



The Novel Implication of Androgen in Diabetes-induced Alzheimer's Disease

Juhyun Song^{1*}, Chaeyong Jung^{1*}, Oh Yoen Kim²

¹Department of Anatomy, Chonnam National University Medical School, Gwangju,

²Department of Food Science and Nutrition, Dong-A University, Busan, Korea

Alzheimer's disease (AD) is characterized by the accumulation of amyloid beta ($A\beta$) and the hyperphosphorylation of tau protein in the brain, leading to the increase in inflammation and neuronal loss. Recently, evidences to support the association between type 2 diabetes mellitus (T2DM) and AD have markedly increased by clinical researches and experimental studies. Reduced insulin action and impaired glucose metabolism in the brain leads to diabetes induced AD. Androgen, a male sex hormone, was known to regulate inflammatory response, $A\beta$ deposition in AD, insulin signaling, and synaptic plasticity in brain. Clinical studies demonstrated that androgen deficiency results in the increased risk of AD and its severe progression in male subjects. We reviewed the significant evidences to support that low testosterone levels are linked to diabetes-induced AD based on previous studies. Thus, we highlight the therapeutic potential of androgen in diabetes induced AD. (**J Lipid Atheroscler 2017 December;6(2):66-74**)

Key Words: Androgen, Alzheimer's disease, Insulin resistance, Inflammation, Cognitive decline

INTRODUCTION

Alzheimer's disease (AD) is characterized by the accumulation of amyloid beta ($A\beta$) protein, hyperphosphorylated tau protein, and synaptic and neuron loss in the brain.^{1,2} Recently, AD is most common neurodegenerative disorder that influences 5 million people in the United States.^{3,4} Current studies have reported that type 2 diabetes mellitus (T2DM) is directly associated with the increased risk of AD^{5,6} and cognitive dysfunction.⁷ Elevated glycemia in normal subjects leads to the increased risk of AD, and also triggers cognitive decline and decreased hippocampal volume.^{8,9} Moreover, AD inci-

dence is positively correlated with insulin resistance which leads to T2DM.¹⁰ Furthermore, sex differences affect the onset of AD, with women accounting for two-thirds of patients with AD.¹¹ In addition, women shows greater severity for AD and mild cognitive impairment compared to men.¹²⁻¹⁴ Generally, AD patients show decreased levels of testosterone in the brain.¹⁵ Clinically, the use of androgen depletion therapy leads to increased plasma levels of $A\beta$ in the brain,¹⁶⁻¹⁸ and lower serum testosterone levels were found in the AD patients compared to non-AD controls.^{19,20} Androgen as a sex hormone has been known to activate a variety of reproductive behavior, and regulate emotion.²¹ mRNA expressions of androgen receptor were

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Corresponding Author: Oh Yoen Kim, Department of Food Sciences and Nutrition, Human Life Research Center, Dong-A University, 37 550 beon-gil Nakdong-daero, Saha-gu, Busan 49315, Korea
 Tel: +82-51-200-7326, Fax: +82-51-200-7353, E-mail: oykim@dau.ac.kr

*These authors contributed equally to this work.

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found in the central nervous system (CNS) including forebrain, midbrain, and spinal cord.²²⁻²⁴ In CNS, androgen have multiple functions such as neuroprotective function, neurite growth, neurogenesis, and neuronal survival,²⁵ and regulate physiological functions including emotion and cognition.²⁶⁻²⁸ Based on the previous researches, this review summarizes recent evidences regarding the role of androgen in diabetic induced AD, suggesting that androgen is associated with glucose metabolism, insulin signaling and cognitive decline in the brain.

THE ASSOCIATION BETWEEN DIABETES AND AD

In the T2DM, the impairment of glycemic control and insulin resistance triggers mild cognitive impairment (MCI).^{29,30} Recent study with functional magnetic resonance imaging reported that patients with T2DM have changed neuronal activity in broad brain regions related with cognitive function.³¹ Imaging studies showed increase of brain atrophy in patients with T2DM which is associated with cognitive decline.^{32,33} Also, the T2DM rat model showed the pathology of AD including neuronal loss, increased A β level, and hyperphosphorylated tau.^{34,35} In the insulin resistance induced AD transgenic mice, high fat diet triggers increase of A β accumulation and decrease of insulin degradation enzyme (IDE).³⁶ APP/PS1 transgenic mice with administration of sucrose-supplemented water showed glucose intolerance, elevation of insulin levels, increase of A β deposition, and memory dysfunction.³⁷ Dysregulation of insulin and glucose have been linked to increases of AD pathology,³⁸ and the expression of insulin receptor was observed in the AD brain.^{39,40} Several clinical studies show that the treatment of T2DM leads to the improvement of AD pathologies such as cognitive deficit⁴¹ by decreasing A β levels^{42,43} and tau pathologies.⁴⁴ One study demonstrated that diet induced obesity in the triple-transgenic mice model of AD showed excessive A β

