Intranasal Insulin to Treat and Protect Against Posttraumatic Stress Disorder

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Lessons learned from research on the treatment of Alzheimer's disease (AD) suggest a new strategy for treating posttraumatic stress disorder (PTSD). The NIH recently selected intranasal insulin as a promising treatment for AD and committed 7.9 million in funding to further test it nationally (Health and Human Services Press Office for Secretary Kathleen Sebelius, 2012). The noninvasive intranasal method for bypassing the blood-brain barrier to target therapeutics (including insulin) to the brain to treat neurodegenerative disorders such as AD and stroke was first discovered in 1989 (Frey, 1991) and was later described specifically for the use of intranasal insulin to target the brain to treat AD and certain other CNS disorders (Frey, 2001). Intranasal therapeutics bypass the blood-brain barrier and rapidly reach the brain by traveling extracellularly along the olfactory and trigeminal neural pathways (Lochhead and Thorne, 2012). This increases efficacy while reducing systemic exposure and unwanted side effects.

Intranasal insulin treatment improves memory in healthy adults, with no change in the blood levels of insulin or glucose (Benedict et al., 2004). Researchers in Germany conducted several additional human clinical trials showing that intranasal insulin improves memory in healthy adults (Benedict et al., 2011). In 2006, Dr Suzanne Craft, at the University of Washington and the Veterans Affairs Puget Sound Health Care System, and colleagues (of whom I was one) reported that intranasal insulin improved memory in only 20 minutes after a single intranasal insulin treatment in patients with AD (Reger et al., 2006). Intranasal insulin (twice a day) also improved memory, attention, and functioning in patients with AD during a 21-day period (Reger et al., 2008) and improved memory and general cognition and reduced loss of brain fludeoxyglucose uptake in patients with AD or amnestic mild cognitive impairment treated with intranasal insulin in a 4-month clinical trial, with no change in the blood levels of insulin or glucose (Craft, 2012).

It is not surprising that intranasal insulin is an effective treatment of AD because glucose uptake and use are significantly decreased in patients with AD (de Leon et al., 1997). Glucose is the only source of energy used by brain cells under normal conditions, and the brain cells of patients with AD are starved for energy. AD has been reported to involve a deficiency of insulin and insulin signaling in the brain (Steen et al., 2005.) Type 2 diabetes is a major risk factor for developing AD.

Intranasal insulin is far more than simply a treatment of AD symptoms. When intranasal insulin reaches the brain, it stimulates the formation of insulin-degrading enzyme, which is capable of degrading beta amyloid, one of the principal abnormal proteins known to accumulate in the brains of patients with AD. Further, the activity of glycogen-synthase kinase-3-beta, the enzyme that phosphorylates tau to create AD neurofibrillary tangles, has been reported to be downregulated in response to insulin. Finally, insulin receptor signaling increases synaptic density, and loss of synapses is key to the neuropathology of AD (Benedict et al., 2011).

Stress has also been found to reduce the uptake and use of glucose by brain cells. In 1986, Sapolsky reported that glucocorticoids released in response to stress could damage neurons in the hippocampus. Multiple mechanisms are likely involved in this action, one of which is the inhibition of glucose use in the hippocampus by glucocorticoids. Cortisol has been reported to reduce hippocampal glucose use in healthy elderly adults on the basis of examination of the brain glucose use (cerebral metabolic rate of glucose consumption) response to hydrocortisone (cortisol; de Leon et al., 1997). It is likely that glucocorticoids also reduce the capacity of the hippocampus to survive neurological insults because glucocorticoids inhibit glucose transport 15% to 30% in both primary and secondary hippocampal astrocytic cultures, and this could impair the ability of astrocytes to aid neurons by removing damaging glutamate from the synapse during times of neurological crisis (Virgin et al., 1991). Glucocorticoids released in response to major stress inhibit local cerebral glucose use throughout the brain and inhibit glucose transport in neurons; glia; and, possibly, endothelial cells in vitro (Sapolsky et al., 2000).

Baker et al. (2005) have reported that mean CSF cortisol concentrations are significantly higher in combat veterans with PTSD than in healthy comparison subjects. Concentrations of CSF

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corticotropin-releasing hormone and CSF cortisol concentrations were positively and significantly correlated. The authors concluded that veterans with PTSD have a higher CNS exposure to cortisol than that of healthy comparison subjects.

In a study assessing the cortisol response to a cognitive stress challenge, patients with PTSD had 61% higher group mean cortisol levels in the time leading up to the cognitive challenge and 46% higher cortisol levels during the period of the cognitive challenge compared with controls (Bremmer et al., 2003). Most recently, glucocorticoids have been shown to induce PTSD-like memory impairments in mice (Kaouane, 2012).

Intranasal insulin (40 IU) treatment of 26 healthy adult men minutes before they were exposed to the Trier Social Stress Test in a placebo-controlled, double-blind, between-subject design significantly diminished both the saliva and plasma cortisol response to the test (Bohringer et al., 2008). Because intranasal insulin attenuates the hormonal response to stress in adult men, it may also be helpful as a way to treat and even protect against PTSD. If so, it would be possible to use insulin nasal sprays targeted to the upper third of the nasal cavity to treat individuals exposed to a traumatic stressful event shortly after it occurred or even to treat individuals, such as military personnel or first responders, who are at immediate high risk for traumatic stress to help protect the brain against the damaging effects of such stress.

DISCLOSURES

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Dr Frey is the listed inventor on numerous patents related to intranasal therapeutics to treat brain disorders but does not have an issued patent or published patent application related to intranasal insulin treatment of PTSD. He consults for many pharmaceutical and biotechnology companies.

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