

INSULIN RESISTANCE AND COGNITION : NEW APPROACH FOR TREATING ALZHIEMER'S

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Summary

The manner in which abnormalities of insulin metabolism contribute to disorders of aging, and in particular to the pathogenesis of Alzheimer's disease has been a topic of recent interest. It has been observed that with direct intracerebroventricular administration of insulin in rodents, as well as with intravenous insulin administration in humans, which induces the transport of insulin into CNS across the blood brain barrier (BBB) there has been an improve in cognition. More recently the facilitation of memory in patients with alzheimer's with intranasal insulin administration has been studied. A number of mechanisms may contribute to insulin-mediated memory facilitation, insulin receptors are present in key brain regions, such as hippocampus, entorhinal cortex, and frontal cortex. Insulin modulates levels of neurotransmitters such as acetylcholine, norepinephrine, and dopamine that play important roles in cognition. Insulin also affects membrane potentials, neuronal physiology, and long-term potentiation, which influence synaptic remodeling processes thought to underlying memory formation.

Key words: insulin, insulin receptor, cognition, alzheimer's, insulin resistance

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Introduction

Insulin and its receptor in the brain have been known to play a very important role in the brain, regulating many key functions like memory, energy homeostasis, food intake, neurodegenerative disorders and reproduction[1,2]. Until recent years, the functions of insulin and insulin receptor (IR) in the central nervous system (CNS) have largely remained unclear. IR is abundantly expressed in several specific brain regions. The presence of insulin in the brain has been recently associated with high cognition. The IR from the periphery and CNS exhibit differences in both structure and function[2-4]. In addition to that from the peripheral system, locally synthesized insulin in the brain has also been identified. Evidence has demonstrated that insulin plays an important role in associative learning, as suggested by results from both interventional and correlative studies. Interruption of insulin production and IR activity causes deficits in learning and memory formation. Abnormal insulin levels are seen in Alzheimer's whereas administration of insulin significantly improves the cognitive performance. At the molecular level, insulin/IR participates in regulation of learning and memory via activation of specific signaling pathways, one of which is shown to be associated with the formation of long-term memory and is composed of intracellular molecules including the shc, Grb-r/SOS, Ras/Raf, and MEK/MAP kinases[2]. The IR pathway associated with these functions is the activation of pi3 kinase, and protein kinase C, as well as with the non-receptor tyrosine kinase pp60c-src. The synaptic bases for the action of insulin/IR include modifying neurotransmitter release processes at various types of presynaptic terminals and modulating the activities of both excitatory and inhibitory postsynaptic receptors such as NMDA and GABA receptors, respectively[3,4]. It has been known that insulin-resistant conditions adversely affect general health status and are a matter of increasing concern in the global population today. Recent findings suggest that insulin contributes to normal brain functioning and that peripheral insulin abnormalities increase the risk for memory loss and neurodegenerative disorders such as Alzheimer's disease[5]. Potential mechanisms for these effects include insulin's role in cerebral glucose metabolism, peptide regulation, modulation of neurotransmitter levels, and modulation of many aspects of the inflammatory network[1-3]. There is clinical evidence suggesting that thiazolidinediones, used in therapy of type2 diabetes, can be used as treatment for Alzheimer's disease. These agents improve insulin sensitivity, reduce hyperinsulinemia, and exert anti-inflammatory actions.

Insulin and cognition:

Insulin administration, intracerebroventricular enhances memory acutely on a passive-avoidance task, whereas control infusions do not enhance memory [7-10]. In rats, insulin administration in healthy older adults and adults with Alzheimer's disease, increasing plasma insulin levels while maintaining euglycemia facilitates recall of verbal declarative memory and enhances selective attention [8]. Studies reveal that raising plasma insulin levels in the presence of euglycemia is sufficient to facilitate memory, but raising plasma glucose in the absence of an endogenous insulin response is not sufficient to facilitate memory. Recently, the focus has been on the intranasal administration of insulin, for direct delivery to the brain, it has shown increased intranasal levels which can be detected within 10 mins, this does not effect the plasma insulin and glucose levels [11,12]. In rats, insulin-like growth factor-1, a peptide closely related to insulin, is transported through channels connecting the nasal cavity to the olfactory bulb and rostral brain regions, including the hippocampus and amygdala, and through channels associated with the peripheral trigeminal system connecting the nasal cavity with the brain stem and spinal cord

[13]. Intranasal insulin administration produces functional and cognitive effects in humans. Acute intranasal treatment modulates auditory-evoked brain potentials and improves verbal memory in patients with Alzheimer's disease, and chronic intranasal treatment for 2 months improves verbal memory and enhances mood in young healthy adults [14-16].