burden, and aggravation of behavior dysregulation.⁴⁵ Another study reported that the metabolic dysfunction and the acceleration of AD related pathologies were found in the insulin receptor substrate 2 knockout AD mice model.^{46,47} Based on the previous evidences, insulin resistance, glucose deregulation, and inflammation may be in the central mechanisms between the onset and progression of T2DM and AD.

AD AND LOW ANDROGEN

Androgen is a sex steroid hormone in men which exerts multiple physiological functions leading to maturation of reproductive systems.⁴⁸ Testosterone, dihydrotestosterone (DHT), androstenedione, dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) have been known as major androgens in males, and play an critical role in cognition, and their RNAs were observed in the AD cerebral cortex and hippocampus.²² Several studies reported that androgens play an important role in memory function in men, and low androgen level is directly linked to the onset of dementia,⁴⁹⁻⁵³ thus androgen deficiency could lead to neural dysfunction in mood and cognition.^{54,55} Low levels of free testosterone were also observed in the brain of AD patients.⁵⁶ Furthermore, low levels of testosterone in blood⁵⁷ or brain^{15,51} lead to the increased risk for developing AD.¹⁵ A strong association between low testosterone levels and insulin resistance was observed in men.^{58,59} In addition, low levels of testosterone were commonly found in the T2DM patients compared with non-diabetic controls.⁵⁸ Therefore, therapy using testosterone may result in the reduction of T2DM features.^{60,61} Also, androgen deprivation therapy has shown reduced insulin sensitivity and glycemic control.⁶² Considering the previous evidences, low levels of testosterone may contribute to insulin resistance, and glucose deregulation in the AD brain.

