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Review article

INSULIN RESISTANCE AS A RISK FACTOR FOR COGNITIVE DYSFUNCTION

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ABSTRACT

Introduction: Epidemiologic, experimental, and clinical data support a link between type 2 diabetes mellitus (T2DM) and dementia due to Alzheimer's disease (AD). The prevalence of both T2DM and AD increases with age, and both diseases are chronic and are among the leading causes of morbidity and mortality. AD incidence in late diabetic patients is two times higher compared with normal elderly people and is thought to arise from impaired insulin secretion and resistance, leading to nervous system damage and ultimately influencing cognitive function in patients.

Material and methods: Using representative keywords, we conducted a comprehensive search in the scientific web databases PubMed and Scopus and limited the publication date of the papers to the last 10 years.

Results: Insulin resistance (IR) causes long-term neuronal exposure to a high-level insulin environment, leading to neuronal degeneration and irreversible memory impairment. The review of the literature outlined several possible mechanisms for IR and cognitive dysfunction interplay: (1) IR affects hippocampal plasticity, (2) IR contributes to altered amyloid precursor protein (APP) metabolism, (3) IR is related to elevated tau protein concentration, (4) IR affects brain inflammatory reaction, (5) oxidative stress is identified as an early event in the development of brain IR, and (6) genetic factors, related to ApoE ε4 allele expression and IR are present.

Conclusion: Although secreted peripherally, insulin plays a profound role in cognitive function, and IR facilitates the brain's susceptibility to neurodegeneration. The brain insulin signaling pathways also offer a promising therapeutic target for managing cognitive disorders.

Keywords: insulin resistance, Alzheimer's disease, cognitive dysfunction,

INTRODUCTION:

Brain insulin plays a critical role in cognitive functions, such as learning and memory, especially in elderly individuals [1]. Additionally, insulin influences metabolic processes, promotes nerve cell growth, regulates neurotransmitter release, and affects feeding behavior. Insulin resistance (IR) is identified as an independent risk factor for mild cognitive impairment (MCI) and is implicated in the pathogenesis of sporadic Alzheimer's disease (AD) within the brain [2, 3]. As dementia rates rise with aging populations, MCI has garnered attention as a stage for potential dementia prevention [4, 5]. Recent research has emphasized the role of IR as a potential link between diabetes and AD, suggesting that disruptions in brain insulin signaling mechanisms contribute to molecular, biochemical, and histopathological changes seen in AD [6].

Insulin signaling in the brain: Insulin's primary role in peripheral glucose regulation has historically overshadowed its significance in brain signaling, though recent decades have seen a resurgence of interest in the function of insulin, insulin-like growth factors (IGF), and their receptors within the central nervous system [7]. The presence of insulin in the brain was first identified in 1978 [8], with subsequent studies revealing high concentrations of insulin not only in human brains but also in several experimental animal models. Insulin governs energy metabolism but also provides nutritional support to nerve cells. Brain insulin is primarily derived from islet β cell secretion and crosses the blood-brain barrier (BBB) through insulin receptor-mediated transport [9], thereby regulating brain glucose levels. The functionality of insulin in the brain is closely tied to the distribution of insulin receptors [10].

A crucial brain function of insulin is its role in regulating learning and memory [11]. Recent research reveals high concentrations of insulin and insulin receptors widely distributed in key brain regions such as the cerebral cortex, hippocampus, hypothalamus, and olfactory bulb [12], all intricately linked to cognitive function. In-

sulin-sensitive glucose carriers are also present in these areas, amplifying the insulin signal to enhance brain glucose utilization and regulate learning and memory [13].

Insulin levels in the cerebrospinal fluid (CSF) are notably lower compared to plasma levels [14], but the levels are correlated, indicating that the majority of insulin in the brain originates from circulating pancreatic insulin. Insulin gains entry into the brain primarily through selective and saturable transport across the capillary endothelial cells of the BBB [15]. This transport process is influenced by various factors, including obesity, inflammation, glycemia, diabetes mellitus, and circulating triglyceride levels [16]. In humans, the ratio of insulin levels in CSF compared to serum is reported to be reduced in the presence of whole-body insulin resistance, advancing age, and disease states like AD [17].

