Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2013 December ; 47: . doi:10.1016/j.pnpbp.2012.08.002.

General anesthetics and β -amyloid protein

Zhongcong Xie, M.D., Ph.D.* [Associate Professor] and Zhipeng Xu, M.D., Ph.D.

Geriatric Anesthesia Research Unit, Department of Anesthesia, Critical Care, and Pain Medicine
Massachusetts General Hospital Harvard Medical School 149 13th Street, Room 4310
Charlestown, MA 02129

Abstract

With roughly 234 million people undergoing surgery with anesthesia each year worldwide, it is important to determine whether commonly used anesthetics can induce any neurotoxicity. Alzheimer's disease (AD) is the most common form of age-related dementia, and a rapidly growing health problem. Several studies suggest that anesthesia could be associated with the development of AD. Moreover, studies in cultured cells and animals show that commonly used inhalation anesthetics may induce changes consistent with AD neuropathogenesis, e.g., β -amyloid protein accumulation. Therefore, in this mini review, we focus on the recent research investigating the effects of commonly used anesthetics including isoflurane, sevoflurane, desflurane, nitrous oxide, and propofol, on A β accumulation *in vitro* and *in vivo*. We further discuss the future direction of the research determining the effects of anesthetics on β -amyloid protein accumulation.

Introduction

General anesthetics have been used clinically for over one hundred and sixty years (Buxton, 1912). Each year, there are about 234 million people in the world who will have surgery under anesthesia. Aging is one of the major risk factors for Alzheimer's disease (AD) with an AD incidence of 13% in people over 65 years of age (Alzheimer's Association. Alzheimer's Disease Facts and Figures. Chicago, IL: Alzheimer's Association; 2011. http://www.alz.org/downloads/Facts_Figures_2011.pdf). Globally, about 66 million patients over the age of 65 have surgery under anesthesia each year. Taken together, there are approximately 8.5 million (13% of 66 million) AD patients who will need anesthesia care every year. AD, an irreversible and progressive brain disease, affects approximately 5.4 million Americans and there are about 36 million AD patients in the world (Alzheimer's Association. Alzheimer's Disease Facts and Figures. Chicago, IL: Alzheimer's Association; 2011. http://www.alz.org/downloads/Facts_Figures_2011.pdf). AD slowly destroys brain function, leading to cognitive decline (e.g., memory loss, language difficulty and poor executive function), behavioral and psychiatric disorders (e.g., depression, delusions and agitation), and decline in functional status (e.g., ability to engage in activities of daily living and self-care). Previous studies have shown that the age of AD onset is inversely related to cumulative exposure to anesthesia and surgery before age 50 (Bohnen et al., 1994a), although anesthesia and surgery may not increase the incidence of AD (Bohnen et al.,

© 2012 Elsevier Inc. All rights reserved.

* Address correspondence to: Zhongcong Xie, M.D., Ph.D., Associate Professor of Anesthesia, Geriatric Anesthesia Research Unit, Department of Anesthesia, Critical Care and Pain Medicine; Massachusetts General Hospital and Harvard Medical School; 149 13th St., Room 4310; Charlestown, MA 02129-2060. (T) 617-724-9308; (F) 617-643-9277; zxie@partners.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1994b). Several recent studies have also suggested that anesthesia may contribute to the development of AD (Bufill et al., 2009; Lee et al., 2005). Finally, Tang et al. have shown that the changes in human cerebrospinal fluid levels of tau and cytokines following anesthesia and surgery are consistent with those found in AD patients (Tang et al., 2011). However, other studies have suggested different findings, and that anesthesia and surgery may not contribute to AD development (Avidan et al., 2009; Gasparini et al., 2002; Knopman et al., 2005). Therefore, more population studies defining the role of anesthesia in AD development are necessary (Harris and Eger, 2008).

Given that it is clinically difficult to either prove or disprove the relationship between anesthesia and AD at the present time, and that the prospective clinical studies may take many years to conduct and analyze, it is equally important to conduct pre-clinical studies on anesthesia neurotoxicity and AD neuropathogenesis. These studies will likely establish a mechanistic hypothesis, vulnerable age windows, less provocative anesthetics, and potential treatments, which may facilitate and guide more focused and uniform clinical research. This mini review describes and discusses the studies assessing the effects of commonly used anesthetics, including isoflurane, sevoflurane, desflurane, nitrous oxide, and propofol, on the processing of amyloid precursor protein (APP) and metabolism of β -amyloid protein (A β), one of the main features of AD neuropathogenesis.

APP processing and A β metabolism

A β , the key component of senile plaques in AD patients (Goate et al., 1991; Masters et al., 1985; Selkoe et al., 1988), was first isolated from meningovascular amyloid deposits in AD and Down syndrome patients (Glennner and Wong, 1984a; Goate et al., 1991). Genetic evidence, confirmed by neuropathological and biochemical findings, indicates that excessive production and/or accumulation of A β plays a fundamental role in the pathology of AD [reviewed by (Selkoe, 2001; Tanzi and Bertram, 2005)]. The amyloid hypothesis of AD, based on these studies, was first proposed by Glennner and Wong (Glennner and Wong, 1984b) and has been further supported by many other AD researchers since [reviewed in (Bertram and Tanzi, 2008; Selkoe, 2001)]. The amyloid hypothesis states that the imbalance between A β generation and A β clearance leads to A β accumulation, one of the molecular features of AD neuropathogenesis.

A β is produced from its large precursor protein APP by sequential proteolytic cleavage through two proteases, α -site APP-cleaving enzyme (BACE) or β -secretase and γ -secretase. Through APP trafficking, the protein undergoes a variety of proteolytic cleavage to release secreted derivatives into vesicle lumens and the extracellular space. First, APP is hydrolyzed in the extracellular domain, either between Met671 and Asp672 or between residues 682 and 683, by aspartyl protease BACE. BACE is a type I transmembrane and glycosylated aspartyl protease that is found in post-Golgi membranes and at the cell surface (Hussain et al., 1999; Sinha and Lieberburg, 1999; Vassar et al., 1999; Yan et al., 1999). The BACE cleavage of APP generates an ectodomain derivative (α -APPs), and retains a 99-residue membrane-associated C-terminus fragment (APP-C99) in the membrane. Then, APP-C99 is further cleaved to release 4-kDa A β and β -amyloid precursor protein intracellular domain (AICD). This cleavage is an unusual form of proteolysis because the protein is cleaved within the transmembrane domain (at residue +40 or +42) by β -secretase (Gu et al., 2001; Sastre et al., 2001; Yu et al., 2001). γ -Secretase, a detergent-sensitive, high molecular weight complex (Li et al., 2000), consists of at least four proteins, presenilin 1/presenilin 2, nicastrin, anterior pharynx-defective 1 (APH-1), and PEN-2 (presenilin enhancer 2) [(Edbauer et al., 2003; Francis et al., 2002; Steiner et al., 2002; Yu et al., 2000), reviewed in (De Strooper, 2003)] (Figure 1).

