Insulin Signaling in the Central Nervous System and Alzheimer’s Disease

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Insulin is produced nearly exclusively in the pancreas and elicits both metabolic and neuro-modulating effects [1]. Though the peripheral hormonal and metabolic effects have been extensively studied, recently there has been a growing interest in the insulin mediated effects in the CNS. Insulin receptors (IR) are widely expressed in the in the CNS (hippocampus, entorhinal cortex and frontal cortex) [2]. Evidence supports insulin’s role in feeding, cognition [2], synaptogenesis, synaptic remodelling and facilitation of memory [3]. Furthermore, in the CNS, insulin modulates the levels of amyloid β peptide (AβP) - a potent mitochondrial poison involved in the pathogenesis of Alzheimer’s disease (AD) and protects neurons against detrimental effects of AβP on synapsis [4-6]. In this editorial, we aim to highlight the available evidence on insulin-signaling in the CNS and its relationships with AD and diabetes mellitus (DM).

Impairment in CNS Insulin-Signaling in DM and in AD

In human studies chronic hyperglycemia inhibits insulin transport across the blood brain barrier (BBB) by several mechanisms. Hyperglycemia leads to an increased concentration of circulating plasma triglycerides that inhibit transport of gastrointestinal hormones such as insulin, leptin and ghrelin across the BBB [7]. It causes disruption of vascular pericytes that physiologically protect BBB from hyperglycemia-mediated mitochondrial damage [8]. Also, it leads to dysfunction of brain endothelial cells that modulate insulin transport at various blood glucose concentrations [9,10].

Both DM and AD are clinical conditions characterized by impaired CNS insulin signaling and a reduced concentration of brain IR. In DM these changes are associated with BBB dysfunctions while in AD are due to intracellular degenerative processes [11,12]. These morphologic changes in the receptors due to degradation of the intracellular IR-dependent molecules (microtubules and tau phosphorylation), creates a clinical link between DM and AD [13,14]. Of interest, although cognitive impairment is common in both DM and AD patients, the cognitive domains affected in these syndromes are different: white matter infarcts and executive functions impairment are more common in DM, while cortical atrophy is more frequent in AD patients [15,16].

AD as a form of Brain Insulin Resistance (Type III DM)

In post mortem human brain tissue obtained from AD patients, extracellular abnormalities of IR were found (especially in the hippocampus and hypothalamus but not in the cerebellum) suggesting that AD is a neuro-endocrine disorder that resembles DM [17]. AD pathophysiology might be in part referred to an intrinsic neuroendocrine disease caused by selective impairment of insulin signaling in the CNS that can be defined as type III DM. There is definitive evidence that impairments in insulin signaling can occur in CNS independently from DM [18,19]. In preclinical studies, streptozotocin-induced chemotoxic depletion of brain IR and CNS insulin signaling causes an AD-type neurodegeneration that resemble DM-dependent neurodegeneration [20,21].

Insulin ss Therapy for AD

Presented links between DM and AD are further strengthened by evidence that supports the therapeutic benefit of insulin and insulin-sensitizer agents in patients with cognitive and memory impaired patients [22,23]. In fact, the high concentration of IR in the hippocampus -a structure that has a relevant role in the formation of declarative and spatial memory- and the positive effect of insulin when administered into the CNS on hippocampus dependent memory, support the possible role of this therapeutic option in patients with cognitive disorders including those with AD [24]. Some researchers have tested intranasal insulin administration and have found it to be a promising approach in the treatment of CNS insulin deficiency and resistance as found in AD [25,26].

In conclusion, insulin brain receptors and insulin signaling appear to be closely linked to cognitive and memory functions and control over vital growth, survival and metabolic functions in the brain. These data are consistent with a neurotrophic role of insulin in the human brain and a disturbance of insulin signal transduction that may be of pathogenetic relevance in AD. The link amongst IR, DM and AD and the concept of resensitizing the brain cells to insulin discloses its potential therapeutic implications in neurodegenerative disorders and provides an impetus for future clinical trials.

References


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