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Effect of Intranasal Insulin on Cognitive Function in Diabetic Patients

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Abstract: ***A clear association between diabetes and cognitive impairment has been demonstrated in past studies, increasing the incidence of neurodegenerative diseases and accelerating the onset of Alzheimer's disease (AD) and other types of dementia. Many hypothesized mechanisms of diabetes leading to cognitive impairment exist, and the mechanism of insulin resistance has been demonstrated. Transnasal administration of insulin improves recall of spatial memory in healthy subjects in addition to verbal working memory, visuospatial working memory, delayed memory, and cognitive performance in cognitively impaired patients. No safety concerns have been identified in retrospective studies of intranasal insulin. This review aims to assess the potential of intranasal insulin as a treatment for cognitive impairment related to diabetes.***

Keywords: Intranasal insulin, Diabetes, Cognitive dysfunction**.**

1. Introduction

Diabetes mellitus is a heterogeneous disease with elevated blood glucose concentrations due to the body's inability to properly metabolize glucose, accompanied by dysregulation of lipid and protein metabolism, leading to structural and functional changes in various organ systems [1,2]. Numerous studies have shown that diabetes can increase the incidence of neurodegenerative diseases, cognitive impairment, and dementia. Diabetes is strongly associated with low performance in several domains of cognitive function and structural brain abnormalities. With the prevalence of diabetes and an aging population, the neurologic complications of diabetes are expected to increase and become a challenge for future health impact. Insulin, a peptide hormone secreted by pancreatic β-cells, is widely used in treating diabetes mellitus by regulating cellular glucose uptake and modulating carbohydrate, lipid, and protein metabolism to maintain normal blood glucose levels. As an essential neurohormone, insulin plays a crucial role in brain energy metabolism, cognitive function, axonal migration, and neurogenesis [3]. There are many existing hypothesized mechanisms of diabetes-induced cognitive impairment, including glucose toxicity, insulin resistance, oxidative stress, inflammatory cytokines, and microvascular and macrovascular diseases, among which insulin resistance is an important pathogenic mechanism of cognitive impairment [4]. Peripheral insulin does not readily cross the blood-brain barrier (BBB) due to its considerable molecular weight, and its saturation-dependent mechanism crosses the BBB and enters the brain mainly through active transport; therefore, insulin resistance in the brain is difficult to reverse by direct peripheral insulin supplementation. In contrast, drugs delivered intranasally are more accessible to the central nervous system (CNS) through both extracellular and intracellular pathways and have the advantages of being non-invasive [5], easy to administer, and avoiding first-pass metabolism in the liver [6]. Many studies have shown that insulin administration can help improve verbal working memory, visuospatial working memory, and cognitive abilities such as word recall and delayed memory in patients with mild cognitive impairment [7–9]. Currently, intranasal delivery of insulin to the brain has been successfully used in many animal experiments and clinical studies, and it is expected to be a reliable and promising method of brain drug delivery.

2. Relationships between Diabetes and Cognitive Impairment

Diabetes mellitus is a heterogeneous disease with elevated blood glucose concentrations due to the body's inability to properly metabolize glucose, accompanied by dysregulation of lipid and protein metabolism, leading to structural and functional changes in various organ systems. Studies have shown that chronic hyperglycemic states, especially type II diabetes mellitus (T2DM), lead to progressive impairment of neuronal function in the brain [10]. Long-term T2DM is also associated with disruption of neurovascular coupling associated with vascular dementia [11]. Hyperglycemia induces basement membrane thickening in neurovascular units, promotes endothelial cell proliferation, and increases permeability, which is associated with an increased incidence of encephalopathy and neurodegenerative diseases, as well as a worsening prognosis in diseases such as stroke [12]. Diabetic encephalopathy is a significant complication of diabetes mellitus that increases the probability of cognitive decline and accelerates the onset of AD and other types of dementia [13].

There is growing evidence that diabetes is associated with low cognitive function, and many hypothesized mechanisms exist, including glucose toxicity, insulin resistance, oxidative stress, advanced glycosylation end products, inflammatory cytokines, and microvascular and macrovascular disease [14], with the mechanism of insulin resistance being widely recognized. Insulin resistance can affect diabetic cognitive impairment through cerebrovascular and non-cerebrovascular mechanisms [15]. In the cerebrovascular pathway, insulin resistance is associated with vascular risk factors such as hypertension [16]. Vascular risk factors increase the risk of minor vessel damage in the brain and are associated with vascular cognitive impairment and vascular dementia [17]. In

non-cerebrovascular pathways, insulin resistance induces chronic hyperinsulinemia in the brain, which can accelerate the formation of neuritic plaques, and amyloid plaques are a prominent feature of AD and amnestic cognitive impairment [18].