Insulin and cognition: molecular mechanisms:

Learning modulates both insulin receptor expression and the insulin signaling cascade in the hippocampus. In rats, spatial learning rapidly up-regulates insulin receptor expression in the dentate gyrus and hippocampal region and modulates levels of tyrosine phosphorylation in cytosolic and membrane proteins [13,17,18]. Hence, learning induces functional changes in the hippocampal insulin receptor or downstream in the insulin signaling cascade. Insulin modulates memory via other molecular events such as long-term potentiation (LTP), a cellular model of learning. At the molecular level insulin promotes cell membrane expression of N-methyl-d-aspartate (NMDA) receptors [19], which increases neuronal calcium influx. calcium influx presumably activates calcium-dependent enzymes, including a calcium- calmodulin-dependent-kinase II (aCaMKII), and strengthens neuronal synaptic associations [19]. Thus, insulin may increase the probability of inducing LTP.

Modulation of cognition via Neurotransmitter modulation

Insulin may modulate cognitive functions through effects on neurotransmission. Acetylcholine plays an essential role in memory formation, and cholinergic blockade impairs memory[20,21]. The cholinergic hypothesis, that acetylcholine is reduced dramatically in the brains patients with Alzheimer's disease, formed the basis for treatment of these patients with AChEI agents. In multiple sclerosis(MS) and cognition, it was suggested that cholinergic changes may account for cognitive decline in MS. Demyelination and axonal damage potentially disrupt cholinergic transmission in MS, and it was recently reported that the AChEI donepezil improved verbal memory in patients with MS [22-25]. It was known that a low, non-hypoglycemic dose of insulin can reverse the amnesic effects of cholinergic blockade [24]. Therefore, changes in CNS insulin levels may influence brain cholinergic transmission. Likewise, insulin may modulate CNS functions via effects on norepinephrine levels. In humans, raising plasma insulin levels while maintaining euglycemia increases CSF norepinephrine levels [26-28]. These findings suggest that insulin contributes to normal memory functions thorough a variety of mechanisms including insulin signaling, glucose metabolism, and neurotransmitter modulation.[27]

Insulin resistance and pathogenesis of alzheimer's:

Already discussed is the fact that high plasma insulin levels an peripheral insulin resistance affects cognition. From such evidence, a model can be constructed describing how this metabolic profile contributes to the pathogenesis of AD.[29] There are likely several etiologies leading to the final common expression of AD pathology. This model depicts the general pathogenesis of alzheimer's disease progression, which relates to a large segment of patients suffering from the disease[30]. The major causes underlining the disease are peripheral hyperinsulinemia and insulin resistance which are mutually exacerbating which may result from a number of causes, including genetic vulnerability and/or environmental factors, such as diet and inactivity. The first component of the model concerns the effects of chronic peripheral hyperinsulinemia and insulin resistance on brain insulin levels[31,32]. Peripheral hyperinsulinemia and insulin resistance down-regulate brain insulin uptake at the BBB, resulting in long-term reduction of brain insulin levels. This phenomenon has been depicted in vivo in dogs with diet and glucocorticoid-induced

