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Role of Insulin Metabolism Disturbances in the Development of Alzheimer Disease: Mini Review

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Alzheimer disease (AD) is the most common form of dementia. Different pathogenic processes have been studied that underlie characteristic changes of AD, including Aβ protein aggregation, tau phosphorylation, neurovascular dysfunction, and inflammatory processes. Insulin exerts pleiotropic effects in neurons, such as the regulation of neural proliferation, apoptosis, and synaptic transmission. In this setting, any disturbance in the metabolism of insulin in the central nervous system (CNS) may put unfavorable effects on CNS function. It seems that disturbances in insulin metabolism, especially insulin resistance, play a role in most pathogenic processes that promote the development of AD. In this article, the relationships of disturbances in the metabolism of insulin in CNS with Aβ peptides aggregation, tau protein phosphorylation, inflammatory markers, neuron apoptosis, neurovascular dysfunction, and neurotransmitter modulation are discussed, and future research directions are provided.

Keywords: Alzheimer disease; dementia; insulin resistance

Introduction

Alzheimer disease (AD) was first described by Alois Alzheimer about 100 years ago at a congress in Tubingen, Germany.[1] AD is the most common form of dementia, accounting for 50% to 60% of all cases.[2] Aging is the most obvious risk factor for the disease, and both genetic and environmental factors play a role in the development of AD. Hypercholesterolemia, hypertension, arthrosclerosis, smoking, obesity, and diabetes are true causal risk factors driving the pathogenic processes resulting in the development of AD.[3] The characteristic lesions in AD are neurotic plaques and neurofibrillary tangles. Different pathogenic processes have been studied that underlie these changes, including Aβ protein aggregation and deposition with plaque development, tau phosphorylation with tangle formation, neurovascular dysfunction, inflammatory processes, oxidative stress, cell cycle abnormalities, and mitochondrial dysfunction.[4] Recently, a considerable amount of studies have been focused on impairment in insulin metabolism in the brain as a new pathogenic process for AD. Individuals suffering from AD had been shown to have lower cerebrospinal fluid (CSF) and higher plasma insulin concentration.[5] In addition, administration of insulin for patients with AD led to improvement in memory and performance.[6] In this review, we studied different features of the effects of insulin on the central nervous system (CNS) and its relation with pathogenic processes that contribute to the development of AD.

Insulin and CNS

Over the past few years, it has become clear that insulin has profound effects on the CNS. In primary fetal brain cell cultures, insulin plays an important role in the control of metabolism and growth.[7] Also, it regulates key processes such as energy homeostasis, reproductive endocrinology, central action on peripheral glucose

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metabolism, learning, memory, and neuronal survival in adults.[8] New findings confirmed that insulin exerts pleiotropic effects in neurons, including the regulation of neural proliferation, apoptosis, and synaptic transmission.[9] The actions of insulin are mediated via insulin receptors (IRs), which belong to the family of tyrosine kinase receptors.[10] To initiate signaling in the CNS, insulin has to reach its receptors, which is separated from circulation by the blood–brain barrier (BBB). IRs are widely distributed in the brain, with the highest concentrations in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum, and hippocampus. Some studies focused on the definition of several conditions that affect insulin transport across the BBB, such as fasting, aging, obesity, and insulin resistance.[11]

Recent findings support the role of insulin in the preservation of normal memory and cognition. It has been shown that intranasal administration of insulin induces facilitation in working memory.[12] It has also been shown that systemic infusion of insulin in euglycemic hyperinsulinemia conditions in healthy humans yields a significant improvement in verbal memory and selective attention.[13] Furthermore, a pronounced negative shift in the transcortical direct current potential has been noticed.[13] Some studies have shown an improving effect of insulin on cognitive function in Alzheimer patients and healthy subjects.[14,15] In this setting, any disturbance in the metabolism of insulin in CNS may cause unfavorable effects on CNS function; for example, individuals suffering from AD and Parkinson's disease show reduced expression of the IR in the brain, raising the question of whether this phenomenon is a cause or consequence of neurodegeneration.[16,17]

Insulin Resistance and Etiologies of AD

As mentioned above, different pathogenic processes were postulated to contribute in the development of AD. It seems that disturbances in insulin metabolism, especially insulin resistance, play a role in the promotion of most of these pathogenic processes. In this section, the relationship of insulin resistance with etiologies of AD is reviewed.

