Special Article

Anesthesia and the Old Brain

Junxia Tang, PhD
Maryellen F. Eckenhoff, PhD
Roderic G. Eckenhoff, MD

The perioperative period may have long-term consequences on cognitive function in the elderly patient. In this special article, we summarize the rationale and evidence that the anesthetic *per se* is a contributor. The evidence at this point is considered suggestive and further research is needed, especially in humans.
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The intricacy and durability of neuronal networks and the relative paucity of progenitor cells render the brain especially vulnerable to the ravages of time. In addition, a variety of disorders, some intrinsic and some environmental, enhance age-associated deterioration to the point where the brain no longer functions normally, behaviorally manifest as "dementia." Dementia currently afflicts more than 25 million people worldwide.[1] It is a health concern of monumental proportion, because people afflicted not only lose their own productivity and independence, but also require continual care in a ratio approaching 1:1, further reducing societal productivity. As the lifespan increases as a result of better hygiene, food, and health care, the fraction of people with, and caring for, dementia therefore is expected to grow exponentially. For example, it is estimated that more than 100 million people will have Alzheimer disease (AD) dementia by 2050.[1] This is truly a health issue of epidemic stature, and without an end in sight.

NEURODEGENERATIVE DISORDERS

AD is the major form of dementia in the elderly. Age is the primary risk factor; over the age of 85 yr, the incidence is about 50%.[1] The causes of AD are likely to be multifactorial, including a host of genetic predispositions and environmental contributors. Most genetic predispositions center around a few cellular pathways. First is the amyloid pathway. Mutations in the amyloid precursor protein (APP) enhance the production of a small series of proteins called the amyloid-betas (Aβ). These soluble, unstable proteins, ranging in size from 38 to 42 residues, when exceeding some solubility threshold, begin to self-associate and form a variety of oligomeric states. The role of these various states in the neuropathology remains a hotly contested topic, but a consensus seems to be emerging that the small oligomers of 10–20 monomers produce neuronal or synaptic damage, whereas the large assemblies of many thousands of monomers are a sequestered pool of very stable and less toxic material.[2,3] This latter pool typically results in senile plaque, a hallmark lesion of AD, along with a host of other inflammatory and protective proteins, such as the heat shock series.

The mechanisms by which Aβ solubility is exceeded are important for our consideration of anesthetics, so a brief discussion is warranted. Aβ peptide levels can be increased through decreases in clearance or scavenging (e.g., ApoEϵ4 genotype)[4,5] or increases in production. Increases in production can occur via enhanced activity or expression of the enzyme, β-site acting cleavage enzyme, or enhanced vulnerability to proteolytic cleavage via APP mutations (e.g., the Swedish mutation—APP_{Swe}).[6,7] In Down syndrome, caused by trisomy 21, amyloidopathy is thought to occur via overproduction of APP, because it resides on chromosome 21.[8] Much recent work has focused on these issues, but in general, such genetic vulnerabilities account for a small number of the AD cases. Less focus has been placed on the factors that control the solubility of Aβ. For example, chemicals could bind oligomers and favor their formation, or the levels of factors that normally enhance solubility of the monomer might be reduced. In either case, levels of Aβ that would normally be soluble and therefore nontoxic are rendered insoluble and begin to oligomerize into disease-causing moieties.

From the Department of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

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Address correspondence and reprint requests to Roderic G. Eckenhoff, MD, Department of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, 305 John Morgan Bldg., 3620 Hamilton Walk, Philadelphia, PA 19104. Address e-mail to roderic.eckenhoff@uphs.upenn.edu.

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The other hallmark lesion of AD is the intracellular neurofibrillary tangle (NFT), composed primarily of the protein tau. In contrast to Aβ or its parent APP, whose normal function is not yet clear, the normal function of tau is known. Dephosphorylated tau binds tightly to microtubules and is thought to provide stability for normal microtubule function. When phosphorylated, tau detaches and becomes cytoplasmic.[9] In pathological conditions, tau can become abnormally hyperphosphorylated, resulting in 2 detrimental outcomes. First, microtubules may become destabilized and disrupted, and second, the hyperphosphorylated tau self-associates to produce a structure known as paired helical filaments, which ultimately form NFTs.[10,11] Whether the NFTs cause cellular dysfunction through interference with trafficking, or whether the lack of microtubule stabilization via depletion of tau causes dysfunction is not yet clear. It is clear that tauopathy alone contributes to dementia, because in frontotemporal lobar degeneration and Parkinsonism linked to chromosome 17, and perhaps others, the tauopathy is not accompanied by amyloidopathy.[12,13] Nevertheless, there is an interaction between amyloidopathy and tauopathy, indicating that the degree of dysfunction is not strictly additive.[14,15]

