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ORIGINAL ARTICLE

A Review on Intranasal Insulin Drug Potential Effect on Alzheimer Disease in Type 2 Diabetic Patients

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ABSTRACT

Massive evidence is available regarding the connection between Alzheimer disease and Diabetes Mellitus and their common pathological mechanisms, including impaired brain insulin signaling that can contribute to alteration of protein, glucose and lipid metabolism, chronic inflammation, oxidative stress, and mitochondrial dysfunction. However, the evidence is limited regarding the exploration of potential disease modifying therapies, which can prevent from progressive neuronal death, leading to cognitive impairment, which is the devastating end stage of Alzheimer. To enhance brain insulin, function a recent approach to mitigate Alzheimer symptoms is to centrally administer insulin is through intranasal delivery. To avoid the blood-brain barrier, a large amount of insulin can be administered intravenously (intranasally) by injecting it directly into the nasal cavity (BBB). In healthy adults, intranasal insulin has been shown to alter CNS measurements. Type 2 diabetics may benefit from an intranasal insulin medication that slows the progression of Alzheimer's disease, according to a new study.

Keywords: Intranasal, insulin, Alzheimer, Diabetes.

Alzheimer Disease (**AD**): It is a neurodegenerative brain disorder that has a negative impact on memory and cognitive functions (1). Declay in the ability of recognizing people, recall specific words, and problem settlement, in addition to cognition impairment including judgment, memory, and communication, are remarkable signs and symptoms of AD (2). As there are more than 100 different types of dementia, AD still the most familiar form among them, and it affects elderly higher than another group by 50%-75% (3,4). Life expectancy average of AD patients are about 7 years after being clinically diagnosed with the disease, however few patients about 3% tends to live more than 14 years, unfortunately by that time the disease is considered untreatable (5).

AD pathological characteristics are represented in loss of neurons in medial temporal lobe and temporo-parietal association cortices, extracellularly plaques consisting of amyloid-beta protein, and neurofibrillary tangled made up of hyperphosphorylated tau. These pathological abnormalities are combined with multiple factors as, mutated Apolipoprotein E, neuroinflammation, mitochondrial dysfunction and oxidative stress, all contribute to elevate the risk of developing AD urged by diabetes (6). The reason why AD is referred to as type 3 diabetes, is mainly because of its pathology that has similar features of Diabetes mellitus to such as, insulin resistance and amyloidogenesis (1).

Finding out certain biomarkers in people with metabolic disorders such as Diabetes mellitus, hypertension, and obesity will facilitate early discovering of the disease and controlling the complexity later, since these population tend to develop greater risk for AD (7).

There are many epidemiological studies that have indicated an elevated chance of developing Alzheimer's disease in people with diabetes. Since there are several common features between insulin-impairment and AD (8,9,10).

Insulin, Diabetes Mellitus and Alzheimer's: World Health Organization (WHO) defines diabetes mellitus (DM) as " a chronic, metabolic disease marked by increased concentrations of glucose (or blood sugar), which over time leads to serious damage to the heart, arteries, eyes and kidneys, and nerves " (11).

Insulin resistance: is a condition where insulin tissue penetrating ability is impaired, due to receptors sensitivity decline (12).

Insulin is a hormonal peptide secreted mainly from the pancreatic beta cell, it regulates metabolism of glucose in the peripheral tissue, and it has a multifarious effect in the CNS. Furthermore, it has a significant impact on the metabolism of energy, inflammation, and brain, synapse, and vascular health (12). Normally, insulin receptors are concentrated in the olfactory bulb, hypothalamus, and hippocampus of the brain, where they play an important role in the regulation of hunger and satiety. Hypothalamus and hippocampus are two of insulin receptors' primary roles: regulating energy metabolism and altering memory (3). A study showed that destruction of brain insulin signaling can negatively affect cognitive functions, and degeneration of neurons, especially in AD. Hence, insulin signaling impairment is a major contributor for the development of DM and pathology of AD (13). it can also be considered as a factor in preventing cognitive impairment (14).

Oxidative stress and mitochondrial impairments have been linked to a wide range of metabolic abnormalities in Alzheimer's disease (AD). Diabetes, mitochondrial oxidative stress, and neurodegeneration are all linked. Mitochondrial Nucleic acids, lipids, and proteins can all be affected by oxidative alterations, which can lead to ROS generation, the accumulation of A, and tau phosphorylation (19,20). In both AD and T2DM patients Inflammation is an early pathological sign that can cause insulin resistance in T2DM and neurodegeneration in AD. In studies done on AD Postmortem, there was an inflammation present along with neurofibrillary plaques (NPs) and neurofibrillary tangles (NFTs) (21).

