Experimental molecular therapy crosses blood-brain barrier to treat neurological disease

February 4 2013

Researchers have overcome a major challenge to treating brain diseases by engineering an experimental molecular therapy that crosses the blood-brain barrier to reverse neurological lysosomal storage disease in mice.

Posted online in *PNAS* Early Edition on Feb. 4, the study was led by scientists at Cincinnati Children's Hospital Medical Center.

"This study provides a non-invasive procedure that targets the blood-brain barrier and delivers large-molecule therapeutic agents to treat neurological lysosomal storage disorders," said Dao Pan, PhD, principal investigator on the study and researcher in the Cancer and Blood Diseases Institute at Cincinnati Children's. "Our findings will allow the development of drugs that can be tested for other brain diseases like Parkinson's and Alzheimer's."

The scientists assembled the large molecular agents by merging part of a fatty protein called apolipoprotein E (apoE) with a therapeutic lysosomal enzyme called a-L-idurondase (IDUA). Naming the agents IDUAe1 and IDUAe2, researchers used them initially to treat laboratory cultured human cells of the disease mucopolysaccharidosis type I (MPS I). They also tested the agents on mouse models of MPS I.

MPS I is one of the most common lysosomal storage diseases to affect the central nervous system, which in severe form can become Hurler

syndrome. In humans, patients can suffer from hydrocephalus, learning delays and other cognitive deficits. If not treated, many patients die by age 10.

Lysosomes are part of a cell's internal machinery, serving as a waste disposal system that helps rid cells of debris to retain normal function. In lysosomal storage diseases like MPS I, enzymes needed to dissolve debris are missing, allowing debris to build up in cells until they malfunction.

In MPS I, cells lack the IDUA enzyme, allowing abnormal accumulation of a group of large molecules called glycosaminoglycans in the brain and other organs. Researchers in the current study used the new therapeutic procedure to deliver IDUA to brain cells. But first they had to successfully engineer the therapy to carry IDUA through the blood-brain barrier to diseased brain cells.

The blood-brain barrier is a physiological blockade that alters the permeability of tiny blood vessels called capillaries in the brain. Its purpose is to protect the brain by preventing certain drugs, pathogens and other foreign substances from entering brain tissues. The barrier has also been a persistent roadblock to treating brain disease with drugs.

The scientists experimented with a set of derivative components of the fatty protein apoE, which binds to fat receptors on endothelial cells that form the inside surface of capillaries in the blood-brain barrier. They discovered that tagging some of the apoE components to the IDUA enzyme allowed the modified protein to attach to endothelial cells and cross through the cells to reach brain tissues.

Researchers injected experimental IDUAe1 into the tail veins of MPS I mouse models. The tests showed that – unlike currently available un-modified enzyme treatments – the modified enzyme penetrated the

blood-brain barrier and entered brain neurons and astrocytes in a dose-dependent manner.

The researchers also reported that brain cells in the treated mice exhibited normalized levels of the glycosaminoglycans and the lysosomal enzyme beta-hexosaminidase. With continued treatment through hematopoietic stem cell gene therapy, normalized levels persisted until the end of a five-month observation period, researchers said.

The scientists are continuing their preclinical studies to further verify the use of the experimental IDUA-based agents for treating MPS I, cautioning that results in laboratory mice may face additional challenges when translating to clinical application in humans.

Researchers are also testing whether the large-molecule therapeutic procedure used in the current study can be leveraged to develop other neurotherapeutic agents that cross the blood-brain barrier.

Also collaborating on the study was Roscoe O. Brady, MD, a researcher and scientist emeritus at the National Institute of Neurological Disorders and Stroke.

Provided by Cincinnati Children's Hospital Medical Center

Citation: Experimental molecular therapy crosses blood-brain barrier to treat neurological disease (2013, February 4) retrieved 23 May 2024 from https://medicalxpress.com/news/2013-02-experimental-molecular-therapy-blood-brain-barrier.html

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