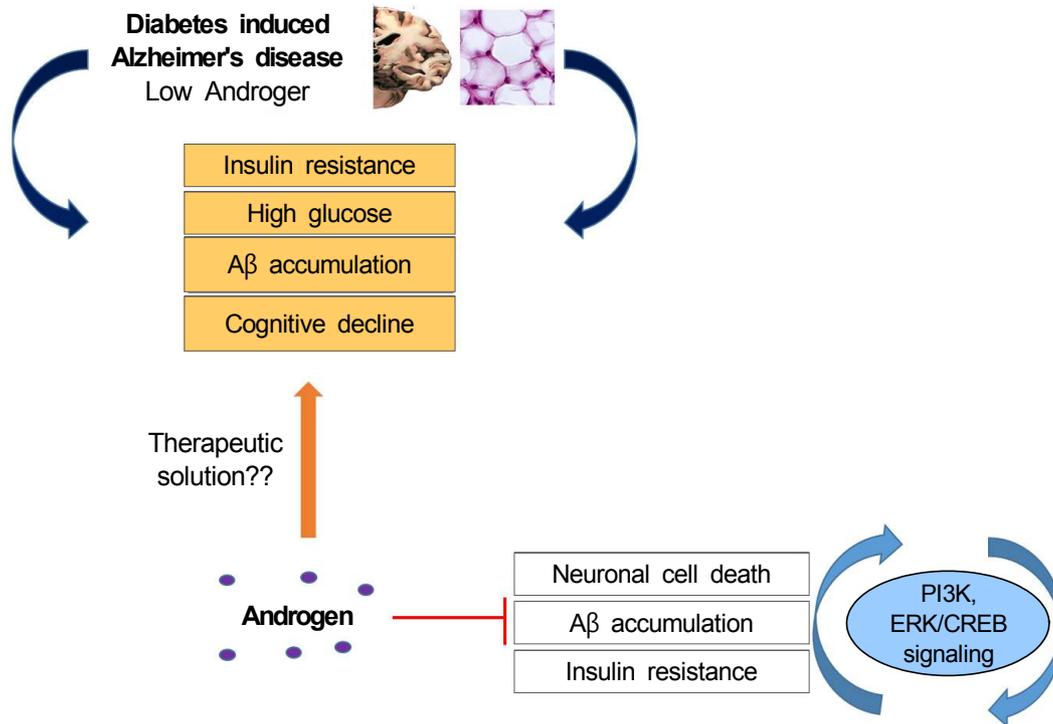


Fig. 1. Systemic images about the relationship between diabetes induced Alzheimer’s disease (AD) and androgen. Diabetes induced is characterized by insulin resistance, high glucose level, Aβ accumulation, and cognitive decline. Androgen could protect neuronal cell death, Aβ accumulation, and insulin resistance in brain through PI3K, and ERK/CREB signaling. This image shows the therapeutic possibility of androgen in diabetes induced AD.

ANDROGEN PROTECTS NEURONAL CELLS AND INVOLVES Aβ ACCUMULATION IN THE AD BRAIN

The accumulation of amyloid plaques is the neuropathological hallmarks of AD.⁶³ According to the study which investigated the regulatory function of androgens on Aβ,⁶⁴ APP metabolism and Aβ production in cortical neurons were regulated by testosterone levels in the brain.^{51,65,66} As mention above, androgen could modulate Aβ production in the AD brain. Furthermore, androgen contributes to the increase of neuronal viability in brain.⁶⁷⁻⁶⁹ Androgen depleted rats exhibited severe neuronal loss in the pyramidal layer of hippocampus⁷⁰ as well as under oxidative stress⁷¹ or Aβ toxicity condition.^{72,73} One study demonstrated that androgens

could activate PI3K signaling through intracellular androgen receptor,^{74,75} and ERK/CREB signaling in neurons.^{76,77} Testosterone could modulate neuronal damage under oxidative stress condition,⁷¹ and reduce neuronal apoptosis and autophagic cell death.⁷⁸ Testosterone reduces neuronal apoptosis through the phosphorylation of ERK as well as through the activation of Bcl2 which increases neuron viability.⁷⁹ Collectively, androgen could protect neuronal cell damage against oxidative stress in brain.

ANDROGEN RECEPTOR COULD CONTROL INSULIN RESISTANCE AND SYNAPTIC PLASTICITY IN THE AD BRAIN

Cross-sectional studies have reported an inverse

association between testosterone levels and insulin resistance in men.⁸⁰ Increased insulin resistance was triggered in men with a 25% decrease of serum testosterone compared to normal men.⁸¹ Acute androgen deprivation could attenuate insulin sensitivity in healthy men,⁸² and reduction of total and free serum testosterone could lead to T2DM in men.⁸³ Moreover, synaptic plasticity is a critical issue in learning and memory function.⁸⁴ In the cerebral cortex of AD patients, alteration of synaptic plasticity occurs prior to formation of A β , and ultimately triggers cognitive deficits.⁸⁴ It has been reported that androgen receptors are involved in memory and learning by involving synapse function.^{85,86} DHT could reduce the binding of N-methyl-D-aspartate (NMDA) receptor antagonist in hippocampus CA1 region,⁸⁷ and control NMDA mediated depolarization in pyramidal neurons.⁸⁸ Recent study reported that androgen inhibits reduction of hippocampal dendritic spine density in rats.⁸⁹ Another study reported that testosterone promotes hippocampal synaptogenesis.⁹⁰ Also, testosterone could enhance the expression of brain derived neurotrophic factor, leading to improvement in hippocampal dendritic spine density, and the phosphorylation of CREB to enhance synaptic plasticity.⁸⁶ Androgens improve spine-synapse density in the CA1 of rodents.⁹¹ Taken together, androgen could improve insulin resistance by binding androgen receptor in brain, enhance synaptic failure, and promote synaptogenesis in the AD brain.

CONCLUSIONS

Here, we reviewed the role of androgen in diabetes induced AD. We highlight the therapeutic potential of androgen in diabetes induced AD brain including the improvement of insulin resistance, the inhibition of A β accumulation, the protection of neuronal cells against oxidative stress, and the suppression of synaptic dysfunction. Given that testosterone supplementation could

improve cognitive decline⁹² and memory function,⁹³⁻⁹⁵ we speculate that androgen can be a good target hormone to alleviate the neuropathology in diabetes induced AD.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

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