levels of APP-Aβ in the brain [138]. These findings support the hypothesis that APP-Aβ contributes to AD neurodegeneration by impairing insulin signaling and promoting insulin resistance. Insulin has a very similar molecular structure to amyloid plaque and thus might compete for the benefits of IDE [139]. Elevated insulin levels have been implicated in the failure of brain cells to clear the β-amyloid. It has been shown that the brains of AD patients have reduced IDE levels [140], and the overexpression of IDE in APP mutant mice reduced plaque formation [141]. Accordingly, Ho and colleagues [142], using an APP transgenic AD animal model, demonstrated that insulin resistance caused by a high fat diet is associated with a decrease in IDE levels and PI3K-Akt activity and an increase in Aβ formation. PKB/Akt is a player in the neuroprotection mediated by insulin signaling. In fact, data show that Akt overexpression in PC12 cells protected the cells from Aβ-induced cell death [143]. Therefore, all of the evidence shown above clearly shows that the insulin signaling dysfunction may be involved in the pathological events that occur in AD brains. Indeed, there is a major abnormality in insulin and IR gene expression in the brains from advanced AD patients, which strongly supports the

notion [62]. Furthermore, excess insulin can increase the risk of AD by stimulating pro-inflammatory molecules in the brain and by impeding the clearance of beta-amyloid. Insulin is partly responsible for the uptake of glucose into neurons. The human brain needs a great deal of glucose for energy metabolism, and individuals who have a greater genetic risk (ApoE4) for AD have lower rates of glucose metabolism. The insulin resistance that underlies T2D/Metabolic Syndrome contributes to decreased brain insulin levels [69], and elevated insulin in the body (periphery) contributes to inflammatory molecules in the brain. Indeed, elevated insulin in the body can have direct and deleterious consequences on brain integrity. However, as an emerging theory and explanation of the cascade of neurodegeneration that characterizes AD, the role of insulin function in the brain and how its dysregulation directly contributes to the cognitive impairment that defines AD has resulted in the development of a neuroendocrine model of AD that seems destined to replace the amyloid theory of AD.

## CONCLUSION

AD is a multifactorial disease that might be linked to several different pathways. The disease emerges from the interactions of environmental factors and genetic susceptibility, and apolipoprotein Eε4 and other genes are important risk factors. A considerable body of experimental and epidemiological evidence supports the association between AD and T2D. This link is also supported by the overlapping molecular and biochemical abnormalities of the two disorders. Impairment in insulin and insulin-like growth factor, as well as signaling mechanisms that lead to the deregulation of glucose metabolism, are at the core of the pathogenesis. Recent research has indicated that tighter control of T2D, including early screening of individuals at risk, might be beneficial to delay cognitive declines and could help prevent progression to AD. Therefore, understanding the T2D physiology associated with AD will allow for the development of more adequate preventive and therapeutic strategies to decrease the burden of AD and T2D.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| AD | = | Alzheimer's disease |
| CNS | = | Central nervous system |
| MCI | = | Mild cognitive impairment |
| T2D | = | Type 2 diabetes |
| IR | = | Insulin receptor |
| IGF | = | Insulin-like growth factors |
| PI3 | = | Phosphatidylinositide 3 kinase |
| Akt | = | Akt kinase |
| GSK-3 | = | Glycogen synthase kinase-3 |
| IRS | = | Insulin receptor substrate |
| PI3K | = | Phosphatidylinositol-3 kinase |
| IDE | = | Insulin degrading enzyme |

## REFERENCES

[1] Andrieu S, Aboderin I, Baeyens JP, *et al*. IAGG workshop: health promotion program on prevention of late onset dementia. J Nutr Health Aging 2011; 15(7): 562-75.

[2] Stefanacci RG. The costs of Alzheimer's disease and the value of effective therapies. Am J Manag Care 2011; 17(Suppl.13): 356-62.

[3] Fiţa IG, Enciu AM, Stănoiu BP. New insights on Alzheimer's disease diagnostic. RomJMorphol Embryol 2011; 52(Suppl 3): 975-9.

[4] Mattson MP, Pedersen WA, Duan W, Culmsee C, Camandola S. Cellular and molecular mechanisms underlying perturbed energy metabolism and neuronal degeneration in Alzheimer's and Parkinson's diseases. Ann NY Acad Sci 1999; 893: 154-75.

