Intranasal Insulin Improves Memory in Patients with Alzheimer's Disease.

Those of us who do not yet have Alzheimer’s disease need to stop and think about how to best develop a way to treat and prevent this disease.

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How Can We Develop Methods for Treating and Preventing Alzheimer’s Disease?

• To treat and prevent Alzheimer’s disease (AD), do we need to discover a new drug or just deliver insulin (available since 1923) to the brain in a new way?
• If reducing brain amyloid is the way to treat AD as most “experts” insist, why have the millions of dollars spent developing drugs that reduce amyloid over the last 30 years not improved memory in patients with AD?
• Should we keep spending money on this failed approach or should we fund a new approach to treatment?
• If a new treatment improves memory in patients, why is it not being fast tracked now for patients who need it?

Overcoming the Blood-Brain Barrier
[Keep it simple, safe, inexpensive and non-invasive.]
Delivery of Intranasal Drugs to the Brain

Intranasal Delivery to the Brain
• Is non-invasive.
• Bypasses the blood-brain barrier.
• Results in rapid delivery to the brain along both the olfactory and trigeminal nerves.
• Reduces unwanted systemic exposure and side effects.
• Does not require modification of the drug.
• Works best for potent drugs.

The Parable of the Blind Men and the Elephant
I.N. Deferoxamine Protects Against AD & Stroke

- Iron is elevated in the brains of patients with AD, stroke, Parkinson’s other brain disorders. This is not because we ingest too much iron, but rather because our brains do not handle the iron properly.
- Deferoxamine (DFO), developed in the 1960s, binds iron very tightly and can help remove it from the body.
- Intranasal DFO reduces brain damage in rats by 55% even when a stroke occurs two days after treatment. DFO preconditions the brain to protect it against damage.
- Intranasal DFO reduces memory loss in a mouse model of AD and improves memory in normal mice.
- Intramuscular DFO cut the rate of functional decline in AD patients by 50% over two years. Intranasal DFO should be more effective and avoid systemic side effects.

Development of I.N. DFO Therapy

- The National Institute of Aging is currently funding safety testing for intranasal DFO to facilitate obtaining approval for clinical trials and the treatment of Alzheimer’s disease.
- We are also developing intranasal DFO for treating head injury, hemorrhage, stroke, Huntington’s disease, ALS and Parkinson’s disease.
Alzheimer’s Patients Do Not Take Up Glucose Properly.

**Glucose Uptake & Utilization**

**FDG-PET**

Alzheimer’s Patient  
Elderly Adult


Alzheimer’s Patients Do Not Take Up Glucose Properly.

**Insulin Deficiency in the Brains of Alzheimer’s Patients**

- Insulin was first discovered and used to treat diabetes in the 1920s.
- In addition to insulin production in the pancreas, insulin is also made in the brain where it is needed, especially in the areas involved in memory.
- The brain production of insulin is drastically reduced in Alzheimer’s disease causing “diabetes of the brain”.
- How can this brain deficiency of insulin be corrected without altering the blood levels of insulin and glucose?


**Intranasal Insulin for Alzheimer’s Disease**

- My discovery of direct intranasal delivery of insulin to the brain to improve memory and treat Alzheimer’s disease has been followed by a number of human clinical trials.
- Born et al. demonstrated that within 10 minutes following intranasal insulin treatment of normal human adults, the CSF level of insulin rises dramatically. However, there was no change in the blood level of either insulin or glucose during this time period. This is not surprising since insulin does not easily cross the nasal mucosa into the blood.

William H. Frey II - Inventor  
Intranasal Insulin Improves Memory in Healthy Adults

- Intranasal insulin for 8 weeks improved memory and mood in normal healthy adults at doses that did not alter blood levels of insulin or glucose.
- Delayed recall of words was improved.
- Similar results were obtained in separate studies with obese men.


Superiority of Insulin Aspart

- Intranasal insulin aspart, a rapid acting form of insulin, improves memory better in normal adults than regular insulin.
- Four doses per day were administered over 8 weeks leading to improved word list recall in both treatment groups compared to placebo.
- Word list recall was significantly improved with intranasal insulin aspart compared even to the intranasal regular insulin.

Benedict et al. (2006) Neuropsychopharmacology

Intranasal Insulin Improves Memory in Alzheimer’s Patients.

- A single intranasal insulin treatment acutely improves verbal memory for adults with Alzheimer’s disease within 15 minutes at doses that do not alter blood levels of insulin or glucose.
- Both total story recall and total word list recall were significantly improved.
- This treatment benefit was seen primarily for Alzheimer’s patients without the APOE ε4 allele.

Intranasal Insulin Improves Memory in Patients with Alzheimer’s Disease or Mild Cognitive Impairment.

Intranasal insulin given twice a day for 21 days enhanced memory and significantly improved attention and functional status in patients in the early stages of AD or with mild cognitive impairment.


Intranasal Insulin 4 Month Trial in AD

• The latest results for a 4 month trial of intranasal insulin treatment of patients in the early stages of AD were presented last July at the International Conference on AD.
• Once again intranasal insulin was found to improve memory in these patients.
• In addition some benefits were also observed using brain scans assessing the uptake and utilization of glucose in the treated patients.
• Minor nasal side effects suggest that we need a better formulation of intranasal insulin to treat patients, and we are currently developing such a formulation.