APP can also be cleaved by another secretase, γ -secretase, at a site close to the transmembrane domain and in the middle of the A β region of APP. This γ -secretase-mediated cleavage of APP releases a large soluble ectodomain (γ -APPs) into the lumen/extracellular space to retain a carboxy-terminus fragment of 83 amino acids (APP-C83) in the membrane. APP-C83 is then cleaved by α -secretase to form p3, an amino-terminally truncated form of A β (Esch et al., 1990; Sisodia et al., 1990), reviewed in (Wolfe, 2003). Therefore, more γ -secretase-mediated cleavage of APP could lead to a lower production of A β .

A β can be metabolized, and its metabolites are less neurotoxic (Miners et al., 2008). Insulin degrading enzyme (IDE) and neprilysin are among the enzymes involved in A β degradation [(Bates et al., 2009; Eckman and Eckman, 2005; Higuchi et al., 2005; Miners et al., 2008; Wang et al., 2006); reviewed in (Qiu and Folstein, 2006)]. Neprilysin is a 90 - 110 kDa plasma membrane glycoprotein of the neutral zinc metalloendopeptidase family (Turner et al., 2000; Turner et al., 2001; Turner and Tanzawa, 1997) that has been shown to cleave A β 40 more than A β 42 (Kanemitsu et al., 2003). IDE, a zinc metalloendopeptidase, is a single polypeptide with a molecular weight of 110 kDa (Affholter et al., 1990). IDE degrades a wide range of substrates including A β (McDermott and Gibson, 1997; Perez et al., 2000; Qiu et al., 1998).

A β can form oligomers through aggregation. A β oligomers are more toxic than A β monomers, leading to synaptic dysfunction and neuronal damage (Ashe and Zahs, 2010; Sakono and Zako, 2010). Inhibition of A β oligomerization has been suggested to be a potential target for preventing and treating AD (Ashe and Zahs, 2010; Sakono and Zako, 2010).

Effects of anesthetics on A β levels

Isoflurane

One of the milestones in the study of anesthesia neurotoxicity was the finding of Dr. Eckenhoff et al. in 2004. Using light scattering, filtration assays, electron microscopy, fluorescence spectroscopy, and size-exclusion chromatography, Eckenhoff et al. found that the inhalation anesthetics isoflurane and halothane enhanced A β oligomerization *in vitro* and potentiated A β -induced cytotoxicity in rat pheochromocytoma cells (Eckenhoff et al., 2004). In 2008, the same group reported that halothane anesthesia led to greater amyloidopathy than either the isoflurane anesthesia or control condition in 12 month-old AD transgenic mice (Tg2576) (Bianchi et al., 2008). Isoflurane impaired learning and memory in wild-type (WT) mice (Bianchi et al., 2008). These findings indicate that inhaled anesthetics may affect cognition and amyloidogenesis *in vivo*, but the mechanistic relationship remains unclear (Bianchi et al., 2008).

In 2006, Xie et al. studied the effects of isoflurane on apoptosis, APP processing, and A β levels in H4 human neuroglioma cells stably transfected to express human full-length APP. They reported that treatment with 2% isoflurane for six hours induced caspase-3 activation, cell death, reduction in levels of APP-c-terminal fragment (CTF), and accumulation of extracellular levels of A β in the cells (Xie et al., 2006). Interestingly, the increases in the levels of APP-CTF following γ -secretase inhibitor N-[N-(3,5-difluorophenacetyl)-L-alanyl]- (S)-phenylglycine t-butyl ester (DAPT) led to the potentiation of isoflurane-induced caspase-3 activation in the cells (Xie et al., 2006). However, all of these studies were carried out in a tumor cell line, therefore, it is necessary to determine the *in vivo* relevance (e.g., mice) of these findings in cultured cells.

In 2008, the same group determined the effects of isoflurane on caspase activation and A β levels in the brain tissues of 5 month-old WT mice (Xie et al., 2008). They found that anesthesia with 1.4% isoflurane for two hours induced caspase-3 activation and modest increases in BACE levels 6 hours after the anesthesia. The isoflurane anesthesia only induced modest caspase-3 activation 12 hours after the anesthesia, but it led to a more robust increase in BACE levels. Finally, the isoflurane anesthesia caused a greater increase in BACE levels and A β accumulation in the mouse brain tissues, but without significant caspase-3 activation, at 24 hours post-anesthesia. Mechanistically, isoflurane might increase BACE levels by reducing BACE degradation. Moreover, the A β aggregation inhibitor clioquinol attenuated the isoflurane-induced caspase-3 activation in the brain tissues of mice (Xie et al., 2008). Taken together, these findings suggest that isoflurane may cause neurotoxicity by inducing caspase activation and apoptosis, and increasing A β accumulation *in vitro* and *in vivo*.

In another study using both wild-type and AD transgenic mice, Perucho et al. compared the effects of isoflurane anesthesia between wild-type mice and AD transgenic mice (A β PP_[swe] mice). They treated 7 month-old mice with 2% isoflurane for 20 minutes, twice a week for three months. They found that the isoflurane anesthesia led to apoptosis, increased microglia activation, increased A β levels and increased A β aggregation in the brain tissues of AD transgenic mice, but not in wild-type mice (Perucho et al., 2010). These data suggest that AD transgenic mice could be more susceptible to developing the neurotoxic effects than WT mice following isoflurane anesthesia.