The impaired insulin signaling pathway also leads to Tau protein hyperphosphorylation, which is vital in AD pathology. Cognitive decline in diabetic patients may also be associated with brain volume loss. In previous studies, type 1 diabetes mellitus (T1DM) is associated with reduced brain volume compared to nondiabetic controls; patients with T2DM also experience brain atrophy, as evidenced by lower total and local white matter, gray matter, and hippocampal volumes of the brain tissue [19]. In a trial examining T2DM about brain atrophy and cognitive function, Michele L. Callisaya et al. found that, in community-dwelling older adults among community-dwelling older adults, T2DM was associated with declines in verbal memory and fluency over 5 years [20]. The effects of diabetes on brain atrophy may begin even earlier (middle age). Perentie DC et al. found that children with T1DM who experienced severe hypoglycemic episodes before the age of 5 years had spatial intelligence deficits and memory delays, suggesting that the developing brain at a very young age may be susceptible to hypoglycemia [21].

3. Cognitive Effects of Intranasal Insulin

3.1 Mechanisms of Cognitive Improvement with Intranasal Insulin

After intranasal administration of insulin, it reaches the brain via the sieve plate via the olfactory and trigeminal pathways or on receptors attached to the blood-brain barrier. The insulin receptor is a tyrosine kinase receptor and heterotetrameric transmembrane protein distributed throughout the brain in the olfactory bulb, cerebral cortex, cerebellum, amygdala, hippocampus, and nasal septum, and the neuronal insulin receptor is expressed both presynaptically and postsynaptically [22]. Tyrosine phosphorylation of insulin receptor substrate (IRS) induces the activation of downstream pathways such as the PI3K and MAPK cascades, and the PI3K and MAPK pathways play a role in the regulation of neurodegeneration, aberrant phosphorylation of tau proteins, insulin resistance, and inflammatory responses [23]. In addition, insulin can stimulate HIF-1 activity through the PI3K and MAPK signaling pathways, thereby promoting cerebral neoangiogenesis [24]. Intranasal insulin also improves synaptic plasticity and regional glucose uptake, and there is some evidence that under conditions of high cognitive demand, insulin enhances local cerebral glucose uptake through activation of type IV neuronal glucose transporter proteins and enhances glycogen uptake in regions such as the basal forebrain, hippocampus, amygdala, and cortex [25]. In addition, Lars P. van der Heide et al. found that insulin modulates activity-dependent synaptic plasticity by activating NMDA receptors and the PI3K pathway to improve learning and memory [26]. William H. Gendron et al. revealed that insulin increases P-Akt signaling in the hippocampus dose-dependently, enhancing cell survival and proliferation, inhibiting glycogen synthase kinase-3β, reducing reactive oxygen species (ROS) production, and decreasing oxidative stress [27]. Another study found that insulin deficiency reduced mitochondrial ATP production and/or citrate synthase and cytochrome oxidase activity in the brain, hypothalamus, and hippocampus, resulting in altered mitochondrial function due to a decrease in mitochondrial fusion proteins and an increase in fission proteins and reduced ATP production and oxidative enzymes affecting neuronal function [28]. In vitro studies have shown that intranasal insulin significantly improves streptozotocin (STZ) in association with restoration of cerebral blood flow (CBF) and cerebral glucose metabolism in the prefrontal and cingulate cortices, reduces astrocyte activation and neuronal loss in the hippocampus, modulates Nrf-2 expression, and improves BDNF levels, CREB activation, and cholinergic function [29,30]. Consistent with this, clinical studies have found that patients with T2DM treated with intranasal insulin improve executive function and verbal memory by decreasing vasoconstrictor reactivity and reducing perfusion deficits in the prefrontal cortex [31].