Although amyloidopathy and tauopathy are the major histological features of AD, there continues to be controversy as to the underlying mechanism of disease. For example, there is emerging evidence that the presenilin mutations give rise to early AD and are associated with calcium dysregulation.[16] Presenilin may be either a calcium channel itself[17] or a modulator of IP3 channels,[18] a major calcium release pathway for the endoplasmic reticulum. The presenilin mutations associated with early onset AD cause excessive calcium release, triggering apoptosis cascades.[16,19] Calcium dysregulation has long been associated with neuronal injury and apoptosis, and it might be the upstream initiator of neurodegeneration in AD and related dementias.[20]

Finally, there are a host of other factors related in still unclear ways to AD and dementia. These include oxidant injury, iron (and other metals) metabolism, dysfunction in the ubiquitin proteasome system, inflammation, and cholesterol homeostasis. These other factors have served to both confuse the field as to the most important underlying contributors to disease, and at the same time present a group of sites along the pathway where intervention may modulate the course of disease. Certainly, it has led to the appreciation of the multifactorial nature of AD.

Other Neurodegenerative Diseases

Although AD is the most prevalent of the dementias, there are others that have similar features and may have similar underlying mechanisms, at least on a biophysical level. These include Parkinson disease, Huntington disease, vascular dementia, and the prion diseases (Creutzfeldt-Jakob and mad cow).[21,22] Each is age related, slowly progressive, and associated with an accumulation of intracellular aggregated protein, although the affected proteins, brain sites, and constellation of symptoms differ. Each, however, is associated with dementia, usually late in the progression of disease. It is beyond the scope of this brief review to cover each in detail; they are mentioned because the similarity may indicate a similar interaction with anesthetics.

ANESTHETIC EFFECTS

As mentioned above, environmental factors may play a role in the onset of dementias. One pervasive environmental factor is drug exposure. For example, certain antibiotics are thought to enhance the pathogenesis, whereas anti-inflammatory and cholinergic drugs may decrease it. Most people receive general anesthetics at some point during their lives, and we and others have proposed that these drugs may contribute to the pathogenesis of neurodegenerative diseases.[22–24] Inhaled general anesthetics are highly lipid soluble and are low affinity, hence they rapidly access the brain in high concentrations. Furthermore, they are promiscuous, acting on many receptors, ion channels (such as *N*-methyl-D-aspartate receptors and γ-aminobutyric acid type A receptors), second messenger systems, enzymes, and even cytoskeletal components. At the organism level, they affect not only consciousness but also hemodynamics, thermal balance, ventilatory control, and possibly immune function. Thus, it is not unreasonable to expect that these drugs may have deleterious effects on brain function. Indeed, postoperative cognitive dysfunction (POCD) is a common complication in the early weeks after surgery and anesthesia.[25–28] Specific domains of cognition are affected, especially memory, and it seems to be associated with increased mortality.[28,29] Whether or not POCD is reversible is still unclear, and whether it is associated with the anesthesia or surgery remains controversial.

Is anesthesia associated with AD or other neurodegenerative diseases? It is interesting to note that POCD has similar risk factors as AD (age, educational level, and apoEϵ4 genotype),[28] but a definitive link among surgery, anesthesia, and AD remains elusive. Several small retrospective studies have examined the interaction between prior surgery or exposure to anesthesia and subsequent AD but produced inconsistent results in support of[30,31] or against a significant association.[32–34] However, most of these studies were underpowered, and many of the negative reports still showed a positive odds ratio for an association. It is interesting to note that anesthesiologists die from Parkinson disease at a significantly higher rate than matched internists.[35] Thus, the relationship among anesthesia, surgery, and AD or other dementias at the human level remains inconclusive.