Given the findings that isoflurane induces both caspase activation and apoptosis, and increases A β accumulation, it is important to understand whether there is any mechanistic relationship between the isoflurane-induced caspase activation, apoptosis, and A β accumulation. Thus, Xie et al. performed mechanistic studies in the naïve H4 human neuroglioma cells and H4 human neuroglioma cells stably transfected to express human full-length APP (Xie et al., 2007). They found that treatment with 2% isoflurane for six hours induced caspase-3 activation and decreased cell viability without significant alterations in the levels of full length APP, APP-CTF, and A β in the naïve H4 human neuroglioma cells. These results suggested that isoflurane might induce caspase activation and apoptosis independent of alterations in APP processing and A β levels. Then, they found that Z-VAD, a caspase inhibitor, attenuated the isoflurane-induced caspase activation, apoptosis, APP processing, and A β accumulation in H4 human neuroglioma cells stably transfected to express human full-length APP. These data suggested that the isoflurane-induced APP processing and A β accumulation were dependent on the isoflurane-induced caspase activation and apoptosis. In addition, they found that isoflurane might increase the levels of BACE and γ -secretase component nicastrin, and that the A β aggregation inhibitors iA β 5 and clioquinol mitigated the isoflurane-induced caspase-3 activation. Finally, they showed that A β potentiated the isoflurane-induced caspase activation. Collectively, these findings suggest a potential pathway of isoflurane neurotoxicity; that isoflurane induces caspase activation and apoptosis, which increases the levels of BACE and γ -secretase, promoting APP process and A β generation. The generated A β may further potentiate the isoflurane-induced caspase activation and apoptosis. This conclusion is also supported by the findings from a recent study, which showed that a reduction in the levels of BACE and A β attenuated the isoflurane-induced caspase activation (Dong et al., 2011).

In the follow-up studies, Zhang et al. found that isoflurane may induce caspase activation and A β accumulation via enhancing cytosolic calcium levels (Zhang et al., 2008b), and isoflurane may induce caspase activation and apoptosis through a mitochondria-dependent pathway of apoptosis (Zhang et al., 2010). In a recent study, Zhang et al. showed that isoflurane increased generation of reactive oxygen species, which caused mitochondrial

damage by opening the mitochondrial permeability transition pore, reducing the mitochondria membrane potential, decreasing ATP levels, inducing caspase activation and apoptosis, and finally leading to the impairment of learning and memory (Zhang et al., 2012b). The mitochondrial permeability transition pore inhibitor cyclosporine A inhibited the isoflurane-induced opening of the mitochondrial permeability transition pore *in vitro*, as well as the isoflurane-induced learning and memory impairment in mice (Zhang et al., 2012b). These findings elucidated, at least partially, the up-stream mechanisms of the isoflurane-induced caspase activation, apoptosis and A β generation.

The genes encoding the APP, presenilin-1 and presenilin-2 have been shown to harbor autosomal dominant AD gene, and the gene APOE-4 is a risk factor of AD (Bertram and Tanzi, 2008). A study by Liang et al. showed that neurons with one of the presenilin-1 mutations were susceptible to the isoflurane-induced cytotoxicity and elevation of cytosolic calcium levels (Liang et al., 2008). Pending further studies, these results suggest that patients with AD gene mutations could be at an increased risk to develop anesthesia-induced neurotoxicity.

Despite these findings that isoflurane may induce neurotoxicity, there have been many reports that isoflurane may protect against neurotoxicity (de Klaver et al., 2002; Gray et al., 2005; Kawaguchi et al., 2004; Li et al., 2008; Raphael et al., 2008; Tyther et al., 2001; Wise-Faberowski et al., 2004; Wise-Faberowski et al., 2001; Xu et al., 2008; Zaugg et al., 2000). Importantly, isoflurane's protection effects have been shown to be dose- and time-dependent. For example, Lee et al. showed that 2% isoflurane might provide protective effects when the treatment time was 20 or 30 minutes. The protective effects disappeared when the isoflurane treatment time was 60 minutes (Lee et al., 2008). Similarly, treatments with 1.5% and 2.0% isoflurane for 30 minutes had protective effects; treatment with 2.5% and 3.0% isoflurane did not (Lee et al., 2008). These results suggest that isoflurane may have concentration- and duration-dependent protection effects. Wei et al. also found that treatment with isoflurane (0.6%, 1.2%, and 2.4%) for one hour dose-dependently inhibited the neurotoxicity induced by 2.4% isoflurane for 24 hours in rat primary cortical neurons and rat pheochromocytoma neurosecretory cells (Wei et al., 2007). Xie's group also found that treatment with 2% isoflurane for either six hours or 30 minutes potentiated, whereas treatment with 0.5% isoflurane for either six hours or 30 minutes mitigated, the A β -induced caspase-3 activation and apoptosis in H4 human neuroglioma cells and mouse primary neurons (Xu et al., 2011). In the mouse studies, anesthesia with 1.4% isoflurane for two hours potentiated, whereas anesthesia with 0.7% isoflurane for 30 minutes attenuated, the A β -induced caspase-3 activation in the brain tissues of wild-type mice. These dual effects of isoflurane on A β neurotoxicity could be due to isoflurane's dual effects on Bcl-2/Bax ratio and cytosolic calcium levels (Xu et al., 2011). The same group has also found the dual effects of isoflurane on hypoxia-induced neurotoxicity (Pan et al., 2011). Collectively, it is conceivable that isoflurane, and perhaps other anesthetics, can have dual effects, induction or potentiation versus attenuation, of neurotoxicity in a dose- and time-dependent manner.

Sevoflurane

Sevoflurane is currently the most commonly used inhalation anesthetic. In 2009, Dong et al. showed that treatment with 4.1% sevoflurane for six hours induced caspase activation and apoptosis, increased BACE levels, reduced levels of APP-C99 and APP-C83, and finally enhanced A β levels in H4 human neuroglioma cells stably transfected to express human full-length APP (Dong et al., 2009). Then, Dong et al. found that Z-VAD, a caspase inhibitor, attenuated the sevoflurane-induced caspase activation, APP processing and A β accumulation in the cells (Dong et al., 2009). Finally, A β potentiated the sevoflurane-induced caspase-3 activation in H4 human neuroglioma cells, whereas the reduction in A β generation by β -secretase inhibitor L-685,458 attenuated the sevoflurane-induced caspase-3 activation (Dong

et al., 2009). These findings suggest that sevoflurane can induce caspase activation and apoptosis, which enhance BACE levels, promote APP processing, and increase A β generation. A β then potentiates the sevoflurane-induced caspase activation and apoptosis (Dong et al., 2009). In the *in vivo* studies, Dong et al. showed that anesthesia with 2.5% sevoflurane for 2 hours induced caspase activation and increased levels of BACE and A β in the brain tissues of 5 month-old WT mice 6, 12, and 24 hours after the anesthesia (Dong et al., 2009).

