Published in final edited form as:
Anesth Analg. 2009 May ; 108(5): 1627–1630. doi:10.1213/ane.0b013e318199dc72.

Consensus Statement:

First International Workshop on Anesthetics and Alzheimer's Disease

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Abstract

In order to review the current status of the potential relationship between anesthesia and Alzheimer's disease, a group of scientists recently met in Philadelphia for a full day of presentations and discussions. This special article represents a consensus view on the possible link between Alzheimer's disease and anesthesia and the steps required to test this more definitively.

There is growing interest in the potential relationship between anesthesia and the onset and progression of neurodegenerative disorders, including Alzheimer's disease. In an initial attempt to address and coordinate the available evidence and hypotheses, a small group of physicians and scientists was convened in May, 2008 at the University of Pennsylvania, for a full day of discussion. Out of these discussions, the following points were distilled:

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1. General anesthetics have provided immeasurable health and societal benefits for almost two centuries. Accordingly, it must be acknowledged at the outset that these benefits likely outweigh the potentially toxic effects discussed below in the vast majority of patients and procedures. The goal of research in this field is to reduce the incidence of neurodegenerative complications, if shown to exist, to the extent possible, through identification of mechanisms, patient risk factors and the use of the least provocative drugs and techniques, without losing sight of the many benefits.

2. Evidence from animal models suggests that inhaled anesthetic exposure increases pathology normally associated with Alzheimer's disease. In adult wild-type rats and mice, isoflurane exposure alone produces decrements in learning and memory that persist for weeks or months.[1-3] Associated with this is evidence in brain tissue of caspase activation,[4] increases in β-amyloid peptide and β-acting cleavage enzyme[5] and phosphorylated tau,[6,7] all of which are known contributors to Alzheimer's pathogenesis. Neurotoxicity after anesthetic exposure is also observed in the neonatal rodent[8,9] although the underlying mechanisms may be distinct from those in the adult. In transgenic models of Alzheimer's disease, halothane exposure increases β-amyloid plaque deposition,[3] and isoflurane increases tau aggregation (Planel E and Whittington R, unpublished results) but decrements in maze or motor performance compared with unexposed transgenic mice were not observed. Surgery may also produce lasting cognitive effects,[10] but this remains an under-studied problem with respect to Alzheimer pathogenesis.

3. *In vitro* studies, defined here as those using isolated proteins, cells in culture and brain slices, provide evidence that inhaled anesthetics interact with recognized pathways of neurodegeneration, and produce effects consistent with increased cellular stress.[4,5,11-15] Most of this work has been done with isoflurane, a drug still commonly used. In some cases, these changes may elicit innate and long-lived responses that protect neurons from apoptosis.[16-20] Resolving these conflicting observations is clearly of major clinical importance. A general hypothesis is that the outcome reflects a balance between induction of endogenous protective responses, the magnitude of anesthetic-induced stress and intrinsic or induced vulnerabilities. Thus, additional stresses or vulnerabilities, such as genetic, pharmacologic or substrate aberrations, could transform an ordinarily well tolerated anesthetic exposure into one that induces apoptosis or other forms of cytopathology.

4. Potential mechanisms for the proposed acceleration of Alzheimer's neuropathology include, at a minimum, neuronal calcium dysregulation *via*, for example, altered ryanodine or IP3 receptor gating, increased amyloid β production and aggregation, and tau phosphorylation and aggregation. Any of these and other effects might be triggered through a single or a few upstream events (e.g., calcium influx), or may represent multiple anesthetic interactions at many points along the diverse pathways. Although mechanistic studies may yield important clues for therapeutic exploitation in the future, the Consensus Group attached a higher priority to first determining the presence and magnitude of anesthetic-induced long-term neurobehavioral effects, preferably in humans.

5. Although rank order effects for their amyloidogenic potential for a range of inhaled anesthetics are available,[11] few *in vitro* or *in vivo* studies have directly compared different general anesthetics, and no human data comparing anesthetic effects on Alzheimer pathways have been reported. Until now, most data have involved isoflurane, but limited data on IV anesthetics are available.[21] Since one strategy for minimizing neurotoxicity is choosing the least provocative drugs, there is a strong need for rank-order potency data. Such data, if including more receptor-specific drugs,

may yield important mechanistic clues in addition to the more immediately applicable clinical relevance.

6. Hypothermia causes tau hyperphosphorylation in animals.[6] Given the involvement of tau phosphorylation in Alzheimer's disease, and the frequency of deliberate or unintended hypothermia in the perioperative period, work on hypothermia as an independent risk factor for Alzheimer's disease or dementia in humans after surgery seems warranted.

7. Whether exposure to anesthetics and surgery at a young age carries implications for cognition later in life has not been examined in clinical studies. In adult humans, postoperative cognitive decline (POCD) is now well described,[22-27] although the etiology, mechanism, time course, and ultimate outcome are as yet unclear. Risk factors for POCD may overlap with those for Alzheimer's disease, although shared mechanisms remain conjectural. Available human studies on anesthesia and Alzheimer's disease are inconclusive because they are under-powered or confounded by coincident illness, independent risk factors for dementia and, of course, surgery.[28-31] Whether coronary artery bypass surgery is associated with a higher risk of Alzheimer's disease remains controversial,[30,31] but POCD and dementia are more common after cardiac surgery than after major noncardiac surgery.[25] Although dementia and Alzheimer's disease are associated with vascular disease,[32,33] there are no data linking them to perioperative events (hypotension, hypoxemia). However, no correlation of such events with POCD has been detected.[22] Prospective studies show that off-pump coronary artery bypass surgery patients receiving total IV anesthesia develop a pattern of cerebrospinal fluid biomarkers (β-amyloid and tau) reminiscent of Alzheimer's disease several months after surgery.[34] There is a strong need for both adequately powered prospective and retrospective studies of the risk of Alzheimer's disease in humans after surgery. All databases with multiple years of individual patient data (e.g., Medicare, Veterans Administration, etc) are candidates for close examination. Moreover, because of the inseparability of anesthesia and surgery in clinical settings, and the debatable correspondence of animal models to neurodegeneration to the human disorder, the need for human studies of anesthesia in the absence of surgery is strongly indicated.

8. Workshop participants agreed that because of the slowly progressive nature of neurodegenerative diseases, like Alzheimer's disease, advanced neuropathology in the absence of symptoms, limited long-term follow-up by anesthesiologists and surgeons and the social stigmata surrounding the diagnosis, acceleration of Alzheimer's disease after anesthesia and surgery may have escaped our collective attention. Given the available evidence, the possibility that anesthetics and surgery may have long-term cognitive effects should be taken seriously, particularly in patients at risk for neurodegenerative conditions. The group strongly agreed, however, that scientists and physicians working and publishing in this area have a responsibility to be objective and candid about the limitations surrounding the clinical implications of their work, particularly with *in vitro* and animal models, as well as with small or retrospective clinical studies.

In summary, there is sufficient evidence at multiple levels to warrant further and more definitive investigations of the onset and progression of Alzheimer's disease and neurodegeneration after anesthesia and surgery. These studies should exploit all appropriate models but emphasize humans whenever possible. Anesthesiologists, working in collaboration with neuroscientists, epidemiologists, and others with relevant expertise, should lead this effort.

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