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Oleic acid, a key to activating the brain's 'fountain of youth'

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Many people dread experiencing the cognitive and mood declines that often accompany reaching an advanced age, including memory disorders such as Alzheimer's disease and mood conditions like depression. While searching for new ways to prevent or treat these and other related conditions, a team at Baylor College of Medicine and the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) at Texas

Children's Hospital identified a missing piece of the puzzle of how memory and mood are sustained and regulated in the brain.

Their study, published in the *Proceedings of the National Academy of Sciences*, reveals that oleic acid produced in the brain is an essential regulator of the process that enables learning and memory and supports proper mood regulation. The finding has paved the path to discovering potential new therapeutic strategies to counteract cognitive and mood decline in patients with neurological disorders.

"Years ago, scientists thought that the adult mammalian brain was not able to repair and regenerate. But research has shown that some brain regions have the capacity of generating new neurons, a process called neurogenesis. The hippocampus region of the adult mammalian brain has the ongoing capacity to form new neurons, to repair and regenerate itself, enabling learning and memory and mood regulation during the adult life," said co-corresponding author Dr. Mirjana Maletic-Savatic, associate professor of pediatrics-neurology at Baylor and Texas Children's and an investigator at the Duncan NRI. "Ever since neurogenesis was discovered, it has been envisioned as 'the fountain of youth.' But, with increasing age, in certain diseases or after exposure to certain drugs or insults, neurogenesis decreases and this has been associated with cognitive decline and depression."

In this study, the team searched for a way to tap into the fountain of youth, to reignite the process of neurogenesis to prevent its decline or restore it.

"We knew that neurogenesis has a 'master regulator,' a protein within neural stem cells called TLX that is a major player in the birth of new neurons. We however did not know what stimulated TLX to do that. Nobody knew how to activate TLX," said co-corresponding author Dr. Damian Young, associate professor of pharmacology and chemical

biology and of pathology at Baylor and Texas Children's and member of Baylor's Dan L Duncan Comprehensive Cancer Center.

"We discovered that a common fatty acid called oleic acid binds to TLX and this increases cell proliferation and neurogenesis in the hippocampus of both young and old mice," said co-first author Dr. Prasanna Kandel, who was in the graduate program of Integrative Molecular and Biomedical Sciences at Baylor while working on this project. "This oleic acid is produced within the neural stem cells in order to activate TLX."

While oleic acid is also the major component in olive oil, however, this would not be an effective source of oleic acid because it would likely not reach the brain, the researchers explained. It must be produced by the cells themselves.

The finding that oleic acid regulates TLX activation has major therapeutic implications. "TLX has become a 'druggable' target, meaning that knowing how it is activated naturally in the brain helps us to develop drugs capable of entering the brain and stimulating neurogenesis," Young said. "This strategy could potentially be used to treat diseases such as major depressive disorders and Alzheimer's disease. This is incredibly exciting because it provides a new way of treating these debilitating diseases in need of effective treatments."

"Beside the scientific progress, I am hopeful that the current findings and ongoing related work will have real impact on people who are in need of improved and effective therapies, like my mother who suffers from clinical depression," Kandel said.

More information: Oleic acid is an endogenous ligand of TLX/NR2E1 that triggers hippocampal neurogenesis, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2023784119

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