In another study, Lu et al. assessed the effects of sevoflurane in young mice and found that anesthesia with 3% or 2.1% sevoflurane for six hours induced caspase activation and apoptosis in the brain tissues of six-day old mice (Lu et al., 2010). Moreover, anesthesia with 3% sevoflurane for six hours induced a greater degree of caspase activation in the brain tissues of AD transgenic mice [(B6.Cg-Tg[APP^{swe},PSEN1^{dE9}]85Dbo/J)] than in those of WT mice. The sevoflurane anesthesia increased A β levels in the brain tissues of six-day-old mice (Lu et al., 2010). Finally, the sevoflurane anesthesia increased levels of pro-inflammatory cytokine tumor-necrosis factor (TNF)- α only in the brain tissues of the AD transgenic mice (Lu et al., 2010). Taken together, these data suggest that sevoflurane can increase brain A β levels even in neonatal mice, and that A β may potentiate the sevoflurane-induced neurotoxicity in developing brain (Lu et al., 2010).

Desflurane

Desflurane, another halogenated ether, is a newer inhalation anesthetic. In an early study, Zhang et al. found that, in contrast to isoflurane and sevoflurane, treatment with a clinically relevant concentration (12%) of desflurane for six hours did not cause caspase-3 activation, APP processing, and A β generation in H4 human neuroglioma cells stably transfected to express human full-length APP (Zhang et al., 2008a). These data were consistent with other studies in human lymphocyte cells that isoflurane and sevoflurane, but not desflurane, induced apoptosis (Loop et al., 2005). In the follow up studies, Zhang et al. found that the desflurane treatment (12% for six hours) did not induce the mitochondria-dependent pathway of apoptosis in primary neurons, whereas isoflurane did (Zhang et al., 2010). Moreover, in a recent study, Zhang et al. found that desflurane, in contrast to isoflurane, did not induce mitochondrial damage in cultured cells and mouse primary neurons, and did not induce caspase activation in both primary neurons and brain tissues of mice. Finally desflurane did not induce learning and memory impairment in mice (Zhang et al., 2012b). A recent pilot human study demonstrated that desflurane might not induce a decline in cognitive function, whereas isoflurane might (Zhang et al., 2012a).

Nitrous Oxide

Nitrous oxide is an anesthetic gas used for years in human medicine and dentistry. Zhen et al. performed studies in H4 human neuroglioma cells and mouse primary neurons. They found that treatment with 70% nitrous oxide for six hours induced neither apoptosis nor A β accumulation in the cells and neurons (Zhen et al., 2009). Similarly, treatment with 1% isoflurane for six hours did not cause apoptosis or A β accumulation. However, the combination of 70% nitrous oxide and 1% isoflurane induced caspase activation, apoptosis, and A β accumulation in the cells and neurons (Zhen et al., 2009).

Collectively, these findings suggest that among the commonly used inhalation anesthetics, nitrous oxide and desflurane may be safer anesthetics than isoflurane and sevoflurane in regards to affecting APP processing and increasing A β accumulation, pending further studies. Future studies are needed to determine the *in vivo* relevance of these *in vitro* findings, and to assess whether nitrous oxide and desflurane will not (or to lesser degree)

enhance the AD neuropathogenesis and cognitive dysfunction as compared to isoflurane and sevoflurane in humans.

Propofol

As early as 2005, Palotas et al. investigated the effects of propofol on APP processing in rats (Palotas et al., 2005). They found that propofol did not significantly affect the protein and mRNA levels of APP in the brain tissues of rats (Palotas et al., 2005). These data suggest that propofol may not promote AD neuropathogenesis. In a recent study, Zhang et al. investigated the effects of propofol on isoflurane-induced caspase-3 activation and isoflurane-induced A β aggregation *in vitro* and *in vivo* (Zhang et al., 2011). They found that propofol specifically attenuated the isoflurane-induced caspase-3 activation in H4 human neuroglioma cells stably transfected to express human full-length APP, and in the brain tissues of AD transgenic mice [(B6.Cg-Tg[APP^{swe},PSEN1^{dE9}]85Dbo/J)] (with higher A β levels). But the attenuation effects of propofol on the isoflurane-induced caspase-3 activation occurred in neither naïve H4 human neuroglioma cells nor the brain tissues of wild type mice (with lower A β levels). Moreover, propofol attenuated the isoflurane-induced oligomerization of A β 42, but not A β 40, in H4 human neuroglioma cells overexpressed A β 40 or A β 42. These data suggest that isoflurane may induce caspase activation and apoptosis by enhancing A β 42 oligomerization. Furthermore, propofol inhibited the isoflurane-induced A β 42 oligomerization, therefore attenuating the isoflurane-induced caspase activation (Zhang et al., 2011).

Future studies

Some anesthetics, e.g., isoflurane and sevoflurane, may increase A β accumulation. However, almost all the studies thus far have been focusing on the assessment of anesthetics on A β generation. Reduction in A β degradation also contributes to A β accumulation. Therefore, future studies should include the assessment of the effects of anesthetics on levels and activities of IDE and neprilysin, the enzymes of A β degradation. These studies would demonstrate the underlying mechanisms by which anesthetics cause A β accumulation – increases in generation and/or decreases in degradation of A β .

Several studies suggest that anesthetics may cause A β generation through caspase activation and apoptosis (Dong et al., 2009; Xie et al., 2007; Zhen et al., 2009). Consequently, it is important to understand the up-stream mechanisms by which anesthetics induce caspase activation and apoptosis. It has been shown that anesthetics may induce caspase activation and apoptosis by causing mitochondrial damage and reduction of ATP (Zhang et al., 2010; Zhang et al., 2012b). However, the mechanisms by which anesthetics can cause mitochondrial damage remain to be determined, and future studies are warranted.

Given the different profiles of anesthetics on neurotoxicity, e.g., A β accumulation, future studies should include the determination and comparison of the effects of commonly used anesthetics, e.g., isoflurane, sevoflurane, desflurane, nitrous oxide and propofol, on AD neuropathogenesis and cognitive function in humans to assess which anesthetics do not (or to a lesser degree) induce AD neuropathogenesis and cognitive dysfunction.

It is also warranted to determine the underlying mechanisms by which different anesthetics, e.g., isoflurane versus desflurane, have different effects on caspase activation, apoptosis, and A β accumulation. The results from these studies may eventually lead to targeted approaches to prevent or treat the anesthesia neurotoxicity.

