Study finds inhaled anesthetics accelerate the appearance of brain plaque in animals

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Researchers at the University of Pennsylvania's School of Medicine have discovered that common inhaled anesthetics increase the number of amyloid plaques in the brains of animals, which might accelerate the onset of neurodegenerative diseases like Alzheimer's. Roderic Eckenhoff, MD, Vice Chair of Research in the University of Pennsylvania's Department of Anesthesia and Critical Care, and his co-authors, report their findings in the March 7th online edition of *Neurobiology of Aging*.

Every year over 100 million people undergo surgery worldwide, most under general anesthesia with an inhaled drug. These drugs clearly affect cognitive ability at least in the short term, but the growing concern is that inhaled anesthetics may affect a person well beyond the perioperative period, even permanently. Several factors appear to play a role in this subtle loss of cognitive ability, most notably age.

A specific effect of these drugs on dementias like Alzheimer's disease, though suspected for many years, has only been recently supported by data. In 2003, Eckenhoff's group showed that the inhaled anesthetics enhance the aggregation and cytotoxicity of the amyloid beta peptide. Just last month, a study reported that these drugs also enhance the production of amyloid beta in isolated cells. But these protein and cell culture studies are a long way from showing that an effect occurs in vivo. This new study provides the first evidence that the predicted effect occurs in animals.

"This animal study data suggests that we have to at least consider the possibility that anesthetics accelerate certain neurodegenerative disorders," said Eckenhoff. "In the field of Alzheimer's research, most effort is focused on delaying, not curing the disease. A delay in the onset of Alzheimer's disease of only three to five years would be considered a success. Therefore, if commonly used drugs, like anesthetics, are accelerating this disorder, even by a few years, then a similar success might follow even small changes in the care of the operative patient."

Mice don't naturally get Alzheimer's, so the animals in this study were genetically engineered to express the human protein responsible, called amyloid beta. "These mice develop a syndrome with many features of the human disease," explains Eckenhoff. Post-doctoral fellow and first author Shannon Bianchi, MD, exposed "middle-aged" Alzheimer mice to anesthetics at low to moderate concentrations for two hours a day over a total of five days, not unusual for a clinical scenario. The cognitive abilities of the mice were then analyzed using standard behavioral tests, and their brains were examined for plaque and cell death.

"Compared to controls, the anesthesia did not appear to worsen cognitive ability, which was already considerably compromised at this age, but it did accelerate amyloid beta aggregation and plaque appearance," said corresponding author Maryellen Eckenhoff, PhD. "We need to test whether anesthetic at earlier, presymptomatic stages, might accelerate both cognitive loss and plaque." This is the main cause of concern because a large fraction of clinical patients receiving inhaled anesthetics during surgery are older, but presymptomatic individuals.

Are there anesthetics that do not accelerate plaque? "We think so, but far more research is necessary to show this with any confidence. We have to take this one step at a time – a problem has still not been demonstrated in humans". It is important to remember that this effect is likely to be subtle, especially with brief surgical procedures, so the risk

of not having needed surgery may exceed any potential risk from this still unproven effect. But this latest study adds a little urgency to the effort to find out. "If inhaled anesthetics are contributing to the rise and early onset of this devastating disease then we need to know, and soon," concludes Eckenhoff.

Source: University of Pennsylvania School of Medicine