IR in the brain: IR is defined as the lack or decreased response of the target tissues to insulin [18]. At the molecular level, IR is caused by a loss/down-regulation of the insulin receptors and insulin receptor substrates (IRS-1 and IRS-2), as well as by impairment of the insulin receptor's binding activity [19]. Functionally, reduced brain sensitivity to insulin can manifest as alterations in neurite outgrowth, impaired neuroplasticity, and disturbances in neurotransmitter release and uptake [20]. Many factors contribute to insulin transport to the brain (e.g., lipotoxicity, glucotoxicity, inflammation, and oxidative stress), and systemic IR may affect cerebral insulin signaling [21, 22].

RESULTS:

The literature review highlighted several potential mechanisms underlying the interaction between IR and cognitive dysfunction. Disturbances associated with IR, such as metabolic syndrome, obesity, and diabetes, are strongly linked to AD. In the brain, insulin promotes most functions that are disrupted in AD, including regulation of cerebral blood flow, inflammatory responses, oxidative stress, Aβ clearance, tau phosphorylation, apoptosis, lipid metabolism, transmitter receptor trafficking, synaptic plasticity, and memory [23]. Therefore, brain insulin resistance may cause or contribute to the full spectrum of pathology and symptoms observed in AD. Although it does not affect glucose uptake by neurons, brain insulin resistance in AD is similar to muscle insulin resistance in type 2 diabetes. In both cases, insulin is unable to effectively activate a specific signaling pathway [21].

The first clear indications that the brain may be insulin resistant in AD come from postmortem studies on the molecular properties of the cortical and hippocampal formation. These studies establish that such tissue in AD shows reduced insulin binding, decreased levels of activated insulin receptors, and increased serine phosphorylation of IRS-1 at sites known to inhibit insulin signaling [22, 23]. How exactly IR is linked to cognitive impairment is still unclear. Some mechanisms suggested in the literature on this matter include effects on hippocampal plasticity, altered metabolism of APP (amyloid precursor protein), tau protein increase, brain inflammation, and ApoE ε4 allele involvement. The key findings on the possible mechanisms that link IR with cognitive dysfunction are summarized in Table 1.

Table 1. Pathological impact of insulin resistance on cognitive function

MECHANISM	PATHOLOGICAL EFFECT	IMPACT ON COGNITIVE FUNCTION
Hippocampal synaptic plasticity impairment	Disrupts learning and memory processes by affecting glutamatergic neurotransmission and synaptic plasticity	Leads to memory deficits and decreased cognitive flexibility
Altered amyloid precursor protein (APP) metabolism	Promotes Aβ aggregation, impairs Aβ clearance, and disrupts APP processing, contributing to plaque formation	Accelerates neurodegeneration and cognitive decline in Alzheimer's disease
Increased tau phosphorylation	Enhances neurofibrillary tangle formation, leading to neuronal dysfunction and cognitive impairment	Correlates with disease severity and progression in AD patients
Neuroinflammation	Increases levels of inflammatory cytokines (IL-1, IL-6, TNF-α), leading to neuronal damage and synaptic dysfunction	Worsens synaptic failure and contributes to the onset of Alzheimer's pathology
Oxidative stress	Causes early neuronal damage, impairs insulin receptor signaling, and contributes to disease progression	Initiates a cascade of neuronal damage, increasing susceptibility to AD
Genetic factors (ApoE ε4 allele involvement)	ApoE ε4 carriers exhibit a higher risk of cognitive decline, increased Aβ deposition, and worsened insulin signaling in the brain	Higher risk of late-onset AD and reduced cognitive resilience

Synaptic plasticity determines higher brain functions like learning and memory. Insulin impacts hippocampal synaptic plasticity, influencing these brain functions. It plays a positive role in memory, and disruptions in the insulin signaling pathway can lead to cognitive impairment [24]. Insulin regulates glutamatergic neurotransmission at synapses, triggering long-term depression (LTD) by reducing AMPA receptors in the post-synaptic membrane [25]. Higher insulin levels promote long-term potentiation (LTP). Insulin affects learning and memory by acting on GABA receptors, supporting their translocation to the plasma membrane, and increasing their functional expression on post-synaptic and dendritic membranes [26].

