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Common anesthetic induces Alzheimer's-associated changes in mouse brains

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For the first time researchers have shown that a commonly used anesthetic can produce changes associated with Alzheimer's disease in the brains of living mammals, confirming previous laboratory studies. In their *Annals of Neurology* report, which has received early online release, a team of Massachusetts General Hospital (MGH) investigators shows how administration of the gas isoflurane can lead to generation of the toxic amyloid-beta (A-beta) protein in the brains of mice.

"These are the first in vivo results indicating that isoflurane can set off a time-dependent cascade inducing apoptosis [cell death] and enhanced levels of the Alzheimer's-associated proteins BACE and A-beta," says Zhongcong Xie, MD, PhD, of the MassGeneral Institute for Neurodegenerative Disease (MGH-MIND) and the MGH Department of Anesthesia and Critical Care, the study's lead and corresponding author. "This work needs to be confirmed in human studies, but it's looking like isoflurane may not be the best anesthesia to use for patients who already have higher A-beta levels, such as the elderly and Alzheimer's patients."

Alzheimer's disease is characterized by deposition of A-beta plaques within the brain. The A-beta protein is formed when the larger amyloid precursor protein (APP) is clipped by two enzymes – beta-secretase, also known as BACE, and gamma-secretase – to release the A-beta fragment. Normal processing of APP by an enzyme called alpha-secretase produces an alternative, non-toxic protein.

Several studies have suggested that surgery and general anesthesia may

increase the risk of developing Alzheimer's disease, and it is well known that a small but significant number of surgical patients experience a transient form of dementia in the postoperative period. Last year the MGH team showed that applying isoflurane to cultured neural cells increased activation of the cell-death protein caspase and raised levels of BACE and gamma-secretase as part of a pathway leading to the generation of A-beta. The current study was designed to see if the same process takes place in mice.

Neurologically normal mice received isoflurane for two hours at doses comparable to what would be administered to human patients. Their brains were examined 2, 6, 12 and 24 hours after they received the anesthesia and compared with the brains of control mice. Results at 6 hours showed that caspase levels were elevated and BACE had modestly increased in mice that received isoflurane. At 12 hours moderate caspase activation persisted, and BACE levels were even higher in the treated mice; and at 24 hours BACE levels were more than four times higher than in controls, and A-beta levels had also risen, while caspase activation had fallen off.

Another group of mice had been treated for seven days with the drug clioquinol before the two-hour isoflurane administration. Laboratory studies have found that clioquinol inhibits the aggregation of A-beta into neurotoxic deposits, and a clioquinol derivative is currently in clinical trials as an Alzheimer's treatment drug. Six hours after they received isoflurane, caspase levels in the clioquinol-treated mice were significantly less than in other animals that had received the anesthetic, suggesting both that A-beta aggregation contributes to a vicious cycle of further cell death – echoing a finding from the team's 2007 study – and that a drug like clioquinol might block isoflurane's neurotoxic effects.

"This study cannot tell us about the long-term effects of isoflurane administration; that's something we will examine in future

investigations," notes Xie, who is an assistant professor of Anesthesia at Harvard Medical School (HMS) and director of the Geriatric Anesthesia Research Unit in the MGH Department of Anesthesia and Critical Care.

"Until we can directly assess the impact of isoflurane on biomarkers like A-beta levels in the plasma or cerebrospinal fluid of human patients, we cannot conclusively determine its role in increasing the risk for Alzheimer's or postoperative dementia," adds Rudolph Tanzi, PhD, director of the MGH-MIND Genetics and Aging Research Unit, senior author of the study, and the Joseph P. and Rose F. Kennedy Professor of Neurology at HMS.

Source: Massachusetts General Hospital