[5] Götz J, Ittner LM, Lim YA. Common features between diabetes mellitus and Alzheimer's disease. Cell Mol Life Sci 2009; 66(8): 1321-5.

[6] de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. J Diab Sci Technol 2008; 2(6): 1101-13.

[7] Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. J Clin Exp Neuropsychol 2004; 26(8): 1044-80.

[8] Mulnier HE, Seaman HE, Raleigh VS, *et al*. Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database. Diabetologia 2006; 49(12): 2859-65.

[9] Driver JA, Smith A, Buring JE, *et al*. Prospective cohort study of type 2 diabetes and the risk of Parkinson's disease. Diabetes Care 2008; 31(10): 2003-5.

[10] Hu G, Jousilahtip P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. Diabet Care 2007; 30(4): 842-7.

[11] Yaffe K, Blackwell T, Kanaya AM, *et al*. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology 2004; 63(4): 658-63.

[12] Ohara T, Doi Y, Ninomiya T, *et al*. Glucose tolerance status and risk of dementia in the community: The Hisayama study. Neurology 2011; 77(12): 1126-34.

[13] Jiménez-Palomares M, Ramos-Rodríguez JJ, López-Acosta JF, *et al*. Increased Aβ production prompts the onset of glucose intolerance and insulin resistance. Am J Physiol Endocrinol Metab 2012; 302(11): E1373-80.

[14] Takeda S, Sato N, Uchio-Yamada K, *et al*. Diabetes-accelerated memory dysfunction *via* cerebrovascular inflammation and Abeta deposition in an Alzheimer mouse model with diabetes. Proc Natl Acad Sci USA 2010; 107(15): 7036-41.

[15] de la Monte SM. Insulin resistance and Alzheimer's disease. BMB Rep 2009; 42(8): 475-81.

[16] Grand JH, Caspar S, Macdonald SW. Clinical features and multidisciplinary approaches to dementia care. J Multidisciplin Healthcare 2011;4: 125-47.

[17] Petersen RC, Smith GE, Waring SC, *et al*. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56(3): 303-8.

[18] Gauthier S, Reisberg B, Zaudig M, *et al*. Mild cognitive impairment. Lancet 2006; 367(9518): 1262-70.

[19] Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia-meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 2009; 119(4): 252-65.

[20] Rountree SD, Waring SC, Chan WC, *et al*. Importance of subtle amnestic and nonamnestic deficits in mild cognitive impairment: prognosis and conversion to dementia. Dement Geriatr Cogn Disord 2007; 24(6): 476-82.

[21] Brooks LG, Loewenstein DA. Assessing the progression of mild cognitive impairment to Alzheimer's disease: current trends and future directions. Alzheimers Res Ther 2010; 2(5): 28.

[22] Belleville S, Sylvain-Roy S, de Boysson C, Ménard MC. Characterizing the memory changes in persons with mild cognitive impairment. Prog Brain Res 2008; 169: 365-75.

[23] Qiu C, Kivipelto M, von SE. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci 2009; 11(2): 111-28.

[24] Simon SS, Yokomizo JE, Bottino CM. Cognitive intervention in amnestic Mild Cognitive Impairment: a systematic review. Neurosci Biobehav Rev 2012; 36(4): 1163-78.

[25] Wimo A, Winblad B. Societal burden and economics of vascular dementia: preliminary results from a Swedish-population-based study. Int Psychogeriatr 2003; 15(1): 251-6.

[26] Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol 2002; 59(11): 1737-46.

[27] Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA 1989; 262(18): 2551-6.

[28] Povova J, Ambroz P, Bar M, et al. Vladimir Janouta. Epidemiological of and risk factors for Alzheimer's disease: a review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2012; 156(2): 108-14.

[29] Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006; 368(9533): 387-403.

[30] Profenno LA, Faraone SV. Diabetes and overweight associate with non-APOE4 genotype in an Alzheimer's disease population. Am J Med Genet B Neuropsychiatr Genet 2008; 147B(6): 822-9.

[31] Akter K, Lanza EA, Martin SA, et al. Diabetes mellitus and Alzheimer's disease: shared pathology and treatment? Br J Clin Pharmacol 2011; 71(3): 365-76.

[32] Martins IJ, Berger T, Sharman MJ, et al. Cholesterol metabolism and transport in the pathogenesis of Alzheimer's disease. J Neurochem 2009; 111(6): 1275-308.