Finally, surgery has been shown to affect APP processing and to increase A β levels in the brain tissues of mice (Wan et al., 2010). Given the findings that anesthetics can increase A β

accumulation, it is important to understand whether anesthetics, e.g., isoflurane, can have a synergistic effect with surgery on A β accumulation, leading to more severe cognitive dysfunction.

Conclusion

In the past, the combined efforts of the anesthesia and cardiac specialties created a guideline for safer anesthesia care of coronary artery disease (CAD) patients. Anesthesia and surgery have been reported to induce cognitive dysfunction, to which AD patients are susceptible. Thus, it is necessary for anesthesia, neurology, and other specialties to develop guidelines to providing safer anesthesia care for AD patients (e.g., to avoid worsening of cognitive dysfunction potentially induced by anesthesia). As the first step, we need to identify anesthetic(s) that will not (or to a lesser degree) enhance caspase activation, apoptosis, A β accumulation, and cognitive dysfunction. This opinion has been emphasized in both the AD and anesthesia research fields (Baranov et al., 2009).

This mini review has summarized the recent studies regarding the effects of the commonly used anesthetics isoflurane, sevoflurane, desflurane, nitrous oxide and propofol on levels of A β , the hallmark of AD neuropathogenesis, *in vitro* and *in vivo* (Table 1). The results from these studies suggest that isoflurane and sevoflurane may induce caspase activation and apoptosis, leading to promotion of APP processing and A β generation in cultured cells, primary neurons, and the brain tissues of mice. Desflurane, nitrous oxide and propofol, on other hand, may not increase A β generation. Therefore, these studies serve as parts of the first step toward the development of a guideline of anesthesia care for AD patients. Moreover, these studies build upon fundamentals for further research in anesthesia neurotoxicity.

References

- Affholter JA, Hsieh CL, Francke U, Roth RA. Insulin-degrading enzyme: stable expression of the human complementary DNA, characterization of its protein product, and chromosomal mapping of the human and mouse genes. *Mol Endocrinol*. 1990; 4:1125–1135. [PubMed: 2293021]
- Ashe KH, Zahs KR. Probing the biology of Alzheimer's disease in mice. *Neuron*. 2010; 66:631–645. [PubMed: 20547123]
- Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, Xiong C, Grant EA, Kaiser D, Morris JC, Evers AS. Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. *Anesthesiology*. 2009; 111:964–970. [PubMed: 19786858]
- Baranov D, Bickler PE, Crosby GJ, Culley DJ, Eckenhoff MF, Eckenhoff RG, Hogan KJ, Jevtovic-Todorovic V, Palotas A, Perouansky M, et al. Consensus statement: First International Workshop on Anesthetics and Alzheimer's disease. *Anesth Analg*. 2009; 108:1627–1630. [PubMed: 19372347]
- Bates KA, Verdile G, Li QX, Ames D, Hudson P, Masters CL, Martins RN. Clearance mechanisms of Alzheimer's amyloid-beta peptide: implications for therapeutic design and diagnostic tests. *Mol Psychiatry*. 2009; 14:469–486. [PubMed: 18794889]
- Bertram L, Tanzi RE. Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. *Nat Rev Neurosci*. 2008; 9:768–778. [PubMed: 18802446]
- Bianchi SL, Tran T, Liu C, Lin S, Li Y, Keller JM, Eckenhoff RG, Eckenhoff MF. Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics. *Neurobiol Aging*. 2008; 29:1002–1010. [PubMed: 17346857]
- Bohnen N, Warner MA, Kokmen E, Kurland LT. Early and midlife exposure to anesthesia and age of onset of Alzheimer's disease. *Int J Neurosci*. 1994a; 77:181–185. [PubMed: 7814211]
- Bohnen NI, Warner MA, Kokmen E, Beard CM, Kurland LT. Alzheimer's disease and cumulative exposure to anesthesia: a case-control study. *J Am Geriatr Soc*. 1994b; 42:198–201. [PubMed: 8126336]

- Bufill E, Bartes A, Moral A, Casadevall T, Codinachs M, Zapater E, Carles Rovira J, Roura P, Oliva R, Blesa R. [Genetic and environmental factors that may influence in the senile form of Alzheimer's disease: nested case control studies]. *Neurologia*. 2009; 24:108–112. [PubMed: 19322689]
- Buxton DW. Crawford Williamson Long (1815-1879): the Pioneer of Anaesthesia and the first to suggest and employ Ether Inhalation during Surgical Operations. *Proc R Soc Med*. 1912; 5:19–45.
- de Klaver MJ, Manning L, Palmer LA, Rich GF. Isoflurane pretreatment inhibits cytokine-induced cell death in cultured rat smooth muscle cells and human endothelial cells. *Anesthesiology*. 2002; 97:24–32. [PubMed: 12131100]
- De Strooper B. Aph-1, Pen-2, and Nicastrin with Presenilin Generate an Active gamma-Secretase Complex. *Neuron*. 2003; 38:9–12. [PubMed: 12691659]
- Dong Y, Xu Z, Zhang Y, McAuliffe S, Wang H, Shen X, Yue Y, Xie Z. RNA interference-mediated silencing of BACE and APP attenuates the isoflurane-induced caspase activation. *Med Gas Res*. 2011; 1:5. [PubMed: 22146340]
- Dong Y, Zhang G, Zhang B, Moir RD, Xia W, Marcantonio ER, Culley DJ, Crosby G, Tanzi RE, Xie Z. The common inhalational anesthetic sevoflurane induces apoptosis and increases beta-amyloid protein levels. *Arch Neurol*. 2009; 66:620–631. [PubMed: 19433662]
- Eckenhoff RG, Johansson JS, Wei H, Carnini A, Kang B, Wei W, Pidikiti R, Keller JM, Eckenhoff MF. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiology*. 2004; 101:703–709. [PubMed: 15329595]
- Eckman EA, Eckman CB. Abeta-degrading enzymes: modulators of Alzheimer's disease pathogenesis and targets for therapeutic intervention. *Biochem Soc Trans*. 2005; 33:1101–1105. [PubMed: 16246055]
- Edbauer D, Winkler E, Regula JT, Pesold B, Steiner H, Haass C. Reconstitution of gamma-secretase activity. *Nat Cell Biol*. 2003; 5:486–488. [PubMed: 12679784]
- Esch FS, Keim PS, Beattie EC, Blacher RW, Culwell AR, Oltersdorf T, McClure D, Ward PJ. Cleavage of amyloid beta peptide during constitutive processing of its precursor. *Science*. 1990; 248:1122–1124. [PubMed: 2111583]
- Francis R, McGrath G, Zhang J, Ruddy DA, Sym M, Apfeld J, Nicoll M, Maxwell M, Hai B, Ellis MC, et al. aph-1 and pen-2 are required for Notch pathway signaling, gamma-secretase cleavage of betaAPP, and presenilin protein accumulation. *Dev Cell*. 2002; 3:85–97. [PubMed: 12110170]
- Gasparini M, Vanacore N, Schiaffini C, Brusa L, Panella M, Talarico G, Bruno G, Meco G, Lenzi GL. A case-control study on Alzheimer's disease and exposure to anesthesia. *Neurol Sci*. 2002; 23:11–14. [PubMed: 12111615]
- Glenner GG, Wong CW. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. *Biochem Biophys Res Commun*. 1984a; 122:1131–1135. [PubMed: 6236805]
- Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun*. 1984b; 120:885–890. [PubMed: 6375662]
- Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature*. 1991; 349:704–706. [PubMed: 1671712]
- Gray JJ, Bickler PE, Fahlman CS, Zhan X, Schuyler JA. Isoflurane neuroprotection in hypoxic hippocampal slice cultures involves increases in intracellular Ca²⁺ and mitogen-activated protein kinases. *Anesthesiology*. 2005; 102:606–615. [PubMed: 15731600]
- Gu Y, Misonou H, Sato T, Dohmae N, Takio K, Ihara Y. Distinct intramembrane cleavage of the beta-amyloid precursor protein family resembling gamma-secretase-like cleavage of Notch. *J Biol Chem*. 2001; 276:35235–35238. [PubMed: 11483588]
- Harris RA, Eger EI 2nd. Alzheimer's disease and anesthesia: out of body, out of mind...or not? *Ann Neurol*. 2008; 64:595–597. [PubMed: 19107997]
- Higuchi M, Iwata N, Saido TC. Understanding molecular mechanisms of proteolysis in Alzheimer's disease: progress toward therapeutic interventions. *Biochim Biophys Acta*. 2005; 1751:60–67. [PubMed: 16054018]

