Mouse model points to potential new treatment for Alzheimer's disease

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Treatment with an inhibitor of 12/15-lipoxygenase, an enzyme elevated in patients with Alzheimer's disease (AD), reverses cognitive decline and neuropathology in an AD mouse model, reports a new study in *Biological*

Psychiatry. The effects were observed after the AD-like phenotype was already established in the mice, which is promising for its potential therapeutic use, as neuropathology tends to develop many years before the appearance of AD symptoms in patients.

The study, by senior author Domenico Praticò and colleagues at Temple University in Philadelphia, Pennsylvania, offers some hope for a new treatment for patients with AD, who currently have no effective therapy options. Past research has focused on prevention of the disease by reducing the levels of proteins that cause brain plaques and tangles and kill nerve cells.

"In this exciting new study, the authors provide support for a new experimental treatment approach that works by helping nerve cells digest toxic proteins that might otherwise cause cell death," said John Krystal, Editor of Biological Psychiatry.

First author Antonio Di Meco and colleagues used a triple transgenic (3xTg) mouse model that displays an AD-like phenotype, including cognitive decline, and Aβ and tau neuropathology characteristic of the disease in humans. They had already shown that early administration of the 12/15-lipoxygenase inhibitor PD146176 could prevent the onset of these features in mice. To achieve a more real-world scenario in this study, they waited until the transgenic mice were a year old, when both cognitive impairments and neuropathology were established, before administering the drug.

"We show for the first time that selective pharmacologic inhibition of the 12/15-lipoxygenase enzyme rescues the entire AD-like phenotype," Praticò said.

Untreated 3xTg mice displayed impaired learning and memory as expected, but 3xTg mice that were administered PD146176 for 3 months

were indistinguishable from normal mice in a memory test. In the same mice, the researchers found that PD146176 treatment significantly reduced the levels of Aβ and insoluble tau proteins.

Inhibition of 12/15-lipoxygenase activated autophagy, the body's natural kill system for cells. The activation was associated with decreased levels of tau, suggesting that the inhibitor works by re-activating the neuronal autophagy machinery to clear cellular buildup of tau.

The results indicate that pharmacological inhibition of 12/15-lipoxygenase reverses learning and memory impairments and reduces Aβ and tau neuropathology, even after their onset in aged mice.

"Our findings have important translational value since they establish this protein enzyme as a novel and viable therapeutic target with real disease-modifying potential for AD," Praticò said.

More information: Antonio Di Meco et al. 12/15-Lipoxygenase Inhibition Reverses Cognitive Impairment, Brain Amyloidosis, and Tau Pathology by Stimulating Autophagy in Aged Triple Transgenic Mice, *Biological Psychiatry* (2017). DOI: 10.1016/j.biopsych.2016.05.023

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