Intranasal Deferoxamine (IN DFO) as a Treatment For Neurodegenerative Disease

Jacob Kosyakovsky, Jared Fine, Benjamin Stroebel, Leah Hanson, Kate Faltesek, William H. Frey II
HealthPartners Neuroscience Center, St. Paul

Abstract

➢Neurodegenerative diseases represent a huge burden of disease and disability with no cure.

➢Intranasally administered deferoxamine (IN DFO), an iron chelator, has decreased memory loss and improved motor function in rodent models of Alzheimer's and Parkinson's disease respectively.

➢DFO's mechanism of memory-improvement may involve chelation of excess iron, activation of HIF-1α, and/or inhibition (phosphorylation) of GSK-3β.

➢DFO shows promise as a potential new therapy for multiple forms of neurodegenerative disease.

Background

Burden of Neurodegenerative Disease

➢Gradual loss of neuronal function leading to progressive cognitive and neurologic dysfunction.

➢One of the leading causes of death and disability
- ➢Alzheimer's Disease (AD):
  - ➢2 mill death/year
- ➢Parkinson's Disease (PD):
  - ➢>100,000 deaths/yr

The Need for Treatment

➢Current treatments can slow progression and partially alleviate the symptoms of neurodegeneration, but we have no curative therapy.

DFO: A Potential Solution

What is DFO?

➢Deferoxamine (DFO) is a metal chelator, binding iron and other metals, allowing their elimination from the body.

How could DFO Help in Neurodegeneration?

➢Iron accumulation and overload is well-characterized in Alzheimer's and Parkinson's Disease and may be involved in the symptoms.

➢DFO may alleviate iron overload (also: anti-inflammatory)

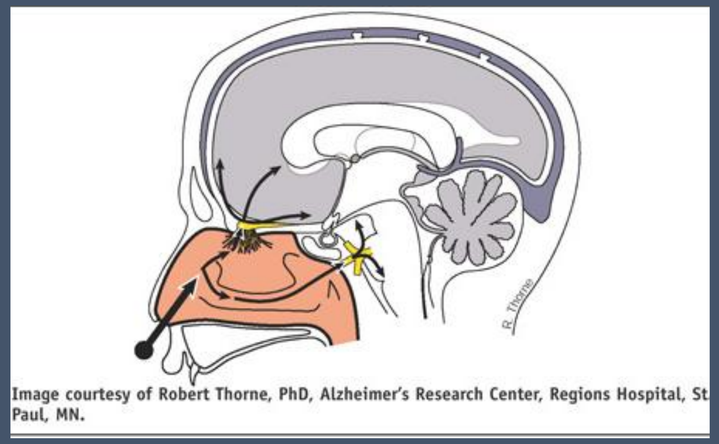


Image courtesy of Robert Thorne, PhD, Alzheimer's Research Center, Regions Hospital, St Paul, MN.

Figure 1: Route of intranasal administration

Rodent Trial Design

➢DFO has been tested in several rodent models of neurodegenerative disease:
- ➢P301L: accumulates hyperphosphorylated Tau (AD)
- ➢APP/PS1: accumulates presenilin, amyloid (AD)
- ➢ICV/STZ: inducible AD model
- ➢6-OHDA: inducible PD model

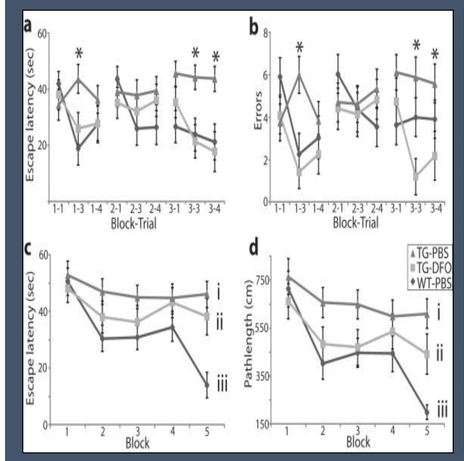
➢After intranasal administration, rodents were assessed using validated tools:
- ➢Morris water maze/Radial arm water maze for learning and memory
- ➢Tapered balance beam, Rearing tube for motor function

➢Rodents were later euthanized, and brain tissue samples taken for biochemical analyses.

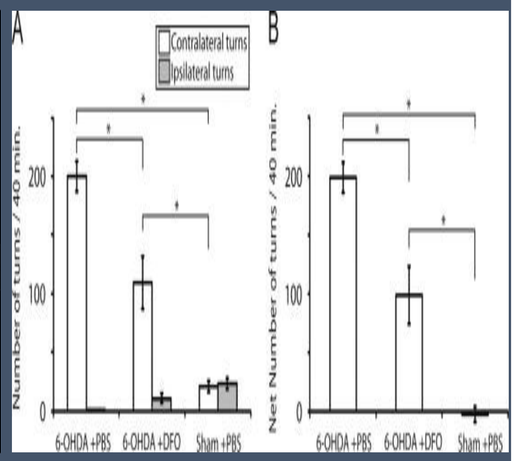
Results

➢In all AD models: DFO significantly improved learning and memory, with shorter escape latencies from water mazes

➢In PD: rodents given IN DFO demonstrated improved motor function

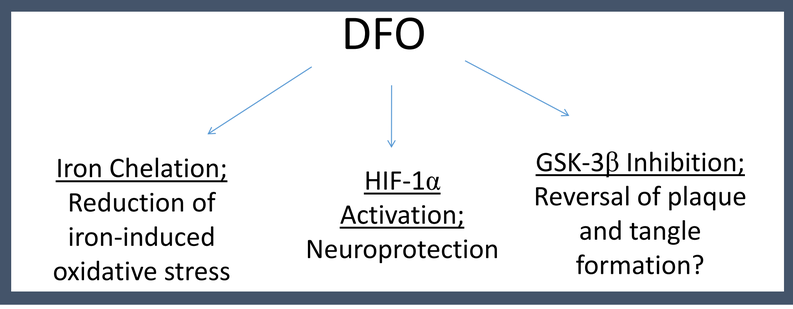


AD-(Fine et. al., 2015)



PD-(Fine et. al, 2014)

Summary of Proposed Mechanisms



Future Directions

➢Thus far, we have shown IN DFO to restore learning, memory, and motor function in rodent models of AD and PD.

➢More work needs to be done in clarifying the molecular mechanism of its action, as well as following the long-term course of its impact on brain function.

➢Once we have further established long-term safety and efficacy in rodent models, we can move forward to clinical trials.

References

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