Can Intranasal Insulin Improve the Brain Pathology of Alzheimer’s Disease?

• Insulin provides energy needed to prevent brain degeneration, replace worn out parts of brain cells and increase synaptic density.
• Reduced insulin signaling is associated with increased tau phosphorylation (tangle formation) and amyloid (plaques).
• Insulin increases insulin degrading enzyme (which also degrades amyloid), reduces GSK3beta, the enzyme that forms Alzheimer’s tangles and maintains nerve connections (synaptic density).
• If humans are given intranasal insulin at the first sign of a deficiency of insulin in the brain, it may be able to delay or even prevent the onset of the disease.

Diabetes is a Risk Factor for Alzheimer’s Disease

- Diabetes doubles the risk for getting Alzheimer’s disease which is not surprising since diabetics have a deficiency of insulin.
- Intranasal insulin prevents cognitive decline and brain atrophy in aging diabetic animals.
- Human studies are needed to determine if intranasal insulin can reduce the risk of Alzheimer’s disease in the millions of people with diabetes.
- Intranasal insulin may also be helpful for patients with attention deficit disorder since it improves attention.


Insulin, Stress and Brain Damage

- Chronic unalleviated stress damages brain cells required for memory.
- Even mild AD patients show evidence of increased stress.
- Intranasal insulin has been shown to reduce the deleterious response to stress in humans.
- Intranasal insulin may therefore help to reduce the death of brain cells caused by chronic unalleviated stress.


Assessing Intranasal Insulin Treatment

- Brain imaging with glucose PET scans should reveal when intranasal insulin is needed to increase glucose uptake and utilization.
- PET can also be used to monitor the brain effects of intranasal insulin treatment.
Conclusions

• Intrasinal delivery bypasses the blood-brain barrier to target insulin and to the brain to treat disease while reducing systemic exposure and unwanted side effects.
• Intrasinal insulin is a non-invasive method of treatment and perhaps prevention of Alzheimer’s disease.
• Preclinical studies suggest that intranasal insulin offers a method of treating and preventing the loss of cognitive function in diabetes and may reduce the risk of developing Alzheimer’s disease in this population.
• Better formulations of intranasal insulin are needed to optimize the treatment of patients with Alzheimer’s disease.

Conclusions

• Unlike other methods of treatment and prevention examined to date, intranasal insulin rapidly improves memory attention and functioning in patients with Alzheimer’s disease and even improves memory in normal adults.
• Additional clinical trials are needed to confirm the safety and efficacy of intranasal insulin and to determine if it can prevent or delay the development of Alzheimer’s disease and its brain degeneration.
• It will take time, funding and cooperation to get FDA approval before intranasal insulin can become available.

What Is Holding Up These Treatments?

• Both insulin and deferoxamine (the iron binding drug) are generic drugs which are relatively inexpensive.
• Generic drugs no longer have patent protection; so any company may be able to compete with the company who first brings the new treatment to market.
• This means that there is a lot of extra financial risk in developing an intranasal generic drug treatment since it will be harder to make a profit on such a treatment.
What Is Needed Now?

- Creativity and a willingness to support new approaches to developing treatments for Alzheimer’s disease.
- Funding for intranasal treatment research and for clinical trial development.
- A willingness to take generic drugs through the FDA clinical trial process and to market them for Alzheimer’s disease.

What Does the Future Hold?

- If we are lucky, intranasal insulin and intranasal deferoxamine will continue to be developed, and one or both of these may become available in the next 8 years.
- Hopefully, these treatments will be combined with improved imaging techniques to help physicians know when to begin treatment.
- Glucose PET scans can reveal when insulin is needed to increase glucose uptake and utilization.
- MRI scans can reveal when iron is abnormally accumulating in the brain and thus when to start treatment with intranasal deferoxamine.
Problems with Implantation of Stem Cells

- Stem cell therapy for brain disorders which utilizes surgical implantation of stem cells has problems with both safety and efficacy due to its invasive nature.
- Surgical implantation leads to neuroinflammation which rapidly kills the implanted stem cells.
- The risk of damaging the brain and/or infection is significant.
- Finally, the cost of neurosurgical implantation is prohibitive.

Intranasal delivery of cells to the brain

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Pathways of Stem Cell Migration

Pathways of cell migration

- olfactory route (OR)
- trigeminal route (TR)
- trigeminal ganglion
- CSF branch of OR
- periventricular branch of OR
Intranasal Stem Cells for Both Parkinson’s and Alzheimer’s Disease

- Intranasal adult stem cells taken from bone marrow reduce brain inflammation, prevent brain damage and improve functioning in an animal model of Parkinson’s disease.
- We have reason to hope that stem cells taken from the bone marrow of patients themselves can also be helpful in reducing brain cell loss in Alzheimer’s disease but need to conduct much more research to test this hypothesis and move this potential new treatment forward.
- There is real reason to hope for new methods of treatment and prevention of Alzheimer’s disease.

Thanks for your help!

- At the HealthPartners Alzheimer’s Research Center and Center for Dementia and Alzheimer’s Care, we are committed to continuing our research to develop the methods of treatment and prevention we all need.
- We are grateful to everyone who has supported our research effort which has allowed us to develop intranasal insulin, intranasal deferoxamine and intranasal adult stem cell treatments for Alzheimer’s disease and other brain disorders.
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