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Early intranasal insulin therapy halts progression of neurodegeneration: progress in Alzheimer's disease therapeutics

Suzanne M. de la Monte, MD, MPH

Departments of Pathology (Neuropathology), Neurology, Neurosurgery, and Medicine, Rhode Island Hospital and the Warren Alpert Medical School of Brown University, Providence, RI

Abstract

Evaluation of Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, et al. Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment: A Pilot Clinical Trial. *Arch Neurol*. 2011 Sep 12. Alzheimer's disease is associated with brain insulin deficiency and insulin resistance, similar to the problems in diabetes. If insulin could be supplied to the brain in the early stages of Alzheimer's, subsequent neurodegeneration might be prevented. Administering systemic insulin to elderly non-diabetics poses unacceptable risks of inadvertant hypoglycemia. However, intranasal delivery directs the insulin into the brain, avoiding systemic side-effects. This pilot study demonstrates both efficacy and safety of using intranasal insulin to treat early Alzheimer's and mild cognitive impairment, i.e. the precursor to Alzheimer's. Significant improvements in learning, memory, and cognition occured within a few months, but without intranasal insulin, brain function continued to deteriorate in measurable degrees. Intranasal insulin therapy holds promise for halting progression of Alzheimer's disease.

Summary of Methods and Results

In the randomized double-blind, placebo-controlled trial led by Dr. Suzanne Craft, the investigators studied 104 adults who had mild cognitive impairment (MCI) or were in the early to moderate stages Alzheimer's disease (AD) (1). The subjects were treated with either a placebo, or one of two doses (20 – 40 IU) of intranasal insulin. At the end of a 4-month protocol, memory and cognitive performance were assessed to objectively determine if the intranasal insulin treatments were effective, and whether the effects were insulin dose-dependent. The investigators found that subjects who received the lower insulin dose had significantly improved performance on memory/recall tasks compared with the placebo group, and that subjects who received either of the intranasal insulin doses had better preservation of cognitive function based on standardized ADAS–Cog and ADCS–ADL scales. In a limited number of subjects, cerebrospinal fluid (CSF) was obtained to examine the effects of intranasal insulin therapy on typical biomarkers of AD, i.e. Aβ42 levels and

Correspondence to Dr. Suzanne M. de la Monte, MD, MPH, Pierre Galletti Research Building, Rhode Island Hospital, 55 Claverick Street, Room 419, Providence, RI 02903. Tel: 401-444-7364; Fax: 401-444-2939; Suzanne_DeLaMonte_MD@Brown.edu.

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Tau–to–Aβ42 ratios. The CSF sub-studies showed that improvements in cognitive performance were correlated with correction of AD biomarkers, reinforcing the concept that effectiveness in AD therapy can be monitored with CSF biomarkers. Finally, neuroimaging studies showed that the placebo group had further reductions in cerebral cortex glucose utilization (energy metabolism) at the end of the study period, indicating that in the absence of intranasal insulin treatments, their neurodegeneration continued to progress. In contrast, the treatment groups showed preservation of brain metabolism. This suggests that intranasal insulin therapy can help to stabilize, slow, or possibly even reverse the course of AD. Altogether, these results support the concept that insulin is needed for cognitive function, and that in MCI and AD, intranasal insulin therapy provides support neurons that are needed for learning, memory, and cognition. The authors demonstrated that intranasal insulin therapy is safe and effective among individiuals in the early stages of AD, and also among those who are at increased risk for developing AD.

Discussion

Alzheimer's disease (AD) is the most common cause of dementia in the Western hemisphere, and equally alarming is the fact that AD is now emerging as a public health problem in developing countries as well. Although aging is the most important correlate of AD, other factors are clearly involved since most elderly individuals do not succumb to AD. For nearly 30 years, researchers focused mainly on the role of genetics as causal agents, despite evidence that the majority of AD cases occur sporadically. Only within the past few years have investigators come to realize that AD rates increased sharply over the past 40–50 years, even after adjusting for aging within the population (2). Certainly such a time course is too brief to account for the shift in trends. What finally caused a C-change in our thinking were the pivotal discoveries that: 1) AD is associated with brain insulin resistance and insulin deficiency, mimicking effects of diabetes mellitus; and 2) the rates of mild cognitive impairment and dementia are significantly higher among diabetics than non-diabetics (3). The concept that AD may be a brain form of diabetes fits well with earlier evidence that deficits in brain energy metabolism, particularly glucose utilization, start early in the course of disease and progress with its severity. Since deficiencies in brain metabolism are detectable by non-invasive imaging techniques, such as positron emission tomography (PET) scans, these types of approaches could be used to help diagnose AD and monitor its progression.

