

## New Insights into the Effect of Diabetes and Obesity in Alzheimer's Disease

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### Abstract

Alzheimer's disease (AD) is the most common cause of dementia in elderly people. The prevalence of Alzheimer diseases is increasing in the world due to population aging. Metabolic disease such as diabetes and obesity play important role in Alzheimer disease. Hyperglycemia can play important role in brain damage. It causes cognitive impairments, functional and structural alterations in the brain. Since insulin has neuro protective effect in vivo, impaired insulin action in brain may affect neurodegenerative diseases. Obesity correlated increased free fatty acid can lead to Alzheimer disease. Free fatty acids agitate the synthesis of amyloid and tau filaments in vitro. In this paper, Alzheimer disease and its mechanism are discussed in section 1. In section 2, diabetes and Alzheimer, brain insulin signaling pathway in AD are explained. Obesity and Oxidative stress in AD are discussed in section 3, 4.

**Keywords:** Alzheimer disease, Diabetes, Obesity

## Introduction

**1 Alzheimer's disease**  
Alzheimer's disease (AD) is the most common cause of dementia in elderly people (1). This disease is considered as one of the most progressive destructive neurodegenerative in selective brain regions involved in cognition and emotional behaviors. The prevalence of Alzheimer diseases is increasing in the world due to population aging (2,3). This disease is the sixth leading cause of death in the United State (4). In 2011, 36 million people in the world had Alzheimer disease. It reaches 115 million people in 2050 (5). Important signs of pathological disease are loss of synapses, an

increase in number of extracellular amyloid beta-peptide (Ab) rich senile plaques (SPs) and an increase in intracellular neurofibrillary tangles (NFTs) composed of aggregated hyper phosphorylated Tau (6).

### *1-2 The Mechanism of amyloid cascade in Alzheimer disease*

The A $\beta$  peptides are produced as a result of excessive processing of the amyloid precursor protein APP. During two steps, A $\beta$  peptide is formed from proteolytic cleavage of Amyloid- $\beta$  precursor protein (A $\beta$ PP). In the first step, A $\beta$ PP is broken by  $\beta$ -secretase to generate CTF $\beta$  (carboxy terminal fragment  $\beta$ ) which in the second step is subsequently cleaved by the

$\gamma$ -secretase complex to generate A $\beta$  peptid. A $\beta$  plays a favorable role in development and progression of neurodegenerative events such as Alzheimer Disease (7).

## 2 Diabetes

Diabetes mellitus is one of the most common diseases caused by a combination of insulin resistance and impaired insulin secretion by pancreatic *B* cells (8,9). More than 200 million people have type 2 diabetes mellitus (T2DM) and the number of patients continues to rise and have reached an epidemic proportion. The total number of people with diabetes is expected to reach 370 million worldwide in 2030 (10,11). Diabetes is associated with several long-term complications such as cardiovascular disease, nephropathy, retinopathy and neuropathy. It is recognized that diabetes has an important impact in brain and vital evidence showed that chronic hyperglycemia and insulin resistance have important role in cognitive dysfunction and Alzheimer disease(5).

### 2-1 Glucose transportation and Alzheimer's disease

Despite about 2 percent of the whole human body mass is formed by the brain, under fundamental situation, 50 percent of consumption of glucose occurs in brain. Glucose is the main fuel for brain tissue and the majority of glucose in brain is transformed to ATP energy for retention of normal neuronal action like cognition. Decreasing of glucose transportation has been seen in regions of brain like hippocampus, cortex and cerebral micro vessels of AD patients (4). Transportation of glucose across the blood brain barrier (BBB) and/or the neuronal plasma membrane can become a rate limiting step under pathological conditions like Alzheimer disease, dementia, epilepsy and traumatic brain injury (4). AD patients showed decreased GLUT-1 and 3 expressions particularly in the cerebral cortex, with remarkable loss of GLUT3 which related to decreased O-GlcNAcylation and tau hyperphosphorylation.

