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REVIEW

Alzheimer's Disease and Insulin Relationship: Type 3 Diabetes

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Abstract

Alzheimer's disease is a disease that occurs with advancing age and is characterized by progressive dementia and neural degeneration. In recent years, it has been stated that insulin deficiency and insulin resistance are associated with neurodegenerative processes in Alzheimer's disease. It has been supported by many recent studies that a decrease in the amount of brain insulin and insulin resistance has a role in the accumulation of amyloid beta and hyperphosphorylated tau protein, which are held responsible for the pathogenesis of Alzheimer's disease and reduces synaptic pilasticity. For this reason, the definition of Type III diabetes has been used for Alzheimer's disease in recent years and has brought a new perspective to the pathogenesis and treatment of Alzheimer's disease. In this study, we aimed to discuss the role of insulin deficiency and insulin resistance in Alzheimer's etiopathogenesis. For this purpose, current articles related to Alzheimer's and Type III diabetes have been reviewed.

Keywords: Alzheimer's disease; Insulin resistance; Type-3-diabetes.

Alzheimer's Disease (AD) is an age-related, progressive neurodegenerative disease that causes dementia. Memory loss, personality changes, negative affect on mood and social life develop with the course of the disease. The etiology of AD is still unknown and multifactorial. Extracellular neuritic plaques, intracellular neurofibrillary tangles and apoptosis are observed in postmortem microscopic examinations of the brains of those with AD. These changes are associated with loss of neural synapses, oxidative stress and mitochondrial structural and functional abnormalities, inflammatory responses, hormonal changes, and cell cycle abnormalities[1,2]. The most important known risk factors in AD are age and positive family history. Almost half of the cases have a first-degree relative with AD. Other factors that may be associated are severe head trauma, female gender, educational background, vascular diseases, and previous depression[1]. As a vascular complication of Type 2 Diabetes mellitus (DM), the incidence of AD is increased in these patients. In Type 2 DM, there is hyperglycemia and increased peripheral insulin resistance. Cognitive dysfunction is seen in Type 2DM due to impaired glucose absorption in neurons and insufficient energy production[3]. It is known that there is a relationship between type 2 DM and AD. This relationship is caused by many reasons such as insulin resistance, insulin-like growth factor (IGF) signaling disorder, inflam-

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matory response, oxidative stress, neurofibrillary tangle formation, amyloid β (Aβ) formation, glycogen synthase kinase 3β (GSK3β) signaling disorder (Fig. 1)[4,5].

There are many recent studies in which AD is presented to be a neuroendocrine disorder and associated with insulin resistance, so it is called Type 3 DM. What is meant by the term Type 3 DM is insulin deficiency and/or insulin resistance in the brain in AD[1,2,6]. Improvement in cognitive functions has been observed in diabetic Alzheimer's disease patients or stroke patients using insulin[7]. It was aimed to increase the central concentration of insulin with the use of intranasal insulin (20 U/day), and it was observed that these patients had an increase in their cognitive abilities without any difference in plasma glucose and insulin concentrations[8].

Relationship between Mitochondrial Dysfunction-Oxidative Stress and AD

When an imbalance begins to occur between the production and elimination of reactive oxygen products, there is an increase in the amount of oxidative stress and free radicals. In both DM and AD, there is free radical production and related cellular damage and development of apoptosis. When oxidative stress and mitochondrial damage occur, ATP production decreases, which again causes free oxygen radical accumulation. With its rich lipid content, brain tissue is very sensitive to oxidative stress and apoptosis. These mechanism similarities have caused AD to be referred to as Type 3 DM[1,2,8]. The cellular damage seen in this disease also causes structural changes in the cell and causes Aβ and tau protein accumulation[9]. In addition, it has been reported that Aβ formed causes mitochondrial dysfunction and neuronal damage (Fig. 2) [10].

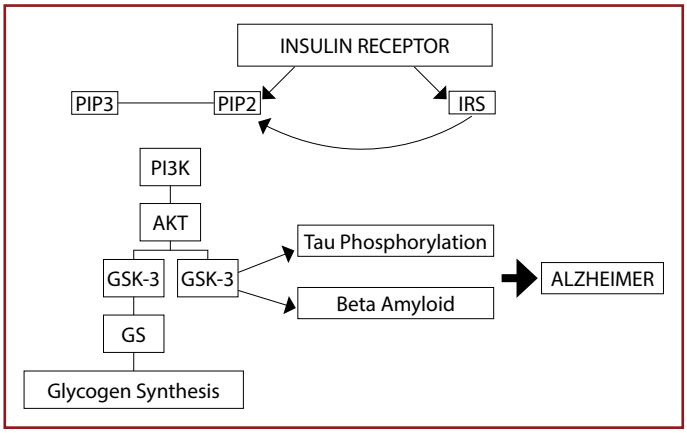

Figure 1. Relationship between tau protein and Aβ formation and insulin in Alzheimer's disease.

