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Intranasal insulin attenuate signs of Alzheimers disease following chronic hypoxia

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Alzheimer???s disease (AD) is a metabolic neurodegenerative disease featured by cerebrovascular dysfunction in addition to cognitive decline. Amyloid ? (A?) plaques followed by up-regulation of amyloid precursor protein (APP) and seladin-1 down-regulation, as well as insulin signaling impairment are associated with this disease. This study was designed to evaluate the effect of insulin on Alzheimer???s signs induced by chronic hypoxia. 24 male rats were randomly divided into four groups: control (C), sham (Sh), hypoxia (H), hypoxia + insulin (HI) and were exposed to hypoxic chamber (8% O2, 92% N2) for 30 days (four hours/day) in H and HI groups. Pro-inflammatory cytokines and insulin receptor substrate (IRS-1) in sera were measured on day 30 after hypoxia period. Intranasal insulin administration was used as a neuroprotective and antidiabetic drug. Spatial learning and memory were analyzed using the Morris water maze task. Amyloid precursor protein gene (APP) and seladin-1 gene expression were studied in the hippocampus by real time-PCR. TNF-?, IL-1? and IRS-1 had significant magnification in H group compared with C and Sh groups ($p<0.05$). Insulin improved Alzheimer???s signs such as seladin-1 fallen, APP risen gene expression and memory impairment. In conclusion, we indicate that chronic hypoxia mediates AD pathogenesis and using insulin hormone as a neuroprotective and antidiabetic drug could be beneficial in neurodegenerative damage induced by hypoxia.

Insulin has a number of important functions in the central nervous system. Brain insulin receptors are densely localized in the hippocampus, the entorhinal cortex, and the frontal cortex and are found primarily in synapses, where insulin signaling contributes to synaptogenesis and synaptic remodeling.1,2 Insulin also modulates glucose utilization in the hippocampus and other brain regions and facilitates memory at optimal levels in normal metabolism.

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The importance of insulin in normal brain function is underscored by evidence that insulin dysregulation contributes to the pathophysiology of Alzheimer disease (AD), a disorder characterized in its earliest stages by synaptic loss and memory impairment. Insulin levels and insulin activity in the central nervous system are reduced in AD.

Insulin has a close relationship with the β-amyloid peptide, a toxic peptide produced by endoproteolytic cleavage of the amyloid precursor protein. Insoluble Aβ deposits in the brain's parenchyma and vasculature in AD. Soluble Aβ species, particularly oligomers of the 42 amino acid species (Aβ42), also have synaptotoxic effects. Insulin modulates the levels of Aβ and protects against the detrimental effects of Aβ oligomers on synapses.

Thus, reduced levels of insulin and of insulin activity may contribute to a number of pathological processes that characterize AD. Restoring insulin to normal levels in the brain may therefore provide therapeutic benefit to adults with AD. Peripheral administration of insulin is not viable owing to the risk of hypoglycemia or induction and/or exacerbation of peripheral insulin resistance. In contrast, intranasal administration of insulin provides rapid delivery of insulin to the central nervous system via bulk flow along olfactory and trigeminal perivascular channels, and slower delivery via olfactory bulb axonal transport, without adversely affecting blood insulin or glucose levels. In rodent models, intranasally administered insulin binds to receptors in the hippocampus and the frontal cortex within 60 minutes.

In human studies, intranasal insulin increases insulin levels in cerebrospinal fluid (CSF) within a similar time frame and acutely enhances memory. Furthermore, a 3-week trial of daily administration of intranasal insulin improved delayed story recall and caregiver-rated functional status in a small sample of adults with AD and in adults with amnestic mild cognitive impairment (aMCI), a condition thought to represent prodromal AD in most cases.

Our study examines the effects of longer-term insulin administration on primary outcome measures determined from the 3-week trial and on measures of global cognition and function used in traditional clinical trials in adults with aMCI or AD. In a subset of participants, we also examined changes in CSF-related AD biomarkers (Aβ42 level and tau protein–to–Aβ42 ratio) and changes in the cerebral metabolic rate of glucose (CMRGlc) utilization assessed by use of positron emission tomography (PET) with fludeoxyglucose F 18 (FDG). Our results showed that the administration of intranasal insulin stabilized or improved cognition and function and preserved CMRGlc in regions affected by AD.

A nurse unaffiliated with the trial used a table of random numbers to randomly assign participants to receive a daily dosage of 20 IU of insulin (ie, 36 participants received 10 IU of insulin twice a day), 40 IU of insulin (ie, 38 participants received 20 IU of insulin twice a day), or placebo (ie, 30 participants received saline twice a day) for 4 months. Participants were stratified by whether or not they were carriers of the APOE ε4 allele. Saline or insulin (Novolin R; Novo Nordisk, Princeton, New Jersey) was administered after breakfast and dinner with a ViaNase nasal drug delivery device (Kurve Technology, Bothell, Washington) designed to deliver drugs to the olfactory region to maximize transport to the central nervous system. This device released a metered dose of insulin into a chamber covering the participant's nose, which was then inhaled by breathing regularly for 2 minutes until the prescribed dose was delivered.

Parallel versions of the cognitive and functional protocol were administered at baseline, months 2 and 4 of treatment, and 2 months after treatment. Testing occurred in the morning after a standard meal. Participants were instructed to skip their morning dose on the day of testing and thus had received their last dose more than 12 hours prior to cognitive testing.