Cholesterol-processing enzyme protects from debilitating brain lesions

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An enzyme that helps break down cholesterol may also be a therapeutic target to stave off neurologic diseases, including Alzheimer's and a rare genetic disorder, according to a new study published in the *Journal of Biological Chemistry*. Researchers from Case Western Reserve University School of Medicine, the National Institute of Standards and Technology, and Karolinska Institute in Sweden discovered that a specific enzyme in the brain could reduce the formation of debilitating brain lesions in the two diseases. A clinical trial to test the enzyme's potential as a therapeutic target is planned for later this year.

The targeted enzyme's primary purpose is to eliminate excess cholesterol from the brain. But the researchers hypothesized it could also help remove another cholesterol-like molecule—cholestanol. Cholestanol is normally found in very low levels in the body, at least 500 times less often than cholesterol, but spikes in people with a rare, uncurable genetic disease called cerebrotendinous xanthomatosis. Patients with the disease slowly accumulate cholestanol in areas of the brain responsible for muscle coordination, causing seizures, involuntary movements, and cognitive decline. With help from the right enzymes, the debilitating accumulations could be eliminated.

"We found that an enzyme called CYP46A1 not only eliminates cholesterol but also cholestanol from the brain," said Irina Pikuleva, PhD, study lead and Professor and Vice Chair of Research in the Department of Ophthalmology and Visual Sciences at Case Western Reserve University School of Medicine. "CYP46A1 also seems to

eliminate cholestanol from many regions of the brain except the cerebellum." The findings explain why people with the rare genetic disease end up with toxic levels of cholestanol in their cerebellums specifically. Without the elimination process in that brain region, cholestanol accumulates and wreaks havoc on brain circuitry.

The discovery is a huge step forward in understanding the mechanism behind the rare genetic disease and its associated brain lesions that have perplexed doctors for decades. Said Pikuleva, "This paper establishes a biochemical basis for the preferential lesion formation in the cerebrotendinous xanthomatosis brain, a finding that nobody could explain since this disease was described by L. von Bogaert in 1937." The study is also the first to implicate the enzyme CYP46A1 in cholestanol metabolism at all, which could inform other research related to lipid storage disorders.

"Cholestanol accumulation in the body reflects an imbalance between its production and its elimination," said Pikuleva. Previous studies, by Pikuleva's study collaborator Ingemar Bjorkhem, PhD of Karolinska Institutet in Sweden, established how cholestanol is produced in the brain. In the new study, the team studied mice genetically engineered to lack enzymes involved in the process to decipher how cholestanol is eliminated. Mice in the experiments metabolized brain cholestanol at different rates in different brain regions, depending on the ratios of cholesterol- and cholestanol-processing enzymes present. Said Pikuleva, "We found there are differences in the way different brain regions eliminate cholesterol and cholestanol."

The researchers suggest that enhancing the activity of CYP46A1 in the brain pharmacologically, or finding ways to steer it closer to pockets of cholestanol could help remove the harmful accumulations. The enzyme can be activated in mice by drugs already FDA-approved, including an HIV medication called efavirenz. Pikuleva is currently developing a

clinical trial to test whether or not the HIV medication can activate CYP46A1 sufficiently in the human brain. The clinical trial is backed by the Alzheimer's Disease Drug Foundation. Said Pikuleva, "If successful, this trial will identify CYP46A1 as a new pharmacologic target not only for the treatment of people with mild cognitive impairment due to early stage Alzheimer's disease, but also for patients with cerebrotendinous xanthomatosis who do not respond to standard treatment."

More information: Natalia Mast et al, Cytochrome P450 27A1 Deficiency and Regional Differences in Brain Sterol Metabolism Cause Preferential Cholestanol Accumulation in the Cerebellum, *Journal of Biological Chemistry* (2017). DOI: 10.1074/jbc.M116.774760

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