Insulin and Aβ Peptide Level Modulation

The central hypothesis for AD pathogenesis is the amyloid cascade hypothesis, which states that an imbalance between production and clearance of β-amyloid in the brain is the initiating event, ultimately leading to impairment in synaptic function with resulting neurotransmitter deficits and cognitive symptoms.[18] The actual amount of this neurotoxic peptide in the brain is determined by (1) Aβ production through amyloid processor protein (APP) processing and (2) Aβ degradation and clearance. It is now believed that increased Aβ production plays a role in familial AD and decreased Aβ clearance is dominant in sporadic AD.[19] Insulin has several effects on the modulation of the Aβ level in the brain, which changes both Aβ production and clearance. Insulin affects APP processing, leading to the release of intracellular Aβ and its trafficking from the Golgi network to the plasma membrane, and also increases the secretion of Aβ into the extracellular space.[20] Insulin degrading enzyme (IDE) is the only protease involved in Aβ degeneration. It likely prevents formation of amyloid deposits by cleaving the component peptides. Aβ protein, insulin, and amylin are among the main substrates for IDE, with these substrates competing with each other to be degraded with IDE. Also, CNS insulin levels has a regulatory effect on IDE levels, which is highly expressed in the brain as well as in the liver, kidney, and muscle.[21]

Taken together, excessively high CNS insulin levels may inhibit Aβ degeneration through competition with Aβ in degeneration by IDE. Conversely, low CNS insulin followed by insulin resistance may reduce the brain IDE level and thereby impair Aβ clearance.[22] Interestingly, it has been demonstrated that peripheral infusion of insulin in healthy older humans increases the CNS Aβ level within 120 minutes, which also was correlated with decreased memory.[23] This can be because of the insulin effect on the degradation of Aβ transported out of the brain. High plasma insulin levels may interfere with the degradation of plasma Aβ, thereby obstructing a peripheral Aβ-clearing sink. This peripheral channel contributes in Aβ clearance; and therefore, its obstruction may result in the excess accumulation of Aβ in the brain and ultimately development of AD. Recent findings have confirmed the elevation of plasma Aβ levels in prodromal and early AD stages.[24] These findings indicated that an optimized brain insulin level promotes Aβ clearance; and therefore, may have protective roles against AD. In contrast, both low CNS insulin and excessively high CNS and plasma insulin levels promote the development of AD.

Insulin and Tau Protein Phosphorylation

Almost all neurofibrillary tangles are composed of abnormally hyperphosphorylated tau proteins. Tau is a normal axonal protein that binds to microtubules through its microtubule domains, thereby promoting microtubule assembly and stability.[25] Tau phosphorylation is regulated by the balance between multiple kinases and phosphatase.[26] Hyperphosphorylation of tau causes disassembly of microtubules and thus impaired axonal transport, compromising neuronal and synaptic function.[27] Previous studies have shown that the activation of IRs can promote tau phosphorylation through several protein kinases, such as extracellular regulated kinase family and glycogen synthase kinase.[28-31] In contrast, IR type 2-deficient mice show tau hyperphosphorylation and develop intracellular deposits of hyperphosphorylated tau during aging.[32] Recent investigations have revealed that peripherally injected insulin directly targets the brain and causes rapid cerebral IR transduction and site-specific tau phosphorylation in vivo, suggesting that insulin action in the brain is directly linked to neurodegeneration by activation of tau phosphorylation.[33]

Insulin and Its Effects on Inflammation Markers

Inflammation has been suggested as a key pathogenic factor in the development of AD.[34] An elevation in the concentration of the inflammatory cytokines interleukin (IL)-6 and the lipid peroxidation marker F_2-isopropan in the CSF[35,36] and tumor necrosis factor (TNF)-α in the brain and CSF[37] has been reported in patients with AD. TNF-α has several effects on the CNS; it inhibits Aβ transport from the brain to the periphery,[38] and therefore, high TNF-α concentration may result in the accumulation of Aβ in the brain. TNF-α has both neuroprotective and neurotoxic effects through 2 different receptor subtypes, TNF-α R_1 and TNF-α R_2. TNF R_1 plays a role in proapoptotic events by its death receptor domain, and conversely, TNF R_2 promotes cell survival. Increased TNF R_1 and decreased TNF R_2 were observed in the brains of patients with AD.[39] In addition, IL-6 and IL-1β have a regulatory effect on the processing of the APP so that there is increased Aβ42 production.[40,41] Inflammatory cytokines and Aβ interact with each other in a cyclically reinforcing manner, indicating that Aβ elevations increase proinflammatory cytokines[42]; consequently, inflammatory cytokines increase Aβ accumulation in the brain by interfering in both Aβ production and clearance. The effect of Aβ on inflammatory reactants can be explained through its effect on CNS norepinephrin, an endogenous anti-inflammatory neuromodulator that blocks IL_1-β expression.[43] It has been reported that increased Aβ plaques associated with AD may cause neuronal loss in the locus coeruleus, which is the primary source of brain norepinephrin.[44] Therefore, decreased norepinephrin activity may result in the increase of inflammatory reactants.

