



Intranasal insulin: is there a promise for treatment of diabetes-related cognitive decline?



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Diabetes mellitus (DM) is a major contributor to morbidity and mortality of all causes worldwide. Type 2 DM affects more than 44 million people in the USA. It has become the fastest growing disease, affecting 27% of older people. DM accelerates brain aging [1], manifests as a widespread generalized atrophy, and promotes earlier onset of vascular dementia and Alzheimer's disease (AD). DM-related atrophy manifests as worse cognitive function, memory and gait, especially during a dual task [2], and even a tight glycemic control did not improve cognitive function in participants of the large clinical trials [3].

Inulin: a key neuromodulator in the brain

Insulin has emerged as a key neurotrophic factor in the CNS and as a promising therapeutic for treatment of amnesic cognitive impairment and AD. Insulin's role in the brain is different from its actions in the periphery. Central insulin plays a role as an important neuromodulator in key processes such as cognition [4,5],

energy homeostasis, food intake, sympathetic activity, neuron–astrocyte signaling, synapse formation and neuronal survival [6].

Intranasal insulin (INI) enters the brain, where it rapidly propagates through perivascular channels and binds to the receptors in the limbic system and memory networks including the hippocampus, hypothalamus, and insular cortex [7]. INI increases blood flow and energy metabolism and improves functional connectivity in these regions. More efficient neuronal signaling within memory networks improves visuospatial memory, learning and other cognitive functions associated with these areas. It may also improve mood, regulate feeding behavior, and increase amyloid- β clearance [8,9]. Furthermore, insulin has been shown to reinforce signaling in the brain-reward dopamine-mediated limbic system and modulate behavioral responses to natural food and other reward stimuli.

Insulin receptors (IRs) are expressed in numerous brain regions, namely in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum and hippocampus [10].

KEYWORDS

• Alzheimer's disease • cognition
• dementia • diabetes • intranasal insulin

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Insulin also contributes to cortical blood flow regulation, as evidenced by the presence of IRs within the neurovascular unit, for example, in neurons, astrocytes and capillaries, and the wall of small vessels. We anticipate that cerebral insulin may directly modulate blood flow and neuron–astrocyte signaling through neurovascular coupling and autonomic control of vascular tone and thus enable better regulation of local and regional perfusion and neuronal activity in response to various stimuli [11].

Neuroprotective effects of insulin [12] have been demonstrated *in vitro* as inhibition of neuronal apoptosis by activation of protein kinase B, and also *in vivo* studies have shown it regulates phosphorylation of tau, amyloid precursor protein and clearance of β -amyloid. Other neuroprotective effects of insulin also involve uptake of γ -butyric acid by astrocytes, protein synthesis, upregulation of glucose metabolism, blood flow and modulation of central autonomic serotonergic and monoaminergic pathways. Central IRs, however, are dependent upon insulin transport from the periphery through the blood–brain barrier. Aging, obesity, diabetes and AD alter insulin transport to the brain. Type 2 DM decreases insulin sensitivity in the brain, insulin transport through the blood–brain barrier, and IRs receptor sensitivity, and it alters glucose metabolism [5,7]. Glucotoxicity and endothelial dysfunction associated with chronic hyperglycemia further affect perfusion, vasoreactivity [13] and metabolism, and thus contribute to neuronal loss. Therefore, inadequate insulin delivery to brain tissue, resulting from these complex interactions, may affect neuronal activity in multiple regions, but namely in the cognitive and brain-reward systems that have high demands on energy.

Intranasal insulin improves cognitive function in clinical studies

The insulin resistance syndrome, characterized by chronic peripheral insulin elevations, reduced insulin activity, and reduced brain insulin levels, is associated with age-related memory impairment and AD [14]. These mild forms of insulin resistance may precede AD pathology for years [5]. The risk of Type 2 DM for dementia and AD in late life has been increasingly recognized in population studies [1], and impaired insulin signaling in the hippocampus and hypothalamus, as seen in

both conditions, may provide a common link between DM and AD [15]. The evidence that INI could be a promising treatment for improving cognitive function is growing. Clinical studies suggest that augmenting cerebral insulin improved performance in specific cognitive domains and memory in healthy young [16] and older adults and patients with mild cognitive impairment and even AD patients [17,18], with both acute and chronic administration. In healthy men, INI also improved mood and regulated food intake [7]. In healthy people, INI administration of rapid-acting insulin (40 IU four-times daily) for 8 weeks improved long-term declarative memory more than regular insulin, and both insulins were better than placebo. No systemic side effects were observed, and serum glucose and insulin levels did not change, and there were no hypoglycemic episodes [16]. Patients with amnesic mild cognitive impairment (MCI) and mild–moderate AD were treated with 40 IU (Novolin®; Novo Nordisk, Copenhagen, Denmark) for 3 weeks. The INI-treated group retained more verbal information and showed greater improvement of attention and functional status than the placebo-treated group. The INI-treated group also had increased short form of β -amyloid peptide 40, without effects on the longer isoform [17]. Acute INI administration improved verbal memory in memory-impaired ApoE4-adults, with best performance at 20 IU; but no improvement was seen at 60 IU. By contrast, memory-impaired ApoE4+ adults showed a decline in verbal memory [18]. The first clinical trial in 104 patients with amnesic MCI or mild–moderate AD over a 4-month period has shown that INI improved delayed memory, and both 20-IU and 40-IU doses preserved caregiver-rated functional ability and general cognitive function. Cognitive performance was better with the 20 IU dose in this population [9].

Our proof-of-concept, randomized, placebo-controlled, crossover pilot study [19] evaluated acute effects of INI or placebo on perfusion and memory in older Type 2 DM adults and healthy controls. We have shown that a single 40-IU dose of INI improved visuospatial memory in DM and controls. In the DM group, INI increased perfusion in the insular cortex, and INI-induced improvement on visuospatial learning and memory was dependent upon greater vasodilation in insular cortex and middle cerebral artery territory. Similarly in

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controls, improvement of verbal memory was also dependent upon vasodilatation. No serious adverse events or hypoglycemic episodes occurred. Furthermore, we have also observed that INI improved functional connectivity in brain default network in diabetic patients.

These findings are highly clinically relevant because of the high prevalence of dementia in DM patients as well as the high prevalence of insulin resistance syndrome in AD patients [5,14,20]. These data suggest that intranasal administration of insulin is a safe and feasible approach to improve central insulin levels. In addition, INI could be a promising method for the treatment of disorders with an etiology

that may involve disturbances in brain insulin signaling, such as AD, obesity and Type 2 DM.

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