Anesthetic may affect tau spread in the brain to promote Alzheimer's disease pathology

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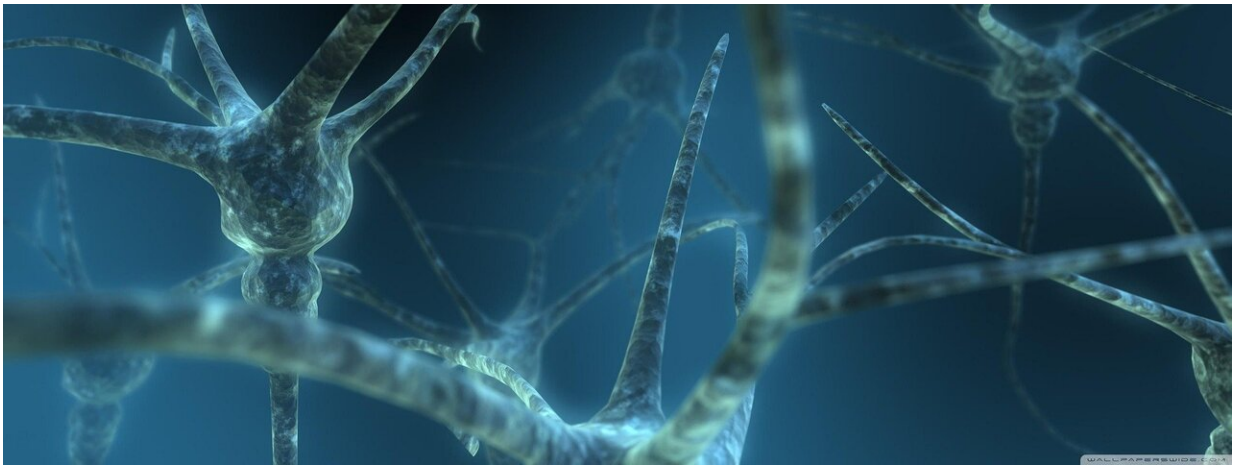

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During the development and progression of Alzheimer's disease, a protein called tau accumulates and spreads in the brain. Understanding the mechanisms behind tau spread—and its consequences—may point to new prevention and treatment strategies for Alzheimer's disease and other forms of dementia. New insights now come from research that was led by investigators at Massachusetts General Hospital (MGH) and involves an anesthetic known to affect cognitive function. The findings are published in *Communications Biology*.

The scientists note that inflammation plays an important role in

Alzheimer's disease, and microglia—immune cells that reside in the brain—are thought to be involved in this process by producing an inflammatory molecule called interleukin-6. To see if tau stimulates microglia to drive the development of Alzheimer's disease pathology, the MGH investigators and their colleagues conducted experiments with an inhaled anesthetic called sevoflurane. Their previous work showed that sevoflurane can cause a change (specifically, phosphorylation, or the addition of phosphate) to tau that leads to cognitive impairment in mice. Other researchers have also found that sevoflurane and certain other anesthetics may affect cognitive function.

In this current study, the team developed a novel method to measure tau levels, called nanobeam-sensor technology. "The nanobeam sensor is ultrasensitive, requires a small volume, and can measure low concentrations of molecules, including tau and phosphorylated tau," says co-lead author Feng Liang, MD, Ph.D., an instructor in the Department of Anesthesia, Critical Care and Pain Medicine (DACCPM) at MGH.

The group conducted experiments in mice and cells and discovered that sevoflurane causes tau to leave neurons and enter microglia, where it stimulates the cells' production of interleukin-6, which in turn leads to inflammation and cognitive impairment. The trafficking of tau from neurons to microglia involves tau phosphorylation and membrane-bound carriers called extracellular vesicles that are released from cells.

"These data demonstrate anesthesia-associated tau spreading and its consequences," says senior author Zhongcong Xie, MD, Ph.D., director of the Geriatric Anesthesia Research Unit in the DACCPM. "This tau spreading could be prevented by inhibitors of tau phosphorylation or extracellular vesicle generation."

Sevoflurane did not increase the release of lactate dehydrogenase, a molecule with a similar size and weight as tau, from neurons. "This

finding indicates that neuronal cell membranes and cell viability were not compromised by sevoflurane treatment and that the sevoflurane-induced leaking of tau was not a passive process," says co-lead author Yuanlin Dong, MD, a research fellow in the department.

Another inhaled anesthetic called desflurane did not have the same effects as sevoflurane. "Our results suggest that the anesthetics sevoflurane and desflurane may have different impacts on tau phosphorylation and tau spreading. More important, sevoflurane may be used as a clinically relevant tool to study tau spreading and its underlying mechanisms," says Xie. "We hope this work will lead to more research on anesthesia, tau proteins, and Alzheimer's disease pathology that will ultimately improve care for patients."

More information: Yuanlin Dong et al, The anesthetic sevoflurane induces tau trafficking from neurons to microglia, *Communications Biology* (2021). DOI: 10.1038/s42003-021-02047-8

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