### 2-2 Diabetes and Alzheimer disease

It is detected that diabetes disease is associated with nearly 20% of neurodegenerative disease like Alzheimer disease (12,13). Hyperglycemia can play an important role in brain damage. Hyperglycemia cause cognitive impairments, functional and structural alterations in the brain of rodents (14). Brain aging acceleration is more in type 2 diabetes than non diabetes and it increases the risk for development of neurodegenerative diseases. Also comparison between AD and non-AD (control) showed that impaired fasting glucose and T2DM is more in AD patients. Also the risk of hippocampal atrophy and severity of these lesions are increased in older adults with type 2 diabetes mellitus (15). Therefore, Type 2 Diabetes can increase progression of disease, but can't be sufficient factor for causing of AD (15). Another study showed cerebral glucose consumption is decreased about 45 percent in early stages of AD, but these abnormalities get worse in later stage (16). These observations suggest that insulin resistance or reduced insulin action in brain is responsible for decreased energy metabolism in AD (16). The relation between AD and diabetes has been evaluated in animal model. For example, increased levels of hyperphosphorylated tau protein and cognitive dysfunction have been shown in diabetic rat models (17). Another study reported impaired insulin signaling, alteration of A $\beta$ PP metabolism and hyperphosphorylated tau protein have been seen in diabetic rat (18). Also [5] showed that mitochondrial abnormalities and oxidative imbalance have been seen in the brain of T2DM mice. Therefore they reported that T2DM is a risk factor for AD (5).

Another study showed metabolic disease such as T1DM is associated with high risk for cognitive dysfunctions and brain structure abnormalities. Acute hyperglycemia and/or hypoinsulinemia play an important role on cognitive function in type 1 diabetes whereas in T2DM, cognitive dysfunction is due to insulin resistance in elderly patients. Therefore, low levels of insulin and decreased

receptor numbers have been seen in central nervous system (CNS) of Alzheimer disease and insulin administration can improve memory in both healthy person and AD patients. Since insulin has neuro protective effect, impaired insulin action in brain may have a critical role for pathogenesis of those neurodegenerative diseases (14,19). Since detected abnormalities in brain were quite analogous to the effects of Type 1 or type 2 diabetes, therefore studies proposed that AD can display a brain- specific form of diabetes and coined the word “type 3 diabetes” (15).

### **2-3 Brain insulin signaling pathway and Alzheimer’s disease**

In throughout of brain, insulin, its receptors and insulin like growth factor-1 receptors are distributed (5). This suggests a main role of insulin in brain glucose metabolism including regulation of neuronal development, memory and learning processes (15). Binding of insulin or IGF-1 increases receptor autophosphorylation, motivates its tyrosin kinase activity and phosphorylates insulin receptor substrate proteins on tyrosine residues. In result, two primary signaling cascades by phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) are motivated. PI3K activates downstream signaling proteins like serine/threonine kinase Akt, are recruited to the plasma membrabe. Then it moves to cytosole and nucleus and phosphorylate target proteins such as glycogen synthase 3-beta (GSK-3b), and insulin-degrading enzyme (IDE) and etc. IDE can play important role in degradation of A $\beta$ . The impairment of insulin signaling pathway has been associated with increased risk of dementia and AD. Deficiency of insulin-PI3K-Akt is observed in Alzheimer disease and diabetes. Also there is reverse correlation between insulin-PI3K-Akt signaling and the level of tau protein phosphorylation and direct relation with protein O-GlcNAcylation.

Therefore, impairment of insulin-PI3K-Akt signaling pathway can cauce neurodegeneration in Alzheimer disease via

down-regulation of O-GlcNAcylation and the consequent advancement of uncommon tau protein hyperphosphorylation and neurodegeneration(5).

Mitogen activated protein kinas (MAPK) can be motivated in AD patients which is associated with increased neuroinflammation, tau protein hyperphosphorylation, A $\beta$ PP trafficking and Ab clearance. Therefore, neurodegeneration and Alzheimer disease is associated with significant disorders in the gene expression of IGF-1, and IGF-2 peptides, their receptors, and downstream signaling mechanisms. These processes are increased in progression of dementia and neurodegeneration (15). In addition, neuronal survival, energy metabolism, mitochondrial function and tau expression were disturbed in Alzheimer disease (15).