The work by Craft, et al represents an important contribution to the field of AD therapeutics. In addition to forwarding research on a newer and probably less costly approach to treatment, the study builds on the emerging concept that AD is fundamentally mediated by progressive brain insulin deficiency and resistance (4, 5). Brain metabolic disturbances, particularly the ability to utilize glucose, its main fuel, arise very early and could possibly initiate disease (6–8). Without insulin, brain cells, including neurons, oligodendrocytes (myelin producing), and vascular elements function poorly and degenerate or die (9). Therefore, early detection and correction of brain insulin deficiency and resistance are critical to our ability to halt AD progression and perhaps prevent its development. The underlying hypothesis embodied in this work is well-supported by experimental evidence that impairments in brain insulin actions cause neurodegeneration with loss of neurons

(brain atrophy), Aβ42 accumulation/toxicity, phospho-tau pathology, and neuroinflammation, and decreased brain metabolism and Aβ42 clearance (3). Early intervention to re-supply the missing trophic factor, i.e. insulin, would support viability and function of the various cell types needed to sustain cognition, and also would likely prevent or slow the process of Aβ42 and phospho-tau induced neurodegeneration.

The article by Craft, et al puts the whole story about the importance of insulin as a neuroprotective agent into excellent clinical perspective because the researchers utilized human subjects in a randomized, double-blind, placebo-controlled trial. Although the study was limited in duration, the results are very promising, particularly for the populations targeted in the study, i.e. MCI and early AD. The authors' conclusion that individuals in the early stages of AD and those with MCI (pre-AD) might benefit from intranasal insulin therapy is correct and supported by the results. The rationale for studying subjects with MCI is thoroughly justified because that group is at significantly increased risk for developing AD, and the ultimate goal of any research in this field is disease prevention. Consideration for the use of insulin therapy in AD is supported by the earlier findings that: 1) diabetic patients who were well-managed with insulin had improved memory and reduced rates of AD progression; 2) elderly diabetics who were treated with insulin had less severe AD brain pathology compared with non-diabetics; 3) short trials of insulin treatment improved cognition and memory in subjects with AD; 4) hyper-insulinemic euglycemic clamping (high insulin with normal glucose) enhances cognition and attention in AD; and 5) in experimental animals, brain insulin treatments improved memory, cognition, and neurotransmitter function (3).

Although the abovementioned observations paint a rosy picture that seems to clear the path toward the use of insulin therapy in AD, from both clinical and public health perspectives, extreme caution must be exercised in utilizing this approach in the targeted geriatric population. Important concerns include inadvertent bouts of hypoglycemia that could lead to traumatic falls and life-threatening metabolic insults, limiting its potential use. Systemic insulin therapy for treating AD in elderly populations requires careful consideration and extensive monitoring to minimize or avoid harm, and therefore is not entirely feasible for routine medical care in geriatric populations. On the other hand, the administration of insulin via the intranasal route holds promise for safety and efficacy as most of the insulin delivered properly in this manner, will go to the brain and not adversely affect peripheral blood glucose levels. In the study by Craft, et al, in addition to demonstrating efficacy, they determined that intranasal insulin therapy was safe for elderly patients.