[33] Haan MN. Therapy Insight: type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease. Nat Clin Pract Neurol 2006; 2(3): 159-66.

[34] Carlsson CM. Type 2 diabetes mellitus, dyslipidemia, and Alzheimer's disease. J Alzheimer's Dis 2010; 20(3): 711-22.

[35] Tchantchou F, Graves M, Ortiz D, et al. S-adenosyl methionine: A connection between nutritional and genetic risk factors for neurodegeneration in Alzheimer's disease. J Nutr Health Aging 2006; 10(6): 541-4.

[36] Chan A, Shea TB. Folate deprivation increases presenilin expression, gamma-secretase activity, and Abeta levels in murine brain: potentiation by ApoE deficiency and alleviation by dietary S-adenosyl methionine. J Neurochem 2007; 102(3): 753-760.

[37] Hughes TM, Kuller LH, Lopez OL, et al. Markers of cholesterol metabolism in the brain show stronger associations with cerebrovascular disease than Alzheimer's disease. J Alzheimer's Dis 2012; 30(1): 53-61.

[38] Wysocki M, Luo X, Schmeidler J, et al. Hypertension is associated with cognitive decline in elderly people at high risk for dementia. Am J Geriatr Psychiatr 2012; 20(2): 179-87.

[39] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011; 10(9): 819-28.

[40] Mehta M, Adem A, Kahlon MS, Sabbagh MN. The nicotinic acetylcholine receptor: smoking and Alzheimer's disease revisited. Front Biosci (Elite Ed) 2012; 4: 169-80.

[41] Fratiglioni L, Launer LJ, Andersen K, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000; 54(11 Suppl 5): S10-5.

[42] Reitz C, Bos MJ, Hofman A, Koudstaal PJ, Breteler MM. Prestroke cognitive performance, incident stroke, and risk of dementia: the Rotterdam Study. Stroke 2008; 39(1): 36-41.

[43] Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005; 366(9503): 2112-7.

[44] Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurol 2000; 54(11 Suppl 5): S4-9.

[45] Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 2007; 29(1-2): 125-32.

[46] Kalaria RN, Maestre GE, Arizaga R, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 2008; 7(9): 812-26.

[47] Al Rajeh S, Bademosi O, Ismail H, et al. A community survey of neurological disorders in Saudi Arabia: the Thugbah study. Neuroepidemiology 1993; 12(3): 164-78.

[48] Farrag A, Farwiz HM, Khedr EH, Mahfouz RM, Omran SM. Prevalence of Alzheimer's disease and other dementing disorders: Assiut-Upper Egypt study. Dement Geriatr Cogn Disord 1998; 9(6): 323-8.

[49] El Tallawy HN, Farghly WM, Shehata GA, et al. Prevalence of dementia in Al Kharga District, New Valley Governorate, Egypt. Neuroepidemiology 2012; 38(3): 130-7.

[50] Maher PA, Schubert DR. Metabolic links between diabetes and Alzheimer's disease. Expert Rev Neurother 2009; 9(5): 617-30.

[51] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27(5): 1047-53.

[52] Curb JD, Rodriguez BL, Abbott RD, et al. Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. Neurology 1999; 52(5): 971-5.

[53] Razay G, Wilcock GK. Hyperinsulinaemia and Alzheimer's disease. Age Ageing 1994; 23(5): 396-9.

[54] Luchsinger JA, Tang MX, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004; 63(7): 1187-92.

[55] Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biol Psychiatry 2010; 67(6): 505-12.

[56] Sima AA, Li ZG. Diabetes and Alzheimer's disease - is there a connection? Rev Diabetes Stud 2006; 3(4): 161-8.

[57] 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 Alzheimer's Dis 2006; 10(1): 89-109.

[58] Hölscher C. Diabetes as a risk factor for Alzheimer's disease: insulin signalling impairment in the brain as an alternative model of Alzheimer's disease. Biochem Soc Trans 2011; 39(4): 891-7.

[59] Sahin M, Karatas M, Ertugrul D, et al. High prevalence of neuropathy in patients with impaired 60-minute oral glucose tolerance test but normal fasting and 120-minute glucose levels. Miner Endocrinol 2008; 33(4): 289-96.

[60] Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol 2004; 490(1-3): 115-25.

