Encouraging findings for Batten disease drug

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The FDA-approved, lipid-lowering medication gemfibrozil may prevent the progression of juvenile Batten disease, according to researchers at RUSH. Results from the study were recently published in *The Journal of Neuroscience*.

Researchers found that gemfibrozil, which has the brand name Lopid, assists with clearing the brain of autofluorescent pigment deposits, which is a hallmark of the disease. Autofluorescent pigment deposits are made up of lipid-protein fragments that increase in the brain over time and suffocate healthy cells by depriving them of oxygen, which leads to neuronal death.

Juvenile Batten disease is a rare but devastating neurodegenerative disorder that begins in childhood, causing loss of vision, seizures, and progressive neurological degeneration, which is a loss of structure and function of the brain.

It occurs in an estimated two to four out of every 100,000 births in the United States. Batten disease is inherited in an autosomal recessive pattern in the loss of a specific gene, CLN3, which provides instructions for making a protein that is found in tissues throughout the body. Currently, no drug is available to slow or halt the disease progression.

"Finding an effective drug to protect the brain and stop the progression of Batten is an important area of research," said Kalipada Pahan, Ph.D., the Floyd A. Davis professor of neurology.

Reduces brain inflammation

Children with Batten disease eventually become blind, bedridden and demented. Juvenile Batten disease is a life-limiting disease. Life

expectancy varies depending on the type or variation. Death usually occurs in the 20s, depending on the speed of disease progression.

"We have found that oral gemfibrozil successfully reduces inflammation in the brain, decreases brain accumulation of toxic autofluorescent pigment deposits and improves locomotor activities in mice that are missing the CLN3 gene," Pahan said.

Removal of toxic materials from the brain requires efficient lysosomes that assist in clearing deposits from anywhere in the body, and the transcription factor EB (TFEB) that is responsible for the production of functional lysosomes. This is the regulation of basic cellular processes that happen to rid the body of harmful waste.

In the process of developing a new mouse model for studying juvenile Batten disease, researchers at RUSH University Medical Center have discovered a new mechanism for stimulating TFEB by PPARα, a molecule that is found in the liver, in fatty acids and in various parts of the brain. The TFEB molecule can remove waste from anywhere in the body and from the brain, which may help prevent further damage in the brain.

"We were excited to see that oral gemfibrozil activates TFEB in the brain, which is the beginning of the process for clearing out dead cells from the body," Pahan said.

'Promising avenue of treatment'

Oral gemfibrozil remains unable to increase TFEB, or decrease autofluorescent materials in the brain and improve locomotor performance of Cln3 mice that lack peroxisome proliferator-activated receptor alpha (PPARα).

The major role of PPARα is to control fat metabolism in the liver. "Our mechanistic finding suggests that gemfibrozil may not be beneficial for Cln3 brain that is lacking PPARα," Pahan said. "The drug was only effective in a Cln3 brain that had PPARα.

Gemfibrozil is scheduled for clinical trial in patients with juvenile Batten disease.

"If these results are replicated in patients, it would open up a promising avenue of treatment of this devastating disease and stop the disease in its tracks," Pahan said.

More information: Malabendu Jana et al, Activation of PPARα Exhibits Therapeutic Efficacy in a Mouse Model of Juvenile Neuronal Ceroid Lipofuscinosis, *The Journal of Neuroscience* (2023). DOI: 10.1523/JNEUROSCI.2447-21.2023

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