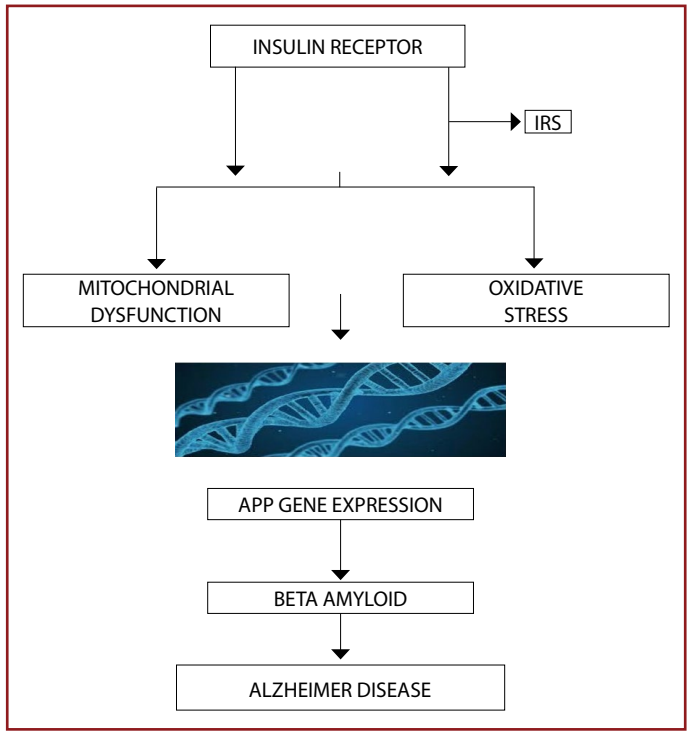

Figure 2. Mitochondrial dysfunction in Alzheimer's disease.

Aβ and Tau Protein Formation Secondary to Oxidative Stress

Aβ is formed by proteolysis of amyloid precursor protein (APP). Many studies have shown that Aβ is formed by a secondary response to neuronal oxidative stress and cellular damage[11,12]. Normally, the inner mitochondrial membrane prevents cellular damage and Aβ formation against oxidative stress, but this protective mechanism is impaired in AD, resulting in the accumulation of Aβ in the cell. Aβ itself also causes cellular damage. Oxidative stress also causes the formation of hyperphosphorylated tau protein, and tau protein forms neurofibrillary tangles[12,13].

Hyperglycemia and Oxidative Stress

Hyperglycemia causes accumulation of advanced glycation end products (AGE). The increase in AGE, H_2O_2 and superoxide production leads to lipid peroxidation and cellular damage. Hyperglycemia and oxidative stress increase the production of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT). These products cause neuronal damage in both DM and AD[14].

Impaired Insulin and IGF Response in the Brain

Cerebral insulin is involved in brain glucose utilization and receptor-mediated glucose transport across the blood

brain barrier. It has been stated that cerebral insulin, insulin-related peptides and insulin resistance also lead to deterioration in cognitive functions with aging[10,12,15]. In a study with rats in which insulin receptors in the brain were blocked, animals had insulin resistance, glucose intolerance, and weight gain[2-4]. In this study, it was seen that insulin in the brain is associated with nutrition and weight regulation. In other words, there is resistance and scarcity of insulin not only in the peripheral tissue, but also in the brain. While insulin resistance in peripheral tissue is the resultant effect in receptor or postreceptor tissue, insulin resistance in the brain manifests itself with changes in insulin receptor functions[5]. As a matter of fact, it has been observed that cognitive functions improve in diabetic Alzheimer's or stroke patients using insulin[16,17]. With the use of intranasal insulin (20 U/day), it was aimed to increase the central concentration of insulin, and it was observed that these patients had an increase in their cognitive skills without any difference in plasma glucose and insulin concentrations[18,19].

Peripheral insulin can cross the blood-brain barrier, but it is also produced in the central nervous system[15,16]. The brain's own insulin and insulin receptor are present in neurons and astrocytic synapses. Insulin m-RNA, insulin, and the insulin receptor are common in nearly the entire brain, however, it is known to be more common in the medial prefrontal cortex, hippocampal pyramidal neurons, entorhinal cortex, thalamus, olfactory bulb, and hypothalamus[17]. The brain areas with the highest insulin concentration are the hippocampus, amygdala, and septum pellucidum, which are memory-related brain areas[3,6,18]. The intensity of insulin in these areas supports its relationship with memory and its role in AD. Insulin transport from the peripheral blood is highest in the olfactory bulb, and it is present in the whole brain, more in the pons, medulla, and hypothalamus[19]. Central insulin, which is independent of blood insulin level, has been associated with learning and memory[20]. Insulin receptor inhibits apoptosis through tyrosine kinase, phosphatidyl inositol-3-kinase and mitogen-activated protein kinase. Together, modulation of the channel via N-methyl-D-aspartate channel phosphorylation and increased calcium flow are involved in the memory formation process[12,13,21]. Rats with silenced insulin receptor substrate gene (IRS-1) appear to have reduced brain volume, decreased proliferation of hippocampal neurons and neurofibrillary tangle deposition[5,7,22,23]. The role of insulin receptor deficiency and abnormal tissue insulin response in AD has been shown in many studies[18,24,25]. Insulin levels were determined to be decreased in cerebrospinal fluid (CSF) samples of AD patients with mild cognitive dysfunction[24]. In the early stages of AD, there is degeneration in neurons carrying insulin and insulin receptors[26,27]. In the advanced stages of the disease, insulin-mediated neurodegeneration is common in the whole brain. In addition, it was observed that there was a correlation between the duration of diabetes and the number of neuritic plaques[24,28]. It has been observed that cognitive functions improve with antidiabetic treatment and prevention of hypoglycemic attacks[21,29].