The Unknown: Massive evidence is available regarding the connection between AD and DM and their common pathological mechanisms, including impaired brain insulin signaling that can contribute to alteration of protein, glucose and lipid metabolism, chronic inflammation, oxidative stress, and mitochondrial dysfunction. However, evidence is limited regarding the exploration of potential disease modifying therapies, which can prevent progressive neuronal death, that leads to cognitive impairment, which is the devastating end stage of AD (5,11).

Response: Our research will explore the potential benefits of intranasal insulin as a potential and promising disease modifying therapy. We will also focus on collecting the updated data on the potential effect of intranasal insulin drug on the progression of Alzheimer disease in type 2 diabetic patients. Most importantly, to enhance brain insulin function a recent therapeutic approach has been spotted to mitigate Alzheimer symptoms (3) incidence, and progression in type 2 diabetes by centrally administer insulin through intranasal delivery.

Although the specific process is uncertain, insulin resistance promotes Abeta production in the brain. It is unclear if diabetes accelerates the development of cognitive deterioration when Alzheimer's disease is identified (7).

Aβ oligomers activate microglia, induce the production of pro-inflammatory molecules (mainly TNFa), and initiate the downstream JNF pathway, which inhibits the brain's insulin receptors once again. Besides Aβ oligomers, ApoE also inhibits insulin receptor signaling by binding to the insulin receptor. ApoE is mainly produced in the glia and then transported by the ABCA1 transporter to produce lipoprotein particles. Aβ oligomers are

destroyed through receptor-mediated absorption by glia and neurons, in addition to proteolytic cleavage by IDE.

Diabetic patients and models have an imbalance between oxidative and antioxidant capacity, which can be seen in the mitochondria. Mitochondrial dynamics (fission and fusion) and biological activities are altered, which leads to mutations in mitochondrial DNA and increases oxidative stress. All these occurrences may result in an inadequate supply of energy and decreased antioxidant enzyme activity in the brain region, increasing the risk of cognitive impairment and memory problems. The bulk flow of CSF and ISF, IDE, and neprilysin are all factors that affect Aβ clearance from the interstitial fluid (ISF). insulin resistance can increase the risk of AD because high levels of insulin lead to IDE saturation and make it unable to degrade Aβ which can lead to Aβ deposition. In some rat experiments, large doses of insulin can decrease Aβ clearance. Distraction of pancreatic cells of mice with AD will decrease the amount of insulin and IDE, which can lead to Aβ accumulation. In insulin pathway, inhibition of PI3K leads to a decrease in secretase activity and APP cleavage which can results in reduction in Aβ production (3).

Tau is a protein manufactured in all neurons, that is attached to tubulin to produce fixed microtubules. In the normal condition, tau functionality depends on its phosphorylation and dephosphorylation dynamic process. In phosphorylation, tau is detached from microtubules to make an easy axonal vesicle transport. in dephosphorylation, tau is reattached to tubulin. The amount of Tau, sequence, phosphorylation state, and Aβ are all factors affect tau pathology (3).Tau dysfunction can lead to impaired insulin signalling and AD. (5) Tau hyperphosphorylation occur when there is an imbalance between tau kinase and phosphatase activity, in this process tau is separated from microtubules and accumulated to form NFTs, Which are Seen in cell bodies and dystrophic neurites of AD patients. AD biomarkers started by the presence of SPs, NFTs formation, and because of the slow process of Protein misfolding and accumulation, it takes more than 10 years for disease progression appeared as neurodegeneration and cognitive decline. (3)

One meta-analysis results concluded that adults with T2DM had an increased amount of CSF tau compared with cognitively healthy adults without diabetes (6). Aβ, islet amyloid polypeptide (IAPP), and tau are proteins involved in AD pathology that promotes the appearance of diabetic phenotypes, which aggravates neurodegeneration (12).

Studies in both clinical and pre-clinical settings have shown that ApoE isoform (5) specially ApoE-e4 can selectively bind to Aβ and control its accumulation and clearance (12) also a mutation of ApoE will cause a defect in the lysosomal pathway which is involved in Aβ degradation. ABCA1 (ATP-binding cassette subfamily A member 1) is a protein that transport cholesterol, its function to increase ApoE lipidation capacity to facilitate the adhesion with soluble Aβ and clearance, any defects in ABCA1 will affect the Lipidated ApoE furthermore it will affect Aβ clearance (5).