Amyloid-beta (Aβ) is a key component of senile plaques and a prominent feature in AD pathology. Insulin directly affects the metabolism of APP, promoting α-secretase activity, which cleaves APP into soluble APPα (sAPPα). Insulin also accelerates the aggregation of APP and Aβ through the regulation of tyrosine kinase receptors and the mitogen-activated protein kinase (MAPK) pathway. Additionally, insulin regulates Aβ levels by facilitating Aβ transport to neuronal gaps and inhibiting Aβ degradation [27].

In rats with IR, there is a significant increase in hippocampal Aβ40 expression and prolonged escape latency periods, indicating cognitive impairment due to elevated Aβ protein levels. In AD transgenic mice, diet-induced IR promotes brain Aβ formation [28]. In IR conditions, insulin's protective effects against Aβ accumulation are diminished, leading to the down-regulation of insulin expression by Aβ deposits. Aβ peptides inhibit insulin binding to its receptors, reduce receptor auto-phosphorylation, and impair insulin-induced signaling pathways [29].

Tau protein phosphorylation is regulated by protein kinases and phosphatases, particularly glycogen synthase kinase-3 beta (GSK-3β) and MAPK, which induce tau phosphorylation. Neurofibrillary tangles composed of hyperphosphorylated tau molecules are a hallmark of AD pathology [30]. In patients with MCI complicated by IR, cerebrospinal fluid tau protein levels are elevated [31].

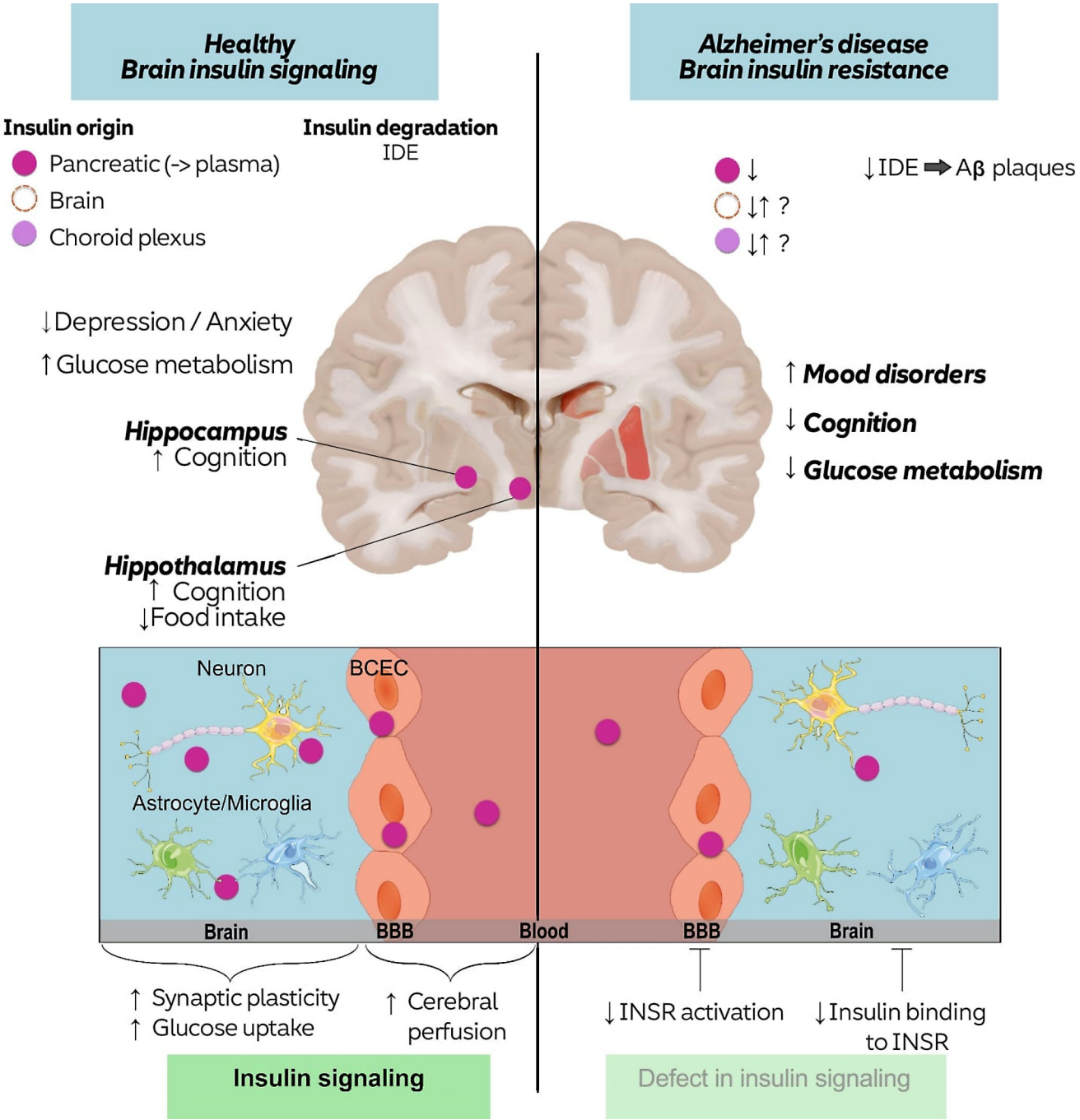
In AD, inflammation is a fundamental pathological mechanism. Inflammatory responses, commonly observed in obesity and T2DM, are closely linked to IR in both peripheral and central tissues, potentially increasing the risk of AD. Brain tissue from AD patients shows increased levels of inflammatory factors such as interleukin-1, interleukin-6 (IL-6), and tumor necrosis factor-alpha, suggesting a nonspecific immune inflammatory reaction during early brain plaque formation [32]. Studies have shown a lower incidence of AD among individuals taking non-steroidal anti-inflammatory drugs (NSAIDs), underscoring the significant role of inflammation in AD development [33]. Elevated levels of inflammatory cytokines can impair spatial learning by affecting hippocampal synaptic plasticity, highlighting the intricate relationship between inflammation, insulin resistance, and cognitive function in AD.