Inflammation and AD

Increased inflammatory mediators such as IL-6, IL-1β, IL-18, TNF-α and CRP are indicative of mitochondrial dysfunction. Increased insulin resistance in both DM and AD leads to the same inflammatory response[30]. Increased IL-6 levels were demonstrated in CSF and senile plaque samples in AD rat models[31]. In addition, it is known that inflammation leads to an increase in AGE, Tau and Aβ levels. The role of diabetic inflammation in AD is supported by the reduction of neurocognitive impairment with anti-inflammatory agents or peroxisome proliferator activated receptor (PPAR) agonist antidiabetics used in these patients[32-34]. Brain insulin and IGF resistance causes increased cerebral inflammatory mediators release in AD. At the same time, the inflammatory response causes neurotoxicity with increased APP gene expression and APP amyloid deposition. In type 2 DM, the TNF-α cascade and the c-Jun N-terminal kinase (JNK) pathway are activated, creating insulin resistance[17,18]. In mouse hippocampal cell culture, it causes IRS-1 inhibition by activation of the TNF-α/JNK pathway and leads to the formation of Aβ amyloid[33,35,36]. Insulin prevents the accumulation of Aβ amyloid, which is the specific pathological manifestation of AD and is responsible for neuronal loss.

AD-Type 3 DM and astrocyte relationship

Mitochondrial damage secondary to insulin resistance and oxidative stress causes both the release of inflammatory mediators and the activation of microglia in the brain. This activation is responsible for the inflammatory response in the brain in both diabetes patients and AD, and this effect has been shown especially in the hypothalamus[34]. Through the synaptic connections of astrocytes and microglia, astrocytes are also affected by this inflammatory response, resulting in increased cytokine release. This mechanism leads to cortical neuronal damage in both advanced diabetes and AD.

Insulin, IGF and Acetylcholine (ACh) Metabolism and their Relationship with AD

Acetylcholine is an important neurotransmitter in neuronal signaling and synaptic plasticity. A relationship was found between decreased ACh levels and progression of the disease in AD[34]. In insulin deficiency, glucose uptake and ATP production decrease and neuronal hemostasis is impaired. Insulin also stimulates cholinacetyl transferase, and the amount of cholinacetyl transferase decreases in the presence of decreased insulin levels or insulin resistance[6-8]. Insulin is thought to play a role in neurotransmitter release and synaptic modulation, and may even act as a transmitter, and in this way be effective in learning and long-term memory[3,9]. In brain autopsies of Alzheimer's patients, a decrease in insulin level, as well as the levels of insulin receptor, IGF-1 and -2, insulin m-RNA, has been reported[10,12-14]. The decrease in insulin receptors is about 80%[15,16]. There is impaired protein synthesis in the neuron endoplasmic reticulum due to a decrease in brain glucose use due to insulin deficiency or resistance. Insulin contributes to synaptic plasticity by modulating GABA and AMPA receptor functions in the membrane[10,20].

Insulin, insulin receptors and IGF are thought to be associated with learning and memory[21,22]. De la Monte et al.[4] showed that IGF is released in the brain. In rats, administration of streptozotocin or alloxan, alkylating chemotherapeutic agents, to the cerebrospinal fluid resulted in a decrease in IGF levels and brain volumes, hippocampal degeneration, and memory loss in animals[1,3,30]. Streptozotocin acts by destroying the neuronal structure that produces insulin. It was observed that there was an improvement in memory functions by reintroducing insulin into the CSF[30,32].

Result

Although AD and DM are completely different diseases, since their pathogenesis is similar, AD was thought to be diabetes of the brain. Inflammatory mediators associated with insulin and IGF signaling impairment, oxidative stress and mitochondrial dysfunction are associated with neurodegeneration in AD. Alzheimer's disease is a multifactorial disease, and multi-agent modalities for etiopathogenesis are recommended for treatment. The role of cerebral insulin resistance or deficiency in the etiopathogenesis of AD has led to this disease being referred to as Type 3 DM. Correction of existing insulin deficiency or insulin resistance in AD may be among the new treatment approaches. Memory and cognitive functions can be preserved and improved in these patients with insulin replacement. It is thought that further studies that will more clearly elucidate the effect of insulin on neuronal signaling and protein synthesis in the endoplasmic reticulum may make great contributions to the treatment. In addition, considering the role of insulin in AD, there are studies conducted with glucagon-like peptide receptor agonists, intranasal insulin, brain natriuretic factor and leptin in treatment research. These findings should be supported by extensive clinical research.

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