Several studies have shown the association between insulin resistance and hyperinsulinemia conditions with elevated inflammatory markers.[35,45,46] Insulin also has regulatory effects on both eicosanoid levels[47] and CNS norepinephrin levels.[48,49] Therefore, increase in eicosanoids, such as F_2-isoprostan, and decrease in CNS norepinephrin related to chronic hyperinsulinemia may exacerbate inflammatory responses and increase the risk of AD.

Insulin and Neuron Apoptosis

As mentioned earlier, cell-cycle abnormalities are one of the pathogenic mechanisms in AD development.[50] Several conditions can contribute in neuronal apoptosis. Among those, we focused on CNS insulin deficiency, impairment of insulin growth factor (IGF) systems, and hyperglycemia.

Insulin plays important roles in the regulation of brain metabolism and neurotrophism. Several studies showed that insulin has antiapoptotic effects in vitro.[51,52] Some studies revealed the inhibitory effect of insulin on neuronal death and neurological disability.[53,54] These neuroprotective effects of insulin are associated with restoration of protein synthesis.[55] Furthermore, it is clear that IRs mediate insulin antiapoptotic effects in neurons.[56] Chronic hyperinsulinemia associated with insulin resistance conditions downregulates BBB IRs; and therefore, reduces the transport of insulin into the brain.[57,58] With regard to reduced expression of the IR in brains of patients with AD[16,59] and the consequent CNS hypoinsulinemia, individuals with AD may be more prone to neuronal apoptosis. A study stated that combination of C-peptide and insulin leads to an enhanced antiapoptotic effect via stimulation of Bcl_2 expression, an antiapoptotic gene, and nuclear factor kappa B (NF-KB).[57] It is known that NF-KB and the genes regulated by this transcription factor, such as those

coding for TNF receptor-associated factor ($TRAF_1$), $TRAF_2$, inhibitor of apoptosis (IAP) proteins C-IAP_1 and C-IAP_2, manganese superoxide dismutase, BCL_2, and BclxL, play important roles in the regulation of apoptosis.[60,61] Therefore, C-peptide and insulin give rise to a significant increase in nuclear NF-KB, suggesting that it exerts its antiapoptotic effect via activation and translocation of NF-KB.[62]

The IGF system (IGF_1, IGF_2, and IGFR) exerts neuroprotective effects through several mechanisms. First, insulin and its associated hormone IGF-1 reduce phosphorylation of tau protein by inhibiting the activity of glycogen synthesis kinase-3,[27] which can phosphorylate the microtubule-associated protein tau in cultured human neuron.[63] As described above, hyperphosphorylated tau is a principle component of paired helical filaments in neurofibrillary lesions associated with AD. Second, insulin and IGF-1 strongly activated protein kinase B (PKB), which in turn causes Bcl_2 release that consequently inhibit apoptosis. Third, in another study it was shown that IGF-1 and IGFR have a protective effect on the development of amyloidosis in Tg2576 mice, an animal model of AD. Furthermore, an increase in the expression of IGF-2, a potent ligand of the IR in the brain, in Tg2576 mice increases PKB phosphorylation and ultimately results in activated survival signaling and lack of neurodegeneration.[64] In addition, a perturbed IGE system has been found in the CNS of diabetes patients.[65]

Hyperglycemia causes increased glucose levels in the brain. It is well established that hyperglycemia causes oxidation stress via several mechanisms, including polyphenol pathway, enhanced glycation end-products, lipid peroxidation, and imbalances in the generation of reactive oxygen species and their scavengers.[66-69] Oxidative stress can contribute to cerebral ischemic injury[70] and neuronal apoptosis.[71,72] Collectively, insulin resistance and hyperglycemia can induce elevated glucose levels in the brain, causing oxidative stress and neuronal loss, especially in hippocampus.