- Hussain I, Powell D, Howlett DR, Tew DG, Meek TD, Chapman C, Gloger IS, Murphy KE, Southan CD, Ryan DM, et al. Identification of a novel aspartic protease (Asp 2) as beta-secretase. *Mol Cell Neurosci.* 1999; 14:419–427. [PubMed: 10656250]
- Kanemitsu H, Tomiyama T, Mori H. Human neprilysin is capable of degrading amyloid beta peptide not only in the monomeric form but also the pathological oligomeric form. *Neurosci Lett.* 2003; 350:113–116. [PubMed: 12972166]
- Kawaguchi M, Drummond JC, Cole DJ, Kelly PJ, Spurlock MP, Patel PM. Effect of isoflurane on neuronal apoptosis in rats subjected to focal cerebral ischemia. *Anesth Analg.* 2004; 98:798–805. table of contents. [PubMed: 14980940]
- Knopman DS, Petersen RC, Cha RH, Edland SD, Rocca WA. Coronary artery bypass grafting is not a risk factor for dementia or Alzheimer disease. *Neurology.* 2005; 65:986–990. [PubMed: 16217048]
- Lee JJ, Li L, Jung HH, Zuo Z. Postconditioning with isoflurane reduced ischemia-induced brain injury in rats. *Anesthesiology.* 2008; 108:1055–1062. [PubMed: 18497606]
- Lee TA, Wolozin B, Weiss KB, Bednar MM. Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. *J Alzheimers Dis.* 2005; 7:319–324. [PubMed: 16131734]
- Li L, Peng L, Zuo Z. Isoflurane preconditioning increases B-cell lymphoma-2 expression and reduces cytochrome c release from the mitochondria in the ischemic penumbra of rat brain. *Eur J Pharmacol.* 2008
- Li YM, Lai MT, Xu M, Huang Q, DiMuzio-Mower J, Sardana MK, Shi XP, Yin KC, Shafer JA, Gardell SJ. Presenilin 1 is linked with gamma-secretase activity in the detergent solubilized state. *Proc Natl Acad Sci U S A.* 2000; 97:6138–6143. [PubMed: 10801983]
- Liang G, Wang Q, Li Y, Kang B, Eckenhoﬀ MF, Eckenhoﬀ RG, Wei H. A presenilin-1 mutation renders neurons vulnerable to isoflurane toxicity. *Anesth Analg.* 2008; 106:492–500. table of contents. [PubMed: 18227305]
- Loop T, Dovi-Akue D, Frick M, Roesslein M, Egger L, Humar M, Hoetzel A, Schmidt R, Borner C, Pahl HL, et al. Volatile anesthetics induce caspase-dependent, mitochondria-mediated apoptosis in human T lymphocytes in vitro. *Anesthesiology.* 2005; 102:1147–1157. [PubMed: 15915027]
- Lu Y, Wu X, Dong Y, Xu Z, Zhang Y, Xie Z. Anesthetic sevoflurane causes neurotoxicity differently in neonatal naive and Alzheimer disease transgenic mice. *Anesthesiology.* 2010; 112:1404–1416. [PubMed: 20460993]
- Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc Natl Acad Sci U S A.* 1985; 82:4245–4249. [PubMed: 3159021]
- McDermott JR, Gibson AM. Degradation of Alzheimer's beta-amyloid protein by human and rat brain peptidases: involvement of insulin-degrading enzyme. *Neurochem Res.* 1997; 22:49–56. [PubMed: 9021762]
- Miners JS, Baig S, Palmer J, Palmer LE, Kehoe PG, Love S. Abeta-degrading enzymes in Alzheimer's disease. *Brain Pathol.* 2008; 18:240–252. [PubMed: 18363935]
- Palotas M, Palotas A, Bjelik A, Pakaski M, Hugyecz M, Janka Z, Kalman J. Effect of general anesthetics on amyloid precursor protein and mRNA levels in the rat brain. *Neurochem Res.* 2005; 30:1021–1026. [PubMed: 16258851]
- Pan C, Xu Z, Dong Y, Zhang Y, Zhang J, McAuliffe S, Yue Y, Li T, Xie Z. The potential dual effects of anesthetic isoflurane on hypoxia-induced caspase-3 activation and increases in beta-site amyloid precursor protein-cleaving enzyme levels. *Anesth Analg.* 2011; 113:145–152. [PubMed: 21519046]
- Perez A, Morelli L, Cresto JC, Castano EM. Degradation of soluble amyloid beta-peptides 1-40, 1-42, and the Dutch variant 1-40Q by insulin degrading enzyme from Alzheimer disease and control brains. *Neurochem Res.* 2000; 25:247–255. [PubMed: 10786709]
- Perucho J, Rubio I, Casarejos MJ, Gomez A, Rodriguez-Navarro JA, Solano RM, De Yebenes JG, Mena MA. Anesthesia with isoflurane increases amyloid pathology in mice models of Alzheimer's disease. *J Alzheimers Dis.* 2010; 19:1245–1257. [PubMed: 20308791]