[61] Bosco D, Fava A, Plastino M, Montalcini T, Pujia A. Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. J Cell Mol Med 2011; 15(9): 1807-21.

[62] Steen E, Terry BM, Rivera EJ, et al. Impaired insulin and insulin-like growth factor expression and signalling mechanisms in Alzheimer's disease--is this type 3 diabetes? J Alzheimer's Dis 2005; 7: 63-80.

[63] Rivera EJ, Goldin A, Fulmer N, et al. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimer's Dis 2005; 8: 247-68.

[64] Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging 1991; 12: 295-312.

[65] Mark A, Fishel G, Stennis W, Thomas J, Montine. Hyperinsulinemia Provokes Synchronous Increases in Central Inflammation and -Amyloid in Normal Adults. Arch Neurol 2005; 62: 1539-44.

[66] Caballero AE. Endothelial dysfunction, inflammation, and insulin resistance: a focus on subjects at risk for type 2 diabetes. Curr Diab Rep 2004; 4: 237-46.

[67] Luchsinger JA, Tang MX, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004; 63: 1187-92.

[68] Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam Study. Neurol 1999; 53: 1937-42.

[69]    Montine TJ, Kaye JA, Montine KS, *et al*. Cerebrospinal fluid abeta42: tau, and f2-isoprostane concentrations in patients with Alzheimer disease, other, dementias, and in age-matched controls. Arch Pathol Lab Med 2001; 125: 510-2.

[70]    Cacquevel M, Lebeurrier N, Cheenne S, Vivien D. Cytokines in neuroinflammation and Alzheimer's disease. Curr Drug Targets 2004; 5: 529-34.

[71]    Sheng JG, Bora SH, Xu G, *et al*. Lipopolysaccharideinduced-neuroinflammation increases intracellular accumulation of amyloid precursor protein and amyloid beta peptide in APPswe transgenic mice. Neurobiol Dis 2003; 14: 133-45.

[72]    Gasparini L, Gouras GK, Wang R, *et al*. Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signalling. J Neurosci 2001; 21: 2561-70.

[73]    Qiu WQ, Walsh DM, Ye Z, *et al*. Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. J Biol Chem 1998; 273: 32730-8.

[74]    de la Monte SM. Insulin resistance and Alzheimer's disease. BMB Rep 2009; 31: 42(8): 475-81.

[75]    Han W, Li C. Linking type 2 diabetes and Alzheimer's disease. Proc Natl Acad Sci USA 2010; 107: 6557-8.

[76]    Moreira PI, Duarte AI, Santos MS, Rego AC, Oliveira CR. An integrative view of the role of oxidative stress, mitochondria and insulin in Alzheimer's disease. J Alzheimer's Dis 2009; 16(4): 741-61.

[77]    Freude S, Plum L, Schnitker J, *et al*. Peripheral hyperinsulinemia promotes tau phosphorylation *in vivo*. Diabetes 2005; 54(12): 3343-8.

[78]    Hoyer S. Brain glucose and energy metabolism during normal aging. Aging 1990; 2(3): 245-58.

[79]    Bingham EM, Hopkins D, Smith D. The role of insulin in human brain glucose metabolism: an 18fluoro-deoxyglucose positron emission tomography study. Diabetes 2002; 51(12): 3384-90.

[80]    Magistretti PJ. Neuron-glia metabolic coupling and plasticity. J Exp Biol 2006; 209: 2304-11.

[81]    Zhao WQ, Alkon DL. Role of insulin and insulin receptor in learning and memory. Mol Cell Endocrinol 2001; 177(1-2): 125-34.

[82]    Tun PA, Nathan DM, Perlmuter LC. Cognitive and affective disorders in elderly diabetics. Clin Geriatr Med 1990; 6: 731-46.

[83]    de Weid D, Bohus B, Wimersma TB, Greidanus. Memory deficit in rats with hereditary diabetes insipidus. Brain Res 1975; 85(1): 152-6.

[84]    Stranahan AM, Arumugam TV, Cutler RG, *et al*. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. Nat Neurosci 2008; 11(3): 309-17.

[85]    D'Ercole AJ, Ye P, Calikoglu AS, Gutierrez-Ospina, G. The role of the insulin-like growth factors in the central nervous system. Mol Neurobiol 1996; 13: 227-55.

[86]    Chiu S, Chen C, Cline H. Insulin Receptor Signalling Regulates Synapse Number, Dendritic Plasticity, and Circuit Function *In Vivo*. Neuron 2008; 58(5): 708-19.