Moreover, insulin signaling pathway dysregulation can promote the production of Aβ by translation of BACE and APP, also formation of NFT due to the increase of GSK-3b phosphorylation. Presence of (ApoE-e4) in T2DM can promote NFTs and SP formation in the brain so, these individuals have a greater risk for vascular dementia and AD development to ApoE-e4 carriers or T2DM alone. Also, ApoE-e4 can decrease insulin-degrading enzyme expression which is responsible for Aβ degradation. Chronic inflammation can generate a peripheral immunological response to increase the production of cytokines to cross the Blood-Brain Barrier (BBB) and cause neuroinflammation. In AD, high levels of Aβ can stimulate TNF-a levels through the NIK-dependent pathway resulting in synaptic plasticity and cognitive deficits. Inflammation inactivate incretin, which have a role in insulin-resistant reduction, while incretin activation can lead to TNF-a inhibition.

Advanced glycation end products (AGE) act as Inflammatory mediators by binding to receptors for advanced glycation end products (RAGE) for NF-kB activation, which have an important role in inflammation in both DM and AD. AGE is highly present and concentrated in neurons, glia, NPs and NFTs of AD patients. Methylglyoxal- imidazolone-H1 (MG-H1) is an AGE that can stimulate the pro-inflammatory properties of Aβ or tau. The presence of (MG-H1) in the brain of older patients is closely related to cognitive impairment, clinical and preclinical studies confirmed the correlation between dietary MG, AGEs and cognitive impairment that assessed by Mini Mental State Examination. AGEs tend to reduce the expression of SIRT-1, Lower levels of sirtuins leads to Aβ formation, tau phosphorylation, furthermore AD development and insulin resistance.

Activation of ApoE can activate the homeostatic microglia for phagocytosis of damaged neurons. Microglia have a role in delaying AD pathology by amyloid plaque phagocytosis. ApoE can enhance the accumulation of monomeric Aβ to form amyloid plaque and activate the fibrillary plaque-associated microgliosis to cause neuroinflammation (5).

BBB limits the exchange of some substance through the brain, for example, cholesterol moving to the brain from plasma lipoprotein. Due to the hyperlipidemia most diabetic patients suffer, they tend to have more disturbances related to BBB permeability and rigidity. These disturbances allow cholesterol levels to be elevated inside the brain, raising cholesterol metabolic disorders to happen. Also, the degree of cholesterol and fatty acids metabolic disorders in AD patients can affect the levels of memory loss decline (12).

Intranasal Insulin Approach: The healing efficacy of intranasal insulin has now been showed with the aid of using some of unbiased research (35). The steady findings have been that, amongst folks that had mind insulin resistance related to MCI, early AD, or Type 2 diabetes mellitus, large upgrades in cognition, reminiscence, interest, and metabolic characteristic took place inside some months of remedy withinside the scientific trials (36,37,38,39).

Intranasal Insulin for Treatment in Individuals with Diabetes Mellitus: Intranasal insulin treatment for mild cognitive impairment and Alzheimer's disease (AD) is the focus of this evaluation. There must be an understanding that the same approach is used to treat systemic insulin resistance and deficiency, raising concerns about the specificity and competence of treatment intended to treat neurodegeneration's off-goal effects. To successfully treat diabetes mellitus, the use of intranasal insulin necessitates the completion of adequate blood glucose levels in the peripheral blood. Intranasal insulin, on the other hand, can be utilised to prevent cognitive impairment as a result of diabetes mellitus secondary effects. Researchers have found a link between mind insulin resistance and innovative cognitive impairment and white matter shrinkage in a mouse form of type I diabetes created with the help of Streptozotocin management. White dependence on loss and signalling deficits via survival and synaptic plasticity pathways were averted with treatment with insulin intranasally (44). Mucosal control of autoantigens prevented type 1 diabetes in another animal model that more closely resembled human disease (45). The attempts to use intranasal insulin to prevent you from type I diabetes as soon as autoantibodies were detected were, however, ineffective (46).

CONCLUSION

Because of its ability to preserve memory and relatively high protection index, intranasal insulin treatment shows promise for treating mind insulin resistance associated with cognitive decline and neurodegeneration, including Alzheimer's disease. There are processes needed to ensure that intranasal insulin is delivered to the central nervous system (CNS) instead of the central nervous system (CNS). Compounds apart from insulin can be introduced thru the intranasal direction to deal with quite a number of CNS illnesses technical obstacles concerning stability, fee of delivery,

and delivery throughout nasal epithelium need to be conquer to optimize intranasal insulin remedy for continual illnesses.

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