3.2 Efficacy of Intranasal Insulin in Cognitive Impairment

In animal studies, Therese S. Salameh et al. found that intranasal insulin rapidly distributed insulin throughout the brain, remained present in all brain regions after 60 minutes, and reversed learning and memory deficits in mice [32]. Yan-Fang Mao et al. found that 6 weeks of intranasal insulin treatment significantly inhibited the activation of c-Jun N-terminal kinase, which is critical to insulin-resistant pathology. -terminal kinase activation was significantly inhibited, which ameliorated brain insulin signaling deficits and reduced anxiety levels in mice with impaired memory plasticity, increasing the growth of new neurons and ameliorating cognitive deficits [33]. Furthermore, in a diabetic rat model, insulin administration increased the expression levels of neurotrophic factors and hippocampal phosphorylation of the insulin receptor through activation of Sirtuin 1 signaling pathway insulin receptors, protecting hippocampal dendritic length and spine densities and thereby inhibiting diabetes-related cognitive decline [34]. More surprisingly, intranasal insulin also reversed central pathology and cognitive deficits in the offspring of diabetic mothers (DMOs).In a study by Juan Jose Ramos-Rodriguez et al., pregnant female rats (diabetic mothers) treated or not with intranasal insulin for 7 consecutive days, maternal diabetes affected neuronal complexity and synaptic density, tau protein hyperphosphorylation, central inflammation, or spontaneous hemorrhage, which was completely reversed by insulin treatment, and spatial and situational memory deficits improved after insulin injection [35].

Good therapeutic results have also been achieved with intranasal insulin in clinical trials. In a clinical trial, older adults with T2DM had increased CBF, faster walking speeds, and better executive function and memory after 24 weeks of treatment with 40 IU of intranasal insulin once daily [31], where slow walking in diabetic patients was a clinical predictor associated with cognitive decline, hospitalization, disability, and death. Resting-state connectivity correlates with cognitive performance, and when resting-state functional connectivity between the hippocampal region and the default mode network (DMN) was quantified using functional MRI (fMRI) at 3Tesla, resting-state connectivity between the

hippocampal region and the medial frontal cortex was increased in elderly patients with T2DM after insulin treatment compared to placebo and was even similar to that of controls [36]. In addition to improving patients with cognitive decline, Christian Benedict et al. found in an experiment that intranasal administration of transinsulin for 8 weeks improved declarative memory in healthy adults [37].

3.3 Advantages of Transnasal Insulin Therapy

Numerous studies have shown that transnasal insulin injections help improve cognitive function, while subcutaneous and intravenous insulin injections increase the risk of dementia. One study suggests that patients using peripheral insulin may have a 50% increased risk of developing dementia due to induced hypoglycemia compared to using other diabetes treatments [38]. Insulin administered intranasally is metabolized differently than peripherally, and numerous studies have shown that intranasal administration does not cause changes in peripheral blood glucose, making intranasal administration a promising mode of delivery.

4. Safety

Studies have shown that the transport of insulin to the brain after intranasal administration involves a mechanism different from the blood-brain barrier and may, therefore, allow us to study the effects on the brain independently of the blood-brain barrier [39]. There are no significant changes in circulating insulin levels following intranasal administration of low-dose insulin [40]; however, a recent study of different doses of intranasal insulin suggests that 160 U of insulin may affect the central and peripheral nervous systems [41]. Most people tolerate intranasal insulin well but may still cause minor adverse effects. Vera Schmid PhD et al. retrospectively analyzed 38 intranasal insulin studies to extract all outcomes and adverse effects. It was found that intranasal administration of insulin and placebo was followed by localized side effects in the nasal region, such as those related to the nose (rhinitis, mild nosebleeds, pain, dripping blood, sneezing), upper respiratory tract infections, headache, dizziness, weakness, hypoglycemia, falls, rash, gastrointestinal symptoms, and, most commonly, other localized side effects (symptoms related to the nose) following rhinitis [42], which may be related to the mode of administration. No symptomatic hypoglycemia or serious adverse events were reported, while other adverse reactions were less frequently reported.

5. Conclusions

Cognitive decline in diabetic patients is a problem that needs to be solved urgently [43]. Among various drugs, insulin has been proven to be an effective way to improve patients' cognition in animal experiments and clinical trials; as summarized above, it can improve metabolism, protect nerve cells, enhance connections between brain regions, and improve cognitive abilities such as verbal working memory, visuospatial working memory, and delayed memory through different mechanism pathways. Moreover, transnasal drug delivery has the advantages of being non-invasive, avoiding hepatic and renal metabolism, and no serious accidents have occurred in numerous trials [44]. However, the optimal delivery concentration has yet to be determined and requires later work. Nasal insulin has a very high potential as a clinical drug for the future treatment of diabetic encephalopathy, and its advantages and disadvantages need to be actively explored in the future.

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