[87]    Havrankova J, Brownstein M, Roth J. Insulin receptors are widely but unevenly distributed in central nervous-system of rat. Clin Res 1978; 26: 491A.

[88]    Havrankova J, Roth J. Insulin receptors are widely distributed in central nervoussystem of rat. Nature 1978; 272(5656): 827-9.

[89]    Marks JL, Porte D, Stahl WL, Baskin DG. Localization of insulin-receptor messenger-RNA in rat–brain by insitu hybridization. Endocrinology 1990; 127(6): 3234-46.

[90]    Zhao WQ, Chen H, Xu H, *et al*. Brain insulin receptors and spatial memory - correlated changes in gene expression, tyrosine phosphorylation, and signalling molecules in the hippocampus of water maze trained rats. J Biol Chem 1999; 274(49): 34893-902.

[91]    Werther GA, Hogg A, Oldfield BJ, *et al*. Localization and characterization of insulin-receptors in rat–brain and pituitary-gland using invitro autoradiography and computerized densitometry. Endocrinology 1987; 121: 1562-70.

[92]    Small SA, Gandy S. Sorting through the cell biology of Alzheimer's disease: Intracellular pathways to pathogenesis. Neuron 2006; 52(1): 15-31.

[93]    Smith MA, Monnier VM, Sayre LM, Perry G. Amyloidosis, advanced glycation end products and Alzheimer disease. Neuro Report 1995; 6: 1595-6.

[94]    Smith MA, Sayre LM, Monnier VM, Perry G. Radical Ageing in Alzheimer's disease. Trends Neurosci 1995; 18(4): 172-6.

[95]    Zhao W, Chen H, Xu H, *et al*. Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signalling molecules in the hippocampus of water maze trained rats. J Biol Chem 1999; 274: 34893-902.

[96]    Kasuga M, Zick Y, Blith DL, *et al*. Insulin stimulation of phosphorylation of the beta-subunit of the insulin-receptor-formation of both phosphoserine and phosphotyrosine. J Biol Chem 1982; 257: 9891.

[97]    Kahn CR, Folli F. Molecular determinants of insulin action. Horm Res 1993; 39(Suppl 3): 93-101.

[98]    Johnson-Farley NN, Patel K, Kim D, Cowen DS. Interaction of FGF-2 with IGF-1 and BDNF in stimulating Akt, ERK, and neuronal survival in hippocampal cultures. Brain Res 2007; 1154: 40-9.

[99]    Johnston AM, Pirola L, Van Obberghen E. Molecular mechanisms of insulin receptor substrate protein-mediated modulation of insulin signalling. FEBS Lett 2003; 546: 32-6.

[100]    Sui L, Wang J, Li BM. Role of the phosphoinositide 3-kinase- Akt-mammalian target of the rapamycin signalling pathway in longterm potentiation and trace fear conditioning memory in rat medial prefrontal cortex. Learn Mem 2008; 15: 762-76.

[101]    Cross DA, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature 1995; 378: 785-9.

[102]    Peineau S, Taghibiglou C, Bradley C, *et al*. LTP inhibits LTD in the hippocampus *via* regulation of GSK3beta. Neuron 2007; 53: 703-17.

[103]    Hooper C, Markevich V, Plattner F, *et al*. Glycogen synthase kinase-3 inhibition is integral to long-term potentiation. Eur J Neurosci 2007; 25: 81-6.

[104]    Zhu LQ, Wang SH, Liu D, *et al*. Activation of glycogen synthase kinase-3 inhibits long-term potentiation with synapse-associated impairments. J Neurosci 2007; 27: 12211-20.

[105]    Ristow M. Neurodegenerative disorders associated with diabetes mellitus. J Mol Med 2004; 82: 510-29.

[106]    Cole GM, Frautschy SA. The role of insulin and neurotrophic factor signalling in brain aging and Alzheimer's Disease. Exp Gerontol 2007; 42: 10-21.

[107]    Le Roith D, Zick Y. Recent advances in our understanding of insulin action and insulin resistance. Diabet Care 2001; 24(3): 588-97.

[108]    Heidenreich KA, Zahniser NR, Berhanu P, Brandenburg D, Olefsky JM. Structural differences between insulin receptors in the brain and peripheral target tissues. J Biol Chem 1983; 258(14): 8527-30.