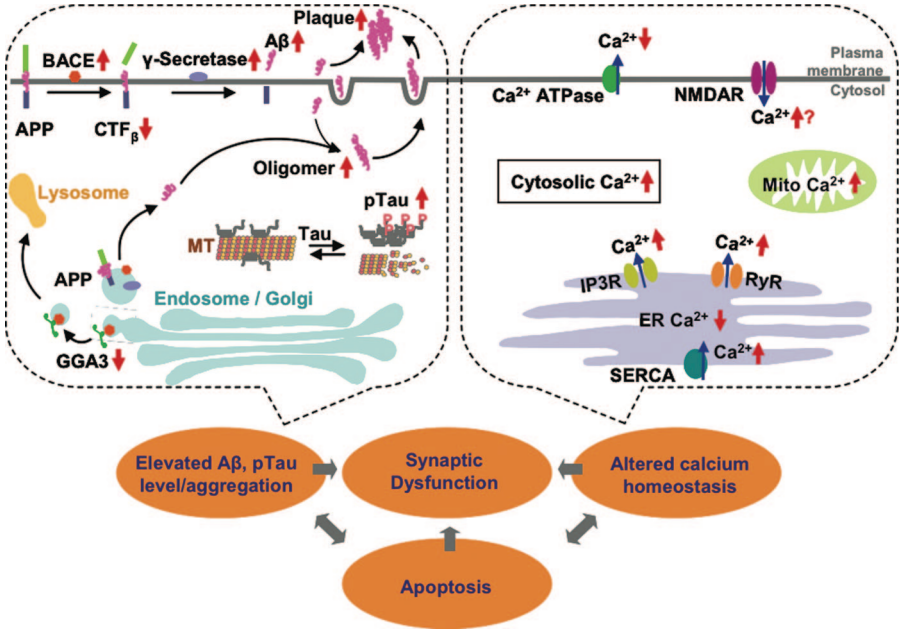

Figure 1. Possible mechanisms by which inhaled anesthetics, through increasing intracellular amyloid-β (Aβ) level, and Aβ and tau aggregation, and/or disruption of intracellular calcium homeostasis, could induce synaptic dysfunction and neuronal apoptosis and ultimately produce cognitive decline in the aged brain. In the amyloid and tau pathway, on the left, β-site amyloid precursor protein (APP)-cleaving enzyme (BACE) generates c-terminal fragments (CTF_β) from membrane bound APP. Cleavage of CTF_β by γ-secretase releases Aβ monomers into the cytosolic and extracellular space. Anesthetic exposure increases the levels of BACE[23,52,53] and γ-secretase,[52] thereby increasing the levels of intracellular Aβ[51–53] and decreasing CTF_β levels.[51,53] Inhaled anesthetics also interact with the Aβ monomers to promote the formation of small soluble oligomers.[41,43] These oligomers further associate to form fibrils and extracellular plaque, which have been found to be increased in mice with transgenic Alzheimer disease (AD) after exposure to halothane.[38] These effects activate caspase, initiating apoptosis,[53,55] and cleaving the adaptor protein GGA3, which is required for BACE lysosomal degradation. This results in increased BACE levels, further enhancing the production of Aβ,[23] and introducing a viscous cycle that ensures apoptosis. Microtubule (MT) bound tau becomes hyperphosphorylated and detached by anesthetics and hypothermia, resulting in tau aggregates and decreased MT stability.[40,56] On the right side of the figure, anesthetics increase cytosolic calcium via several mechanisms. For example, inhaled anesthetics activate the endoplasmic reticulum (ER) membrane inositol 1,4,5-trisphosphate receptors (IP3R)[47–49] and ryanodine receptors (RyR),[55] increasing cytosolic calcium and depleting ER calcium. These drugs also activate the sarcoplasmic/ER calcium adenosine triphosphatase (ATPase) (SERCA1)[50,57] further enhancing the activity of ER calcium release pathways. Further increases in cytosolic calcium levels might be caused by activation of *N*-methyl-D-aspartate receptors,[50] and inhibition of calcium clearance via plasma membrane calcium ATPase.[58] Increased cytosolic calcium loads the mitochondria with calcium,[49] releasing cytochrome c, further contributing to apoptosis. Finally, ER calcium depletion via the above mechanisms can induce apoptosis directly.[16,49] Both the Aβ/tau and calcium pathways contribute to synaptic dysfunction and apoptotic responses.

Animal models may provide an alternative way to enhance the power and examine the influence of anesthesia and surgery independently. Furthermore, they allow the exploration of potential mechanisms by which these features of the perioperative experience may accelerate the pathogenesis of AD. Thus, there is mounting laboratory evidence for a detrimental effect of anesthetic exposure in adult rodents. For example, cognitive dysfunction lasting weeks to months after anesthetic exposure has been clearly identified in wild-type mice and rats.[36–38] Furthermore, exposure of wild-type mice to modest concentrations of isoflurane resulted in caspase-3 activation (a marker for initiation of apoptosis) and increased levels of β-site APP-cleaving enzyme and Aβ mice up to 24 h later.[23] In adolescent or middle-aged rodents, less effect on cognitive function attributable to the anesthetic has been noted.[36,39] Thus, it may be that the elderly brain demonstrates enhanced vulnerability to mild insults.

Because wild-type rodents do not develop AD neuropathology, transgenic mouse models are used. In the Tg2576 mice, which harbor the human APP-Swedish mutation, increased Aβ plaque deposits were observed 3 wk after exposure to halothane[38] and in transgenic mice expressing a mutant human tau transgene, anesthesia-induced hypothermia increased tau hyperphosphorylation and aggregation.[40] These results from transgenic animals suggest that anesthesia may indeed enhance the underlying neuropathology in individuals with a genetic predisposition to AD.