- Qiu WQ, Folstein MF. Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. *Neurobiol Aging*. 2006; 27:190–198. [PubMed: 16399206]
- Qiu WQ, Walsh DM, Ye Z, Vekrellis K, Zhang J, Podlisny MB, Rosner MR, Safavi A, Hersch LB, Selkoe DJ. Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. *J Biol Chem*. 1998; 273:32730–32738. [PubMed: 9830016]
- Raphael J, Zuo Z, Abedat S, Beeri R, Gozal Y. Isoflurane preconditioning decreases myocardial infarction in rabbits via up-regulation of hypoxia inducible factor 1 that is mediated by mammalian target of rapamycin. *Anesthesiology*. 2008; 108:415–425. [PubMed: 18292679]
- Sakono M, Zako T. Amyloid oligomers: formation and toxicity of Abeta oligomers. *FEBS J*. 2010; 277:1348–1358. [PubMed: 20148964]
- Sastre M, Steiner H, Fuchs K, Capell A, Multhaup G, Condron MM, Teplow DB, Haass C. Presenilin-dependent gamma-secretase processing of beta-amyloid precursor protein at a site corresponding to the S3 cleavage of Notch. *EMBO Rep*. 2001; 2:835–841. [PubMed: 11520861]
- Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev*. 2001; 81:741–766. [PubMed: 11274343]
- Selkoe DJ, Podlisny MB, Joachim CL, Vickers EA, Lee G, Fritz LC, Oltersdorf T. Beta-amyloid precursor protein of Alzheimer disease occurs as 110- to 135-kilodalton membrane-associated proteins in neural and nonneural tissues. *Proc Natl Acad Sci U S A*. 1988; 85:7341–7345. [PubMed: 3140239]
- Sinha S, Lieberburg I. Cellular mechanisms of beta-amyloid production and secretion. *Proc Natl Acad Sci U S A*. 1999; 96:11049–11053. [PubMed: 10500121]
- Sisodia SS, Koo EH, Beyreuther K, Unterbeck A, Price DL. Evidence that beta-amyloid protein in Alzheimer's disease is not derived by normal processing. *Science*. 1990; 248:492–495. [PubMed: 1691865]
- Steiner H, Winkler E, Edbauer D, Prokop S, Basset G, Yamasaki A, Kostka M, Haass C. PEN-2 is an integral component of the gamma-secretase complex required for coordinated expression of presenilin and nicastrin. *J Biol Chem*. 2002; 277:39062–39065. [PubMed: 12198112]
- Tang JX, Baranov D, Hammond M, Shaw LM, Eckenhoff MF, Eckenhoff RG. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. *Anesthesiology*. 2011; 115:727–732. [PubMed: 21857497]
- Tanzi RE, Bertram L. Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. *Cell*. 2005; 120:545–555. [PubMed: 15734686]
- Turner AJ, Brown CD, Carson JA, Barnes K. The neprilysin family in health and disease. *Adv Exp Med Biol*. 2000; 477:229–240. [PubMed: 10849750]
- Turner AJ, Isaac RE, Coates D. The neprilysin (NEP) family of zinc metalloendopeptidases: genomics and function. *Bioessays*. 2001; 23:261–269. [PubMed: 11223883]
- Turner AJ, Tanzawa K. Mammalian membrane metallopeptidases: NEP, ECE, KELL, and PEX. *FASEB J*. 1997; 11:355–364. [PubMed: 9141502]
- Tyther R, Fanning N, Halligan M, Wang J, Redmond HP, Shorten G. The effect of the anaesthetic agent isoflurane on the rate of neutrophil apoptosis in vitro. *Ir J Med Sci*. 2001; 170:41–44. [PubMed: 11440412]
- Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, et al. Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science*. 1999; 286:735–741. [PubMed: 10531052]
- Wan Y, Xu J, Meng F, Bao Y, Ge Y, Lobo N, Vizcaychipi MP, Zhang D, Gentleman SM, Maze M, Ma D. Cognitive decline following major surgery is associated with gliosis, beta-amyloid accumulation, and tau phosphorylation in old mice. *Crit Care Med*. 2010
- Wang DS, Dickson DW, Malter JS. beta-Amyloid degradation and Alzheimer's disease. *J Biomed Biotechnol*. 2006; 2006:58406. [PubMed: 17047308]
- Wei H, Liang G, Yang H. Isoflurane preconditioning inhibited isoflurane-induced neurotoxicity. *Neurosci Lett*. 2007; 425:59–62. [PubMed: 17723266]
- Wise-Faberowski L, Aono M, Pearlstein RD, Warner DS. Apoptosis is not enhanced in primary mixed neuronal/glia cultures protected by isoflurane against N-methyl-D-aspartate excitotoxicity. *Anesth Analg*. 2004; 99:1708–1714. table of contents. [PubMed: 15562059]