[109]    Stolk RP, Pols HA, Lamberts SW, *et al*. Diabetes mellitus, impaired glucose tolerance, and hyperinsulinemia in an elderly population. The Rotterdam Study, Am J Epidemiol 1997; 145(1): 24-32.

[110]    Stolk RP, Breteler MM, Ott A, *et al*. Insulin and cognitive function in an elderly population. The Rotterdam Study. Diabet Care 1997; 20(5): 792-5.

[111]    Kalmijn S, Feskens EJ, Launer LJ, Stijnen T, Kromhout D. Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. Diabetologia 1995; 38: 1096-102.

[112]    Frolich L, Blum-Degen D, Bernstein HG, *et al*. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neural Transm 1998; 105(4-5): 423-38.

[113]    Frolich L, Blum-Degen D, Riederer P, Hoyer S. A disturbance in the neuronal insulin receptor signal transduction in sporadic Alzheimer's disease. Ann NY Acad Sci 1999; 893: 290-3.

[114]    De la Monte SM. Insulin resistance and Alzheimer's disease. BMB Rep 2009; 4298): 475-81.

[115]    Alper J. Biomedicine: new insights into type 2 diabetes. Science 2000; 289: 37-9.

[116]    Jonsaton AM, Pirola L, Van Obberghen E. Molecular mechanisms of insulin receptor substrate protein-mediated modulation of insulin signalling. FEBS Lett 2003; 546: 32-36.

[117]    Schlessinger J. Cell signalling by receptor tyrosine kinases. Cell 2000; 103: 211-25.

[118]    Giovannone B, Scaldaferri ML, Federici M, *et al*. Insulin receptor substrate (IRS) transduction system: distinct and overlapping signalling potential. Diabetes Metab Res Rev 2000; 16: 434-41.

[119]    Sun XJ, Crimmins DL, Myers MJ, Miralpeix M, White MF. Pleiotropic insulin signals are en gaged by multisite phosphorylation of IRS-1. Mol Cell Biol 1993; 13: 7418-28.

[120]    Paz K, Hemi R, LeRoith D, *et al*. A molecular basis for insulin resistance. Elevated serine/threonine phosphorylation of IRS-1 and IRS-2 inhibits their binding to the juxtamembrane region of the

insulin receptor and impairs their ability to undergo insulin-induced tyrosine phosphorylation. J Biol Chem 1997; 272: 29911-98.

[121]  Lam K, Carpenter CL, Ruderman NB, Friel JC, Kelly KL. The phosphatidylinositol 3-kinase serine kinase phosphorylates IRS-1. Stimulation by insulin and inhibition by Wortmannin. J Biol Chem 1994; 269: 20648-52.

[122]  Dudek H, Datta SR, Franke TF, *et al*. Regulation of neuronal survival by the serine-threonine protein kinase Akt. Science 1997; 275: 661-5.

[123]  Condorelli F, Salomoni P, Cotteret S, *et al*. Caspase cleavage enhances the apoptosis-inducing effects of BAD. Mol Cell Biol 2001; 21: 3025-36.

[124]  Halestrap AP, Doran E, Gillespie JP, O'Toole A. Mitochondria and cell death. Biochem Soc Trans 2000; 28: 170-7.

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

[126]  Eckman EA, Eckman CB. Abeta-degrading enzymes: Modulators of Alzheimer's disease pathogenesis and targets for therapeutic intervention. Biochem Soc Trans 2005; 33: 1101-5.

[127]  Farris W, Mansourian S, Chang Y, *et al*. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain *in vivo*. Proc Natl Acad Sci USA 2003; 100: 4162-7.

[128]  Fewlass DC, Noboa K, Pi-Sunyer FX, *et al*. Obesity-related leptin regulates Alzheimer's Abeta. FASEB J 2004;18(15): 1870-8.

[129]  Phiel CJ, Wilson CA, Lee VM, Klein PS. GSK- 3alpha regulates production of Alzheimer's disease amyloid-beta peptides. Nature 2003; 423: 435-9.

[130]  Cole AR, Astell A, Green C, Sutherland C. Molecular connexions between dementia and diabetes. Neurosci Biobehav Rev 2007; 31: 1046-63.

[131]  Ling Y, Morgan K, Kalsheker N. Amyloid precursor protein (APP) and the biology of proteolytic processing: relevance to Alzheimer's disease. Int J Biochem Cell Biol 2003; 35: 1505-35.

