Toxic fatty acids to blame for brain cell death after injury

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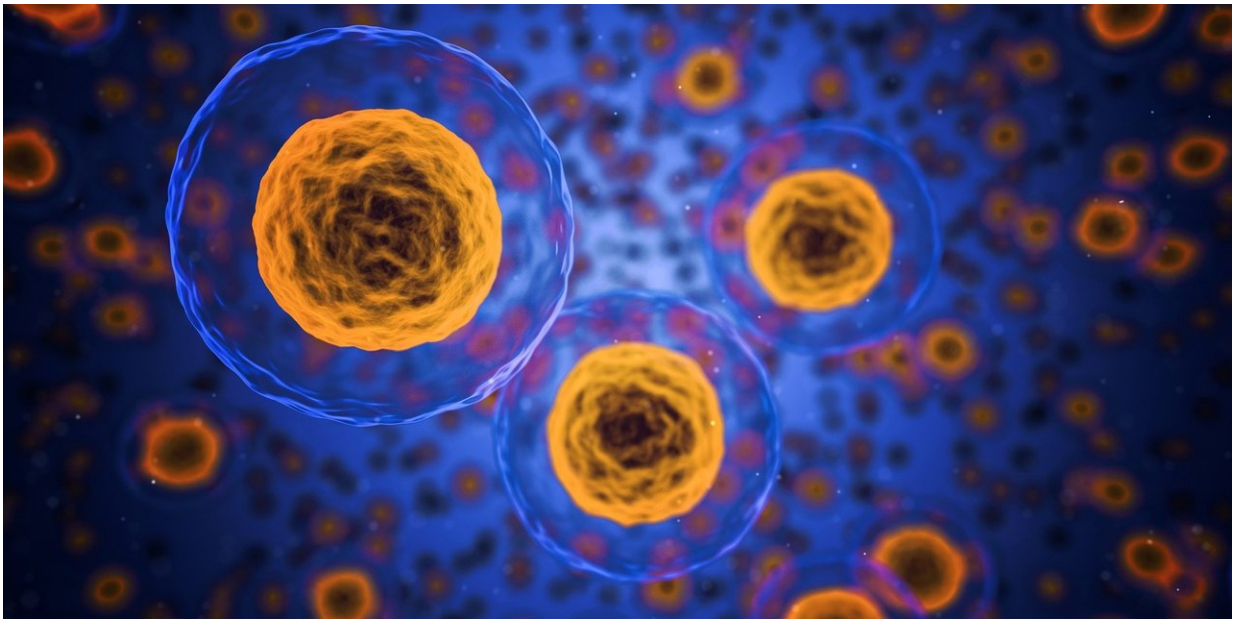

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Cells that normally nourish healthy brain cells called neurons release toxic fatty acids after neurons are damaged, a new study in rodents shows. This phenomenon is likely the driving factor behind most, if not all, diseases that affect brain function, as well as the natural breakdown of brain cells seen in aging, researchers say.

Previous research has pointed to astrocytes—a star-shaped glial cell of

the central nervous system—as the culprits behind cell death seen in Parkinson's disease and dementia, among other neurodegenerative diseases. While many experts believed that these cells released a neuron-killing molecule to "clear away" damaged brain cells, the identity of this toxin has until now remained a mystery.

Led by researchers at NYU Grossman School of Medicine, the new investigation provides what they say is the first evidence that tissue damage prompts astrocytes to produce two kinds of fats, long-chain saturated free fatty acids and phosphatidylcholines. These fats then trigger cell death in damaged neurons, the electrically active cells that send messages throughout nerve tissue.

Publishing Oct. 6 in the journal *Nature*, the study also showed that when researchers blocked fatty acid formation in mice, 75 percent of neurons survived compared with 10 percent when the fatty acids were allowed to form. The researchers' earlier work showed that brain cells continued to function when shielded from astrocyte attacks.

"Our findings show that the toxic fatty acids produced by astrocytes play a critical role in brain cell death and provide a promising new target for treating, and perhaps even preventing, many neurodegenerative diseases," says study co-senior author Shane Liddelow, Ph.D.

Liddelow, an assistant professor in the Department of Neuroscience and Physiology at NYU Langone Health, adds that targeting these fats instead of the cells that produce them may be a safer approach to treating neurodegenerative diseases because astrocytes feed nerve cells and clear away their waste. Stopping them from working altogether could interfere with healthy brain function.

Although it remains unclear why astrocytes produce these toxins, it is possible they evolved to destroy damaged cells before they can harm

their neighbors, says Liddelow. He notes that while healthy cells are not harmed by the toxins, neurons become susceptible to the damaging effects when they are injured, mutated, or infected by prions, the contagious, misfolded proteins that play a major role in mad cow disease and similar illnesses. Perhaps in chronic diseases like dementia, this otherwise helpful process goes off track and becomes a problem, the study authors say.

For the investigation, researchers analyzed the molecules released by astrocytes collected from rodents. They also genetically engineered some groups of mice to prevent the normal production of the toxic fats and looked to see whether neuron death occurred after an acute injury.

"Our results provide what is likely the most detailed molecular map to date of how tissue damage leads to brain cell death, enabling researchers to better understand why neurons die in all kinds of diseases," says Liddelow, also an assistant professor in the Department of Ophthalmology at NYU Langone.

Liddelow cautions that while the findings are promising, the genetic techniques used to block the enzyme that produces toxic fatty acids in mice are not ready for use in humans. As a result, the researchers next plan is to explore safe and effective ways to interfere with the release of the toxins in human patients. Liddelow and his colleagues had previously shown these neurotoxic astrocytes in the brains of patients with Parkinson's, Huntington's disease, and multiple sclerosis, among other diseases.

More information: Neurotoxic reactive astrocytes induce cell death via saturated lipids, *Nature* (2021). DOI: 10.1038/s41586-021-03960-y , www.nature.com/articles/s41586-021-03960-y

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