Apolipoprotein E (ApoE) is a protein with common genetic variants known as E2, E3, and E4, which are encoded by the ε2, ε3, and ε4 alleles, respectively. These variants have population frequencies of approximately 8%, 77%, and 15%, respectively. ApoE4 has been identified as a significant factor contributing to dementia and the progression of cognitive impairment in older individuals [34]. The interaction between ApoE protein, amyloid-beta, and tau protein is believed to play a specific role in the biological mechanisms underlying the effect of ApoE on dementia development. The ApoE ε4 allele polymorphism is an independent risk factor for MCI, and individuals carrying the ε4 allele tend to have lower cognitive levels compared to non-carriers. The incidence of the ApoE ε4 allele is notably higher in MCI patients compared to the general population. Additionally, the risk ratio for late-onset AD in ApoE ε4 carriers is approximately three times higher than in non-carriers [35, 36].

Fig. 1. (p.6072)

Future perspectives: Prompted by recent findings on the role of insulin in cognitive function, researchers have proposed that increasing brain insulin concentrations in individuals with AD could have preventive, disease-modifying, or symptomatic therapeutic effects. Studies have shown that intranasal insulin administration improves memory function in both healthy individuals and those with insulin resistance [38, 39]. Similar benefits were observed in patients with AD and MCI, particularly in those without an APOE ε4 allele [40]. In addition to direct insulin therapy, medications used to improve insulin sensitivity in T2DM have gained interest as potential treatments for brain insulin resistance in Alzheimer's disease and related dementias (ADRD) [41]. This evolving research suggests promising avenues for exploring novel therapeutic strategies targeting brain insulin dysfunction in the context of cognitive disorders like AD.

Fig. 1. Insulin signalling in healthy brain and AD disease. [37]



CONCLUSION:

Globally, the escalating epidemics of T2DM and AD pose significant human suffering and economic burdens. Urgent action is required to expedite the development of preventive, disease-modifying, and symptomatic treatments through empirically and rationally designed studies that delve into the underlying mechanisms of these diseases. The relationship between T2DM and AD is intriguing: they may either be parallel phenomena stemming from similar factors related to insulin resistance and metabolic dysfunction, or they could be synergistic diseases linked in a vicious pathophysiological cycle. Advancing interdisciplinary knowledge of the commonalities and distinctions in insulin resistance between the body and the brain promises to enhance our comprehension and management of both T2DM and AD.

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