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Commonly used seizure drug could treat severe genetic liver disease: study

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The liver scarring of [alpha]1-antitrypsin (AT) deficiency, the most common genetic cause for which children undergo liver transplantation, might be reversed or prevented with a medication that has long been used to treat seizures, according to findings from Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh School of Medicine that will published in *Science* and are available online today through the *Science Express* website.

Because the anti-seizure drug is familiar to doctors and has a well-understood safety profile, clinical trials could begin immediately to see whether it can help patients with AT deficiency, said senior author David H. Perlmutter, M.D., physician-in-chief and scientific director, Children's Hospital, and Vira I. Heinz Professor and Chair of the Department of Pediatrics, Pitt School of Medicine.

In the classic form of the disease, which affects 1 in 3,000 live births, a gene mutation leads to an abnormal protein, dubbed ATZ, that unlike its normal counterpart is prone to aggregation.

"These aggregates of ATZ accumulate in the liver cells and eventually lead to scarring, or fibrosis, of the organ and set the stage for tumor development," Dr. Perlmutter said. "The disease sometimes doesn't show itself until adulthood, when the liver starts to fail due to cirrhosis or cancer."

For the study, he and his colleagues treated an ATZ cell line with

carbamazepine, or Tegretol. Although this drug has been used primarily to treat seizure disorders, some recent work has suggested that it could enhance a natural cellular pathway called autophagy, or self-digestion, and so the Pitt researchers reasoned that it might be able to rid the cells of the toxic aggregated ATZ.

They found that carbamazepine did, indeed, cause a marked decrease in ATZ because the abnormal proteins were degraded more quickly via autophagy, and so they did another experiment in a mouse model of AT deficiency.

"The amount of ATZ decreased in the livers of the mice treated with carbamazepine," Dr. Perlmutter said. "The most amazing finding was that the drug reversed the fibrosis in the livers of the mice and, after two weeks of treatment, the liver tissue resembled that of a healthy mouse."

The ability of carbamazepine and drugs like it to "soup up" the cell's autophagy machinery might have value in other disorders — such as Alzheimer's disease, Huntington's disease and Parkinsonism — that are thought to be caused by toxic effects of protein clumping in the brain. Dr. Perlmutter and his colleagues are now exploring these possibilities in preclinical studies.

Provided by University of Pittsburgh