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Invited critical review

Insulin resistance and cognitive dysfunction

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ABSTRACT

Epidemiologic and biologic studies support a link between type 2 diabetes mellitus and Alzheimer's disease, but the precise mechanism linking the two remains unclear. Growing evidence supports the concept that insulin resistance is important in the pathogenesis of cognitive impairment and neurodegeneration. Insulin plays a profound role in cognitive function. Impaired insulin signaling in the advancement of cognitive dysfunction is relevant to the pathophysiologic mechanisms of cognitive impairment. In this paper we discuss the relationship between insulin resistance and cognitive impairment and review potential mechanisms of this disease process. Evidence, to date, suggests that brain insulin resistance is an independent risk factor for cognitive impairment.

Contents

1. Introduction

Epidemiologic and biologic evidence supports a link between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD), ie, those with T2DM have a higher incidence of cognitive decline [1]. The prevalence of both T2DM and AD increases with age, and both diseases are chronic and are the leading causes of morbidity and mortality. Mild cognitive impairment (MCI) is a state between normal aging and AD. The MCI conversion rate to AD is high [2], and there is a high risk of MCI developing into dementia. Moreover, the incidence of MCI increases to 32.7% in diabetic patients [3]. The precise mechanism linking T2DM and cognitive impairment remains to be found out. Growing evidence supports the concept that insulin resistance (IR) plays an important role in the pathogenesis of cognitive impairment and neurodegeneration [1].

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Glucose is an important energy source for the brain and subsequent insulin release from neuronal vesicles. Insulin is an active substance that can affect neurons in the brain and periphery, and has multiple biological functions including regulation of blood glucose and energy metabolism. Research has shown that brain insulin plays an important role in cognitive activities (such as learning and memory) in elderly people [4], in addition to metabolic and feeding effects, promoting nerve cell growth and development, and regulation of neurotransmitter release. Advanced age, low education degree, hypertension, hyperlipidemia, heart disease, diabetes, transient ischemic attack, smoking, drinking, and apolipoprotein E (ApoE) 4 allele polymorphism have all been shown to be risk factors for MCI development [5–7]. Vascular risk factors play an important role in MCI pathogenesis, and early and effective control of vascular risk factors of cognitive function can reduce the incidence rate of cognitive function decline and dementia in old age [8,9].

There is convincing epidemiological evidence showing an increased risk of dementia in people with diabetes, but there are few mechanistic studies that provide a clear pathophysiological link, although the cause may be multifactorial [1]. IR is an independent risk factor for MCI, and in the brain, may be associated with sporadic Alzheimer's disease [10,11]. Dementia prevalence is increasing with rapid aging in the population, and MCI as an intervention stage to prevent dementia has become a research hotspot [12,13]. Most recent studies have focused on the role of IR as possible links between diabetes and AD, and the disturbances in brain insulin signaling mechanisms may contribute to the molecular, biochemical, and histopathological lesions in AD [1,14]. Therefore, in this paper, how IR and cognitive impairment are mutually linked and the possible mechanisms are discussed.

2. Insulin resistance

2.1. Physiological functions and secretion regulation of insulin

Insulin is a small molecule protein composed of 51 amino acid residues arranged into an A chain of 21 peptides and B chain of 30 peptides that are linked by two disulfides and has a molecular weight of 5808 Da [15]. The metabolic effect of insulin is predominantly regulated by binding to various insulin receptors [16]. Insulin receptor was located and quantified in the central nervosa system in 1978 [17,18]. Signal transduction post-receptor binding commonly involves the insulin receptor substrate (IRS), with IRS-1 and IRS-2 present in muscle, fat, and islet B cells, and IRS-3 in brain tissue [19–21]. IRS phosphorylation by a variety of protein kinases and phosphatases via the anchoring domain and activation site, and link proteins to phospholipase and ion channel facilitation factors mediate downstream reactions. Insulin regulates metabolism and maintains balance in energy function within the body.