[132]  Mukherjee A, Song E, Kihiko-Ehmann M, *et al*. Insulysin hydrolyzes amyloid beta peptides to products that are neither neurotoxic nor deposit on amyloid plaques. J Neurosci 2000; 20: 8745-9.

[133]  Qiu WQ, Ye Z, Kholodenko D, Seubert P, Selkoe DJ. Degradation of amyloid beta-protein by a metalloprotease secreted by microglia and other neural and non-neural cells. J Biol Chem 1997; 272: 6641-6.

[134]  Vekrellis K, Ye Z, Qiu WQ, *et al*. Neurons regulate extracellular levels of amyloid beta-protein *via* proteolysis by insulin-degrading enzyme. J Neurosci 2000; 20: 1657-65.

[135]  Qiu WQ, Folstein MF. Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. Neurobiol Aging 2006; 27: 190-8.

[136]  Sudoh S, Frosch MP, Wolf BA. Differential effects of proteases involved in intracellular degradation of amyloid beta-protein between detergent-soluble and -insoluble pools in CHO-695 cells. Biochemistry 2002; 41: 1091-9.

[137]  Xie L, Helmerhorst E, Taddei K, *et al*. Alzheimer's beta- amyloid peptides compete for insulin binding to the insulin receptor. J Neurosci 2002; 22(10): RC221.

[138]  Cook DG, Leverenz JB, McMillan PJ, *et al*. Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's disease is associated with the apolipoprotein E-epsilon4 allele. Am J Pathol 2003; 162: 313-9.

[139]  Alafuzoff I, Aho L, Helisalmi S, Mannermaa A, Soininen H. beta-Amyloid deposition in brains of subjects with diabetes. Neuropathol Appl Neurobiol 2009; 35: 60-8.

[140]  Cook DG, Leverenz JB, McMillan PJ, *et al*. Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's disease is associated with the apolipoprotein E-epsilon4 allele. Am J Pathol 2003; 162: 313-9.

[141]  Leissring MA, Farris W, Chang AY, *et al*. Enhanced proteolysis of beta amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death. Neuron 2003; 40: 1087-93.

[142]  Ho L, Qin W, Pompl PN, *et al*. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. FASEB J 2004; 18: 902-4.

[143]  Martín D, Salinas M, López VR, *et al*. Effect of the Alzheimer amyloid fragment Abeta(25-35) on Akt/PKB kinase and survival of PC12 cells. J Neurochem 2001; 78: 1000-8.

[144]  Kounnas MZ, Danks AM, Cheng S, *et al*. Modulation of g-secretase reduces b-amyloid deposition in a transgenic mouse model of Alzheimer's disease. Neuron 2010; 67: 769-80.

[145]  Tanzi RE, St. George-Hyslop PH, Haines JL, *et al*. The genetic defect in familial Alzheimer's disease is not tightly linked to the amyloid b protein gene. Nature 1987; 329: 156-7.

[146]  Levy-Lahad E, Wasco W, Poorkaj P, *et al*. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 1995; 269: 973-7.

[147]  Bertram L, Tanzi RE. Thirty years of Alzheimer's disease genetics: Systematic meta-analyses herald a new era. Nat Rev Neurosci 2008; 9: 768-78.

[148]  Lambert J, Heath S, Even G, *et al*. Genome-wide association study identifies variants at CLUand CR1 associated with Alzheimer's disease. Nat Genet 2009; 41(10): 1094-9.

[149]  Harold D, Abraham R, Hollingworth P, *et al*. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 2009; 41(10): 1088-93.

[150]  Seshadri S, Fitzpatrick AL, Ikram MA, *et al*. Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA 2010; 303(18): 1832-40.

[151]  Hollingworth P, Harold D, Sims R, *et al*. Common variants at ABCA7: MS4A6A/MS4A4E, EPHA1: CD33 and CD2AP are associated with Alzheimer's disease. Nat Genet 2011; 43(5): 429-35.

[152]  Naj AC, Jun G, Beecham GW, *et al*. Common variants at MS4A4/ MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet 2011; 43: 436-41.

[153]  Reiman EM, Webster JA, Myers AJ, *et al*. GAB2 alleles modify Alzheimer's risk in APOE 14 carriers. Neuron 2007; 54: 713-20.