### **2-4 Insulin degrading enzyme**

Insulin degrading enzyme (IDE), a 110 kDa zinc metalloendopeptidase, (19) can degrade insulin. It is increasingly expressed in brain, testis, muscle and liver (20). Some peptides with molecular weigh 3-10 KDa can be as substrate for IDE like insulin, IGF-1, IGF-2, amylin and A $\beta$  (19). Increased level of cerebral A $\beta$  and glucose intolerance is associated with disruption in IDE gene in mice (4). Because of the ability of IDE for degrading of A $\beta$ , defects in its activity can be a direct trigger for developing of Alzheimer’s disease (19). Degradation of A $\beta$ PP-A $\beta$  (32), A $\beta$ PP-A $\beta$  (33), A $\beta$ PP-A $\beta$ (1-40) and A $\beta$ PPA $\beta$  (1-42) can performed by IDE. The C terminal cleavage products of A $\beta$ PP can ban insulin binding and insulin receptor via decreasing affinity of insulin binding to own receptor. Since A $\beta$ PP-A $\beta$  and insulin compete together for receptor binding, incompetent degradation of soluble A $\beta$ PP-A $\beta$  can illustrate a main mediator of brain insulin resistance in AD. Increased levels of A $\beta$ PP-A $\beta$  are correlated with decreased levels of insulin and insulin growth factor-1 in CNS (16).

### **3 Obesity and Alzheimer’s disease**

Obesity is a fundamental characteristic in metabolic syndrome (21). It is main cause of

insulin resistance and 80 percent of obese people are insulin resistant. Generally, midlife obesity can be an important risk factor for later dementia. Free fatty acid (FFA) is a serious link between obesity and insulin resistance. Under normal condition, insulin bans adipocyte hormone-sensitive lipase activity. This process decreases FFA release from adipose tissue.

Obesity and insulin resistant lead to continuous FFA elevation. Obesity correlated increased FFA leads to AD pathogenesis. FFA bans insulin-degrading enzyme (the metalloprotease that plays a key role in clearance of A $\beta$  and that is also essential for occurrence normal insulin signaling). Free fatty acids agitate the synthesis of amyloid and tau filaments in vitro. They also persuade inflammation via reaction with tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ). Adipose tissue of obese insulin-resistant rodents and humans over express tumor necrosis factor  $\alpha$ . Neutralization of TNF  $\alpha$  is essential for increasing insulin sensitivity and decreasing plasma FFA levels. The elevation of tumor necrosis factor  $\alpha$  has been seen in brains and cerebrospinal fluid of AD patients. This bans A $\beta$  transportation from the brain to the periphery. The elevation of TNF  $\alpha$  is associated with insulin resistance, obesity and hyperinsulinemia. This process can result to accumulation of A $\beta$  (22), but in another study, relation between obesity and dementia among those without diabetes mellitus showed that diabetes mellitus may not totally explain the relation (21).

#### 4 Oxidative stress, Diabetes and Alzheimer's disease

An imbalance between radical generating and radical scavenging systems leads to oxidative stress. Hyperglycemia induces glucose oxidation and initiates an non-enzymatic glycation of proteins, which in turn leads to

enhanced production of reactive oxygen species (ROS)(9). Insulin/IGF resistance can cause oxidative stress, mitochondrial abnormality and DNA damage. The development of worsening insulin/IGF resistance with stage of AD is related to increased oxidative stress, DNA damage and apoptosis (16). Oxidative stress is increased in both insulin-dependent (IDDM), and noninsulin-dependent (NIDDM) diabetes mellitus and it could cause initial  $\beta$  cell damage in type I diabetes, or impaired insulin production, release or function of insulin in type II Diabetes mellitus (23). Oxidative stress can increase amyloid-b generation in AD patients. Therefore Amyloid-b (Ab) synthesis and secretion are increased under conditions of oxidative stress (24). Oxidative stress in brain of Alzheimer disease causes lipid peroxidation which is indexed by increased level of malondialdehyde, isprostanes, thiobarbituric acid, 4-hydroxy-2-trans-nonenal, acid nucleic oxidation that is indexed by increased of 8-hydroxy-2-deoxyguanosine (8OHdG) and 8-hydroxyguanosine (8OHG), sugars modification such as elevated glycation and glycooxidation. Also oxidative stress can cause protein oxidation via modification of amino acid side chains such as arginine, lysine, threonine and proline residues (24,25).

#### Conclusion

Metabolic disease can play an important role in Alzheimer disease. Diabetes is associated with increased risk of dementia and AD and impaired insulin signaling pathway can be a main issue for understanding the pathogenesis of AD. Given that there should be greater emphasis on early diagnosis of metabolic syndrome like type 2 diabetes, obesity and insulin resistance.

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