Insulin and Neurovascular Dysfunction

The comorbidity of cerebrovascular disease and also brain microvascular system with AD has been demonstrated.[73] The neurovascular hypothesis suggests that abnormal blood vessels could impair delivery of nutrients to the brain and Aβ efflux from the brain, contributing to cognition impairment.[74] It has been revealed that ischemia followed by cerebrovascular conditions results in the upregulation of APP expression and therefore Aβ deposition.[75,76] Vascular-related risk factors associated with insulin resistance have been indicated as evidence linking insulin resistance with AD and affective disorders.[77] It has been revealed that insulin increases the low-density lipoprotein receptor-related protein, which promotes intake of apolipoprotein-E (ApoE) enriched lipoprotein and degradation of the isoform of APP.[78] With regard to the association of AD with coronary artery disease and arthrosclerosis and the effect of insulin on the degradation of ApoE-enriched lipoprotein, it seems that insulin resistance can lead to vascular dysfunction and consequently increased risk of AD.

Insulin and Neurotransmitter Modulation

Insulin may modulate cognitive functions through effects on neurotransmission. Acetylcholin (Ach) plays an essential role in memory function.[79] The cholinergic hypothesis, which indicates a dramatic reduction of Ach in the brains of patients with AD, formed the basis for treatment of these patients with acetylcholine esterase inhibitor agents (AchEI). A low, nonhypoglycemic dose of insulin can reverse the amnesic effects of cholinergic blockade.[80] Several studies have shown that the impairment in glucose usage as a result of insulin resistance may lead to decreased Ach synthesis and subsequent memory impairment.[81,82] Furthermore, cholinergic treatment increases regional brain glucose uptake in both rodents[83] and humans[84]; therefore, by increasing brain glucose, insulin may augment Ach synthesis and release, finally leading to improvement in memory performance.[85]

Another study described the association between both AD and affective disorders and reduced serotonergic (5-HT) activity and hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis.[86-89] It has been demonstrated that 5-HT and its major metabolite 5-hydroxyindolacetic acid concentrations decreased in the brains of patients with AD, particularly in the temporal cortex[90] and in the CSF.[91] Insulin can increase CNS 5-HT levels by facilitating transport of the serotonin precursor, tryptophan, across the BBB,[92,93] thereby increasing serotonin synthesis. According to these findings, insulin abnormalities, such as insulin resistance, can result in

CNS 5-HT depression. In addition, activation of the HPA axis has been associated with impaired glycemic control, which has been reported in both AD and affective disorders.[94,95] Several studies have shown the association of increase HPA activity (eg, hypercortisolemia) and insulin resistance.[96] This association may be a result of high IR concentration in the hippocampus, a key area in the regulation of HPA axis activity.[97] According to the glucocorticoid cascade hypothesis of aging, increasing HPA axis activity results in hippocampal atrophy,[98] a structure that supports memory. Therefore, insulin resistance promotes cortisol neurotoxicity in the hippocampus.[99]

Summary and Future Directions

This review showed that disturbances in metabolism of glucose play a considerable part in the promotion of the main etiologies of AD. In conclusion, it can be postulated that the disorders associated with disturbances in the metabolism of glucose may make patients prone to the development of AD. Patients with depressive disorders, multiple sclerosis, and polycystic ovary syndrome may be at higher risk for development of AD.[100-102] As early detection of AD can play an important role in the prevention of disease progression, identification of groups at higher risk for development of AD is helpful for considering suitable therapeutic strategies. For this purpose, many attempts have been made to visualize AD-specific pathological changes in the brain. Currently, functional imaging with single photon emission computed tomography and positron emission tomography can provide the clinician with additional information complementary to morphological assessment, thus contributing to achieve a more adequate diagnosis, including information regarding prodormal stages of AD.[103] In addition, these modalities can demonstrate functional disturbances in glucose metabolism in the brain, which can be applied by researchers to evaluate the correlation of glucose metabolism disturbances and AD-specific changes in the brains of studied populations. On the other hand, it seems that treatment of underlying causes of disturbances in the metabolism of glucose in the brain, such as insulin resistance, can be better investigated in target populations as a novel therapeutic strategy. To evaluate if these agents are effective in preventing the progression of AD, the target populations could be patients with early stages of AD or even patients with more advanced disease.

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