insulin resistance [33] and was also observed in diet-induced insulin resistant Tg 2576 mice, a rodent model of AD. Furthermore, it is known that patients with AD have lower CSF insulin levels, higher plasma insulin levels, and reduced CSF to plasma insulin ratios compared to healthy controls [3,34-37]. Epidemiological work largely supports the association between Alzheimer's disease and insulin-resistant conditions, including type diabetes and hyperinsulinemia. In the Honolulu-Asia Aging Study, type 2 diabetes was associated with an increased risk for incident dementia, incident Alzheimer's disease, and incident vascular dementia for a cohort of Japanese-American men who were followed for 3 years [38]. In the Rotterdam and the Mayo studies, type 2 diabetes increased the risk for Alzheimer's disease, independent of vascular dementia [39,40]. Luchsinger[10] and colleagues reported that hyperinsulinemia was a risk factor for both Alzheimer's disease and general memory decline in their sample of 683 older adults [10]. Likewise, peripheral and CNS insulin abnormalities have been reported in Alzheimer's disease patients. These patients have an increased risk for hyperinsulinemia and hyperglycemia, relative to healthy controls [41]. Collectively, these findings suggest that Alzheimer's disease may be associated with insulin resistance [42-45]. Hoyer proposed that desensitization of the neuronal insulin receptor contributes to Alzheimer's disease pathophysiology [46]. In his model, declining CNS insulin levels, insulin receptor expression, and insulin signaling events result in reduced acetylcholine levels and cerebral blood flow[47,48]. Furthermore, these defects are associated with chronic deficits in brain oxidative metabolism[49]. Increased intracellular acidosis in the Golgi apparatus and endoplasmic reticulum interferes with processing of proteins such as amyloid (Ah), a peptide strongly implicated in the pathogenesis of Alzheimer's disease[50]. Consistent with this theory, Alzheimer's disease brains show reduced insulin receptor density and tyrosine kinase activity markers [49]. Low brain insulin may reduce the release of Ah from intracellular to extracellular compartments, where it can be cleared. The greatest increases in Ah were associated with reduced memory performance, showing that rises in Ah levels may oppose the beneficial effects of insulin on memory[51]. Insulin may also modulate Ah degradation by regulating levels of insulin-degrading enzyme, which is highly expressed in brain as well as liver, kidney, and muscle[50,51]. Decreased insulin-degrading enzyme activity, levels, and mRNA have been observed in Alzheimer's disease brain tissue. There are a number of studies providing evidence that insulin-degrading enzyme gene polymorphisms may be related to hyperinsulinemia, AD, and Ah levels [52-56]. These observations suggest that optimal brain insulin levels promote the clearance of Ah, and thus may be protective against Alzheimer's disease. In contrast, low CNS insulin may reduce insulin-degrading enzyme levels in brain and thereby impair Ah clearance. Excessively high insulin levels may act as a competitive substrate for insulin-degrading enzyme and inhibit its degradation of Ah. Consistent with this notion, diet-induced insulin resistance in the T2576 mouse model of Alzheimer's disease resulted in high peripheral levels of insulin and low brain levels of insulin and insulin-degrading enzyme [9]. Diet-induced insulin resistance also caused two-fold increases in Ah levels. Thus, high plasma insulin levels may interfere with degradation of Ah transported out of the brain. Obstruction of Ah clearance through peripheral channels may ultimately result in excess accumulation in brain. For some patients with Alzheimer's disease, high peripheral insulin levels and low brain insulin levels would result in reduced clearance of Ah both in brain and in the periphery. Thus, insulin's effects on Ah clearance likely contribute to the development of Alzheimer's disease. Insulin's effects on inflammation may further elucidate Alzheimer's pathophysiology.

Approaches for treatment:

The lowering of peripheral insulin levels and enhancing insulin sensitivity may improve cognitive function in aging. Lifestyle interventions such as exercise have potent insulin-sensitizing effects and may provide real benefit in this regard. Pharmacologic treatment with insulin-sensitizing compounds such as the thiazolidinediones (TZD) may offer some therapeutic relief. Thiazolidinediones are agonists of the peroxisome proliferator-activated receptor- γ (PPAR γ), a ligand-activated nuclear transcription factor. Their antidiabetic action is correlated with their PPAR γ potency [57]. In the periphery, PPAR γ is expressed highly in adipocytes, where it plays a crucial role in adipogenesis, triglyceride storage, and regulation of free fatty acid levels. Individuals with heterozygous loss of function mutations within the PPAR γ ligand binding domain have insulin resistance, early onset type 2 diabetes, and dyslipidemia [57]. PPAR γ effects on insulin sensitivity likely reflect activity in adipocytes, where PPAR γ activation (1) increases fatty acid influx into adipocytes and reduces fatty acid availability for muscles, (2) decreases TNF α expression, and shifts fat from visceral to subcutaneous depots [58]. Each of these actions can improve insulin sensitivity and reduce inflammation. Apart from this administration of insulin directly into the brain may be a future method for the treatment of Alzheimer's. Recently the delivery of insulin via intra nasal route has been in research. The modern formulation scientist needs to devise a technique a delivery route and a formulation suitable to the delivery of insulin directly to the brain.

Summary and future directions

Until recent years, the brain has been described as an insulin-insensitive organ; however, evidence demonstrates that insulin participates in a number of normal and pathophysiological functions in the CNS. Insulin plays an important role in memory and other aspects of brain function. Peripheral hyperinsulinemia and insulin resistance induce a number of deleterious effects in the central nervous system that interfere with these functions, in a manner that is exacerbated by obesity and aging. It is likely that insulin modulates memory through diverse mechanisms including effects related to insulin receptor expression, the insulin signaling cascade, cerebral glucose metabolism, neurotransmitter expression, and long-term potentiation. It is not surprising, therefore, that insulin abnormalities have been implicated in cognitive dysfunction. Type 2 diabetes mellitus, chronic peripheral hyperinsulinemia, and impaired glucose tolerance have been associated with impairments in memory and other cognitive functions. Paradoxically, chronic peripheral hyperinsulinemia can reduce insulin transport across the BBB, resulting in low levels of insulin in the brain. In contrast, raising brain insulin levels facilitates memory, suggesting that central hypoinsulinemia is, in part, responsible for memory impairments related to insulin resistance. Accumulating evidence points to a role for insulin resistance

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Declaration of interest:

The authors have no conflict of interest