- Wise-Faberowski L, Raizada MK, Sumners C. Oxygen and glucose deprivation- induced neuronal apoptosis is attenuated by halothane and isoflurane. *Anesth Analg*. 2001; 93:1281–1287. [PubMed: 11682415]
- Wolfe MS. The secretases of Alzheimer's disease. *Curr Top Dev Biol*. 2003; 54:233–261. [PubMed: 12696752]
- Xie Z, Culley DJ, Dong Y, Zhang G, Zhang B, Moir RD, Frosch MP, Crosby G, Tanzi RE. The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid beta-protein level in vivo. *Ann Neurol*. 2008; 64:618–627. [PubMed: 19006075]
- Xie Z, Dong Y, Maeda U, Alfilie P, Culley DJ, Crosby G, Tanzi RE. The common inhalation anesthetic isoflurane induces apoptosis and increases amyloid beta protein levels. *Anesthesiology*. 2006; 104:988–994. [PubMed: 16645451]
- Xie Z, Dong Y, Maeda U, Moir RD, Xia W, Culley DJ, Crosby G, Tanzi RE. The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid beta-protein accumulation. *J Neurosci*. 2007; 27:1247–1254. [PubMed: 17287498]
- Xu X, Feng J, Zuo Z. Isoflurane preconditioning reduces the rat NR8383 macrophage injury induced by lipopolysaccharide and interferon gamma. *Anesthesiology*. 2008; 108:643–650. [PubMed: 18362596]
- Xu Z, Dong Y, Wu X, Zhang J, McAuliffe S, Pan C, Zhang Y, Ichinose F, Yue Y, Xie Z. The potential dual effects of anesthetic isoflurane on A β -induced apoptosis. *Curr Alzheimer Res*. 2011; 8:741–752. [PubMed: 21244349]
- Yan R, Bienkowski MJ, Shuck ME, Miao H, Tory MC, Pauley AM, Brashier JR, Stratman NC, Mathews WR, Buhl AE, et al. Membrane-anchored aspartyl protease with Alzheimer's disease beta-secretase activity. *Nature*. 1999; 402:533–537. [PubMed: 10591213]
- Yu C, Kim SH, Ikeuchi T, Xu H, Gasparini L, Wang R, Sisodia SS. Characterization of a presenilin-mediated amyloid precursor protein carboxyl-terminal fragment gamma. Evidence for distinct mechanisms involved in gamma -secretase processing of the APP and Notch1 transmembrane domains. *J Biol Chem*. 2001; 276:43756–43760. [PubMed: 11583985]
- Yu G, Nishimura M, Arawaka S, Levitan D, Zhang L, Tandon A, Song YQ, Rogaeva E, Chen F, Kawai T, et al. Nicastrin modulates presenilin-mediated notch/glp-1 signal transduction and betaAPP processing. *Nature*. 2000; 407:48–54. [PubMed: 10993067]
- Zaugg M, Jamali NZ, Lucchinetti E, Shafiq SA, Siddiqui MA. Norepinephrine-induced apoptosis is inhibited in adult rat ventricular myocytes exposed to volatile anesthetics. *Anesthesiology*. 2000; 93:209–218. [PubMed: 10861165]
- Zhang B, Dong Y, Zhang G, Moir RD, Xia W, Yue Y, Tian M, Culley DJ, Crosby G, Tanzi RE, Xie Z. The inhalation anesthetic desflurane induces caspase activation and increases amyloid beta-protein levels under hypoxic conditions. *J Biol Chem*. 2008a; 283:11866–11875. [PubMed: 18326038]
- Zhang B, Tian M, Zhen Y, Yue Y, Sherman J, Zheng H, Li S, Tanzi RE, Marcantonio ER, Xie Z. The effects of isoflurane and desflurane on cognitive function in humans. *Anesth Analg*. 2012a; 114:410–415. [PubMed: 22075020]
- Zhang G, Dong Y, Zhang B, Ichinose F, Wu X, Culley DJ, Crosby G, Tanzi RE, Xie Z. Isoflurane-induced caspase-3 activation is dependent on cytosolic calcium and can be attenuated by memantine. *J Neurosci*. 2008b; 28:4551–4560. [PubMed: 18434534]
- Zhang Y, Dong Y, Wu X, Lu Y, Xu Z, Knapp A, Yue Y, Xu T, Xie Z. The mitochondrial pathway of anesthetic isoflurane-induced apoptosis. *J Biol Chem*. 2010; 285:4025–4037. [PubMed: 20007710]
- Zhang Y, Xu Z, Wang H, Dong Y, Shi HN, Culley DJ, Crosby G, Marcantonio ER, Tanzi RE, Xie Z. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. *Ann Neurol*. 2012b; 71:687–698. [PubMed: 22368036]
- Zhang Y, Zhen Y, Dong Y, Xu Z, Yue Y, Golde TE, Tanzi RE, Moir RD, Xie Z. Anesthetic propofol attenuates the isoflurane-induced caspase-3 activation and A β oligomerization. *PLoS One*. 2011; 6:e27019. [PubMed: 22069482]
- Zhen Y, Dong Y, Wu X, Xu Z, Lu Y, Zhang Y, Norton D, Tian M, Li S, Xie Z. Nitrous oxide plus isoflurane induces apoptosis and increases beta-amyloid protein levels. *Anesthesiology*. 2009; 111:741–752. [PubMed: 19741497]

APP, amyloid precursor protein; BACE, β -Site APP-cleaving enzyme; PS, presenilin; APH1, anterior pharynx-defective 1; NCT, nicastrin, and PEN2, presenilin enhancer 2.

Figure 1. Generation of A

APP is cleaved by BACE to generate APP-C99. APP-C99 is further cleaved to release 4-kDa A β and -amyloid precursor protein intracellular domain (AICD) by γ -secretase, which consists of at least four proteins, presenilin 1/presenilin 2, nicastrin, APH-1, and PEN-2.

Table 1Summary of commonly used anesthetics on A β accumulation and A β oligomerization

	Cells	Animals	Humans
Isoflurane	Positive a. 0 - 10 mM isoflurane (Eckenhoff et al., 2004). b. H4 human neuroglioma cells; 1.4% isoflurane for six hours (Xie et al., 2006; Xie et al., 2007).	Positive a. Wild-type mice; 1.4% isoflurane for two hours (Xie et al., 2008). b. AbetaPP[swe] mice; 2% isoflurane for 20 minutes twice a week for three months (Perucho et al., 2010).	Unknown
Sevoflurane	Positive H4 human neuroglioma cells; 4.1% sevoflurane for six hours (Dong et al., 2009).	Positive a. Wild-type mice; 2.5% sevoflurane for two hours (Dong et al., 2009). b. Wild-type mice; 3% sevoflurane for six hours (Lu et al., 2010).	Unknown
Desflurane	Negative H4 human neuroglioma cells; 12% desflurane for six hours (Zhang et al., 2008).	Unknown	Unknown
Nitrous oxide	Negative H4 human neuroglioma cells; 70% nitrous oxide for six hours (Zhen et al., 2009).	Unknown	Unknown
Propofol	Negative a. 0 - 100 uM (Eckenhoff et al., 2004). b. 100 uM propofol, H4 human neuroglioma cells (Zhang et al., 2011).	Unknown	Unknown