The main objectives of the study by Craft, et al, were to examine the effects of intranasal insulin on cognitive function, cerebral glucose metabolism, and CSF biomarkers related to MCI and AD. The sub-text of their study design and conclusions is that while intranasal insulin monotherapy can benefit individuals in the early stages or pre-stages of AD, given our understanding about how AD progresses, it is unlikely that this approach will be as effective in patients who have reached later stages of neurodegeneration. Researchers studying AD realize that once AD gets established and reaches a certain stage, it is difficult and perhaps impossible to slow its course or halt its progression. Insulin therapy may improve cognitive performance as long as neurons and other cell types in the brain retain

their capacities to survive and function in response to insulin stimulation. As AD progresses into the later stages of disease, the brain becomes increasingly more insulin resistant, just like the problem in Type 2 diabetes (3, 5). As AD progresses, intranasal insulin monotherapy may support fewer and fewer cells in the brain, necessitating the use of additional therapeutic targets and approaches.

Certainly, the demonstration that intranasal insulin monotherapy is safe and effective for treating individuals with MCI and early AD, particularly in light of the objective and accepted standard measures used to document outcomes. Extensions of this trial to larger populations with well defined clinical criteria for MCI or early AD diagnoses should be considered high priority in the near future. However, moving beyond the present and near future, consideration should be given to the next steps that would take into account our current limitations in efficiently detecting and diagnosing MCI and AD. Researchers throughout this field recognize that neurodegeneration is a progressive process that eventually seems to drive itself. Crrespondingly, there is considerable evidence that Aβ42 toxicity impairs insulin signaling and promotes tau pathology, and that both tau and Aβ42 pathology promote oxidative stress, inflammation, metabolic embarrassment, and cell loss, which worsen brain insulin resistance (10). In other words, each component of neurodegeneration negatively impacts the others and thereby advances the pathology that mediates AD dementia. Since all components of the cascade eventually contribute to neurodegeneration, the later stages of AD will require multi-pronged therapeutic measures to be effective. Fortunately, there is already a wealth of information available about the treatment and management of Type 2 diabetes which fundamentally is caused by insulin resistance in the body, and is now recognized to be associated with cognitive impairment and contribute to early dementia.

Future Perspective

In the near future, therapeutic measures for AD will likely shift toward the use of alternatives to insulin to improve efficiency of drug delivery. In this regard, incretins, such as glucagon-like peptide-1 (GLP-1) (11–13), are promising because of their ability to restore insulin levels and functions in the brain (14). GLP-1 is an insulinotropic peptide generated by cleavage of proglucagon (14). Because GLP-1 is rapidly degraded by dipeptidyl peptidase-4, it is quite safe. GLP-1 stimulates insulin gene expression and secretion, and suppresses glucagon (12). GLP-1 also restores insulin sensitivity and consequently lowers blood glucose in individuals with Type 2 diabetes (12). The dual actions of incretins in stimulating insulin secretion and enhancing insulin responsiveness make them very attractive for treating AD. Like insulin, GLP-1 stimulates neuritic growth in cortical neurons and exerts neuroprotecive actions against glutamate-mediated excitotoxity, oxidative stress, trophic factor withdrawal, and cell death (12, 15). Importantly, GLP-1 can cross the blood-brain barrier, and effectively reduce brain AβPP-Aβ burden in AD (12, 14, 15). Already attention has been focused on extending the half-life of GLP-1 to enhance its practical use for treating insulin-resistance diseases, including AD. One important approach has been to develop synthetic long-lasting analogues (receptor agonists) of GLP-1, e.g. Geniposide or Extendin-4, which are also neuroprotective and neuro-stimulatory, and can help preserve cholinergic neuron function (14, 16, 17). Finally, a future approach could be to genetically

modify mesenchymal or stem cells to provide sustained delivery of neuro-stimulatory and neuro-protective agonists (18–20), including GLP-1.

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Executive Summary

- Intranasal insulin therapy improves memory and cognitive performance in people with mild cognitive impairment or early Alzheimer's disease.
- Intranasal insulin improves objective biomarker indices of neurodegeneration related to amyloid deposits and tau pathology in brains with early Alzheimer's disease.
- Therapeutic effects of intranasal insulin are detectable within a relatively short period (a few months), whereas without the treatments, neurodegeneration progresses in measurable degrees.
- Intranasal insulin is safe for use in elderly individuals who are in the early stages of Alzheimer type neurodegeneration.