There are several potential mechanisms that might underlie the delayed effects of general anesthetics on cognitive function and AD (Fig. 1). The initial, proposed molecular mechanism is a biophysical enhancement of Aβ oligomerization.[41] Inhaled anesthetics are now known to bind and stabilize protein complexes with interfacial hydrophobic cavities.[42] Indeed, *in vitro* experiments showed that inhaled anesthetics can

interact with Aβ and promote its oligomerization[41,43] and enhance the cytotoxicity of this AD-associated protein in cell culture.[41] The small, soluble oligomers that anesthetics seem to favor are now thought to be the Aβ species responsible for synaptic dysfunction, apoptosis, and neurodegeneration.[44,45] Other studies have identified increased intracellular calcium levels that are triggered by anesthetics as another possible mechanism for the neurotoxicity of general anesthetics in the aged brain.[24] Isoflurane enhances the activity of the endoplasmic reticulum ryanodine receptor[46] and, more recently, has been shown to activate the membrane bound IP3 receptor, both actions producing excessive calcium release and triggering apoptosis in cells.[47] Neurons with enhanced IP3 receptor activity, as in the familial form of AD, may be more susceptible to the cytotoxic effects of isoflurane.[47,48] Furthermore, there is a rank order of effect among inhaled anesthetics, with halothane and isoflurane having greater potency for cytotoxicity than sevoflurane or desflurane.[41,49] The inhibition of this calcium influx by IP3, ryanodine receptor, or *N*-methyl-D-aspartate receptor antagonists[47,50] prevents the isoflurane-induced capsase-3 activation and apoptosis. Isoflurane[51,52] and desflurane combined with hypoxia[53] have also been shown to enhance capsase-3 activation and apoptosis, as well as increased Aβ production in APP and presenilin PS1 transfected cell lines.[48,52] Aβ itself causes an increase in intracellular calcium concentrations and calcium-mediated neurotoxicity[16] and, thus, it is not surprising that, if anesthetics increase Aβ and intracellular calcium concentrations, this will enhance neurotoxicity. These findings also suggest that patients with increased Aβ levels could be more vulnerable to isoflurane-induced neurotoxicity.

Anesthesia is rarely given without an associated painful procedure such as surgery, and yet the influence of surgery itself has received little attention. A recent report found that surgery plus anesthesia produced worse POCD than anesthesia alone in animals.[54] The mechanism for an effect due to surgery *per se* remains unclear, but the possibilities are strong given that inflammatory cascades, microglia activation, and immune function are strongly implicated in both surgery and neurodegeneration.

Thus, although the overall impact on brain function remains unclear, it appears that anesthetics interact with AD neuropathology at multiple levels and points in the involved pathways. This is in keeping with the promiscuity of these compounds and suggests the need for further studies to develop rational protection schemes for those unavoidably requiring general anesthesia. Furthermore, it suggests the need for better anesthetics with reduced promiscuity.

FUTURE DIRECTIONS

If the perioperative experience is contributing to the dementia burden and loss of independence in our elderly, then it is crucial that we identify it quickly. Experiments in proteins, cells, and animals will not accomplish this. Studies in humans and with human data must be implemented immediately.

The most straightforward means of getting a rapid estimation of the potential magnitude of an effect of surgery and anesthesia on dementia is to carefully interrogate and analyze large patient databases. The most logical start in the United States would be the Medicare database. Although limited in quality and depth, this database is large and captures hospital care (e.g., surgery), diagnoses (e.g., dementia), and medications (e.g., Aricept) for all those older than 65 yr. Because of enormous numbers, many careful controls and matches can be performed, making it likely that we can answer the question of whether surgery is associated with dementia. This approach seems unlikely to provide false negative associations, but false positives would need further study to determine which of the many features surrounding the perioperative experience is contributing. Other databases (e.g., Veteran's Administration) might possess greater granularity and therefore allow more definitive queries. This work is considered of greatest priority because of the speed and avoidance of further risks.

Biomarker and imaging studies in humans hold great promise of specifically addressing the hypotheses in a prospective manner in smaller numbers of patients. For example, careful examination of cerebrospinal fluid Aβ and tau in patients before and after surgery, and with different anesthetics, may provide useful information on dynamics and magnitude of changes in the appropriate neurobiologic pathway. Blood and urine biomarkers (e.g., isoprostanes) are considered less reliable and specific but may add to such investigations. Most exciting are the emerging imaging tools. For example, the ^{11}C-labeled Pittsburgh compound B is hypothesized to label a relatively stable pool of amyloid plaque. Thus, positron emission tomographic scanning pre- and postoperatively may allow estimation of an anesthetic or surgical effect on this material. Also, 2-deoxyglucose use has been found to correlate with neurodegeneration and may also provide an index of surgery-induced changes on a more rapid and functional level. Finally, magnetic resonance images of more structural features, such as hippocampal volume, may provide a more long-term look at the effect of prior surgery.

We are aware of very early forays into several of these areas, which suggest that answers to the question of whether the perioperative experience contributes to neurodegeneration should be forthcoming in the near future.

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