2.2. The role of insulin in the nervous system

The role of insulin is best known in peripheral glucose homeostasis, and insulin signaling in the brain received less attention in the past decades. Nowadays, the function of insulin, the insulin-like growth factors (IGF) and their receptors in central nervous system has been a live topic [22]. The presence of insulin in the brain was first detected in 1978 [23], then high concentrations of insulin were reported not only in the human brain but also in several experimental animals [24]. IRS distribution is concomitant with insulin receptors in the brain [25]. Insulin and insulin receptors in nerve tissue stimulate release of a variety of enzymes involved in glucose metabolism, including choline acetyltransferase (ChAT). An important brain function of insulin is regulation of learning and memory [26]. Insulin not only regulates energy metabolism, but also provides nutritional support to nerve cells [27]. Brain insulin is obtained mainly from islet β cell secretion, and crosses the blood brain barrier via insulin receptor mediated transport [28], thereby regulating brain glucose. Insulin function in the brain is related to insulin receptor distribution [29]. Recent findings show a high concentration of insulin in brain extracts [30], the expression of insulin and insulin receptors are widely distributed in brain neurons and glial cells, especially in the cerebral cortex, hippocampus, hypothalamus, and olfactory bulb [31], all areas closely related with cognition. Insulin-sensitive glucose carriers are found in these areas, and can enhance the insulin signal, increase brain glucose use, and regulate learning and memory [32]. Insulin receptor mRNA is located in neuronal cell bodies, with receptor protein distributed in pyramidal cell axons, hypothalamic-adrenergic neuronal terminals, CA1 region of the hippocampus, and membrane surface of synaptosomal branches in the rat olfactory bulb [33–35]. High concentrations of insulin receptor are found in the thalamus, caudate–putamen, and some mesencephalic and brainstem nuclei during neurogenesis, but these same areas have a low insulin receptor density in adult rat brains, which indicates that insulin receptor density between the embryonic and adult brain has a significant difference [36].

2.3. The role of insulin resistance in the nervous system

IR refers to reduced sensitivity of insulin on target organs, and is a characteristic metabolic defect that coexists with hyperinsulinemia. Long-term hyperinsulinemia can damage blood brain barrier function and insulin activity [37]. IR causes long-term neuronal exposure to a high level insulin environment, leading to neuronal degeneration and causing irreversible memory impairment [38,39]. IR in the peripheral tissues facilitates IR in the brain by reducing brain insulin uptake and increasing levels of beta amyloid (Aβ) [40]. AD incidence in late diabetic patients is two times higher compared with normal elderly people [41], and thought to arise from islet β cell dysfunction that causes impaired insulin secretion and resistance, leading to nervous system damage and ultimately influencing cognitive function in patients [41].

3. Insulin resistance and cognitive impairment

AD and diabetic mellitus have a shared pathogenesis in IR. Diabetes transmits peripheral insulin resistance to the central nervous system through the “liver brain axis”, which promotes cognitive dysfunction [42].

3.1. Insulin resistance is an important risk factor for cognitive impairment

Brain insulin deficiency and plasma insulin resistance may promote cognitive dysfunction. Central obesity is highly correlated with impaired cognitive function in the elderly [43]. Moreover, cognitive function in patients with metabolic syndrome was lower than a control group, and incidence of cognitive impairment significantly higher than controls over 6-month and 1-year periods [44]. IR promotes development of MCI and AD [45]. Studies have found that AD patients have low insulin levels in the brain and cerebrospinal fluid (CSF), and high insulin levels in plasma, which is related with impaired insulin signal transduction [46–48]. High levels of circulating insulin may be the consequence of insulin resistance, while the reduction in CSF insulin may be related to a decrease in insulin clearance and/or to a reduction in insulin uptake from a peripheral source through the blood brain barrier [46–48]. In addition, the expression mRNA and protein levels of insulin and IGF1 and the downstream signaling elements in the brain of AD patients are decreased [47]. An aberrant decline in IGF1 values was also suggested to play a role in the development of AD [22].

3.2. Insulin can improve cognitive dysfunction caused by insulin resistance

Deregulation of brain insulin signaling plays an important role in the development of AD. IR promotes development of cognitive dysfunction by hyperinsulinemia and impaired insulin signaling; therefore determining if insulin or insulin sensitizing agents are neuroprotective has become a research hotspot. Insulin is an important long-term neuroprotectant, and severe lack of it leads to neurodegeneration [49].