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Anesthetic effects in Alzheimer transgenic mouse models

Junxia X Tang and **Maryellen F Eckenhoff**
Department of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104 USA

Abstract

Research has improved the diagnosis of Alzheimer's disease, and at earlier stages, but effective therapy continues to be elusive. Current effort is focused on delay. Environmental factors are thought to interact with genetics to modulate the progression of the disease, and one such environmental factor is exposure to general anesthetics. The possibility that some anesthetic effects have long-term consequences is of general interest and concern. The difficulty of studying a chronic, age-related disease in humans combined with the fact that anesthetics are rarely given without surgery, has led to a focus on animal models. Transgenic mouse models have been developed to mimic the hallmarks of Alzheimer's disease, including amyloid beta accumulation (plaque), neurofibrillary tangles, and cognitive dysfunction. While none of the models recapitulate the human disease with high fidelity, they allow a first look at anesthetic - Alzheimer interactions in a reasonable time frame. In studies found to date, none have concluded that anesthetics alone cause a significant change in cognitive decline, but rather an acceleration in Alzheimer neuropathology. Further studies are required to define the best anesthetic paradigm for our elderly population to mitigate changes in neuropathology and potentially cognition.

Keywords

isoflurane; sevoflurane; desflurane; amyloidopathy; tauopathy; anesthetic sensitivity

1. Introduction

The number of potential Alzheimer patients is increasing every year along with the average life expectancy, and thus ways to delay the onset are critical in order to decrease the prevalence of this devastating dementia. Although still not fully elucidated, the neuropathogenesis of Alzheimer's disease (AD), as well as other neurodegenerative diseases, begins decades before the first onset of symptoms. Genetic factors have been identified in a minority of Alzheimer patients, thus it is clear that environmental factors must play an influential role in the onset and progression of the late onset disease. Recently, a hypothesis has been advanced that exposure to inhaled general anesthetics accelerate Alzheimer's neuropathology and the consequent cognitive decline (Baranov et al., 2009). While the mechanisms of general anesthetic action are still unclear, we do know that anesthetics are promiscuous (Eckenhoff, 2001), and act within the brain to cause loss of

Corresponding author: Maryellen F Eckenhoff, PhD, Department of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, 3620 Hamilton Walk, 305 John Morgan, Philadelphia, PA 19104 USA, P: 001-215-615-3426, F: 001-215-349-5078, Maryellen.Eckenhoff@uphs.upenn.edu.

consciousness, memory and pain. The possibility that some of these effects may have long-term consequences was not considered until recently. Patients and their families have expressed this concern for many years (Bedford, 1955), but the human data in the aging population are conflicting (Avidan et al., 2009; Ehlenbach et al., 2010), in part due to long time delays between neuropathology and symptoms, and in part due to the fact that anesthetics are rarely given in the absence of surgery. Thus, animal studies in transgenic mouse models of disease are crucial to investigating what effects, if any, general anesthetics may have on an Alzheimer vulnerable brain. This brief review summarizes the studies that have appeared in the last few years, although it bears emphasis that much more such work is needed.

2. Alzheimer transgenic mouse models

In addition to the progressive loss of cognitive functions, AD neuropathology is characterized by the appearance of amyloid beta (Aβ) plaques, tau neurofibrillary tangles and decreased brain size. In addition, accumulation of intraneuronal amyloid beta and neuroinflammation also play roles in the initiation and progression of AD. Mutations in three genes, amyloid precursor protein (APP), presenilin-1 (PSEN1) and Presenilin-2 (PSEN2) have been identified in familial Alzheimer's disease (FAD), and when combined with the neuropathologic hallmarks of disease, strongly implicate the amyloid cascade as causative in FAD. Sporadic, or late onset, AD is far more common, yet specific genetic defects have not been identified. However, the neuropathology of sporadic Alzheimer's is very similar to that of FAD, therefore mutations in APP and PSEN1 have been used to derive AD transgenic mouse models. Because neurofibrillary tangles (NFTs) are also a hallmark of the disease, transgenic mouse models including tau mutations have also been derived, even though isolated tau mutations have not been associated with human Alzheimer's disease. Transgenic mouse models have been developed with single (APP or tau), double (APP and PSEN1) or triple (APP, PSEN1 and tau) mutations (for review, Chin, 2011).

Examples of all three types of models have been used to study the effects of anesthetics on the pathogenetic and behavioral progression of AD (Table 1). The Tg2576 model (Hsiao et al., 1996), containing the Swedish mutation (K670N/M671L) (APPswe), which overexpresses APP, has been the most widely studied transgenic AD mouse model. This model is characterized by early cognitive decline, around 9 months of age, followed by appearance of extracellular Aβ plaques. Similarly, the APP23 mouse model (Sturchler-Pierrat et al., 1997), which uses a different promoter, Thy-1, also overexpresses human APP and produces age-dependent cognitive decline beginning around 3 months of age and amyloid plaque beginning at 6 months of age. Abundant plaque was found to be localized around the cerebral vasculature, a location commonly observed in AD patients. This model is also used as a model for cerebral amyloid angiopathy. Hyperphosphorylated tau is observed in this model, but not aggregated, insoluble tau in the form of neurofibrillary tangles. There exists no isolated PSEN transgenic mouse, but there are several models that have combined the APP and PSEN mutations, using different promoters, with the main effect of accelerating the onset of cognitive dysfunction and plaque formation. For example, the APPswe, PSEN1dE9 mouse (Jankowsky et al., 2001) develops plaque around 6–7 months and cognitive deficits at 7 months. Several models of tauopathy exist, which are generally characterized by the appearance of NFTs. For instance, the JNPL3 model of tauopathy (Lewis et al., 2000), with the tau P301L mutation, develops significant and widespread NFTs by 10–12 months and neuronal loss in the spinal cord and brain stem evident at 6.5 months. These effects result in ataxia and hind limb paralysis, but not cognitive decline. The hTau model (Andorfer et al., 2003), derived from mating 8c and tau knock-out mice, expresses 6 isoforms of human tau and no mouse tau. These mice

accumulate pathologic phosphorylated tau in cell bodies as early as 3 months with significant somatodendritic accumulation by 9 months of age in the neocortex and hippocampus. In contrast to the JNPL3 model, the hTau mouse does not accumulate phosphorylated tau in the spinal cord, brain stem or cerebellum and does not exhibit motor deficits. Though neuronal loss has been reported at 15 months in the hTau model, cognitive dysfunction has not been reported. The triple transgenic AD mouse model (3xTgAD) (Oddo et al., 2003) incorporates three human mutations, APPswe, PSEN1 and Tau P301L. This model demonstrates intraneuronal Aβ around 4 months of age, with plaque beginning between 10–12 months and NFTs from 12–15 months in the cortex and hippocampus. Cognitive decline has been reported to start anywhere from 9 to 15 months of age. By 24 months, plaque, NFTs and cognitive dysfunction are severe. While neuronal loss has not been reported in this model, synaptic deficits and LTP impairment are evident. Thus, when the human genes associated with familial Alzheimer's disease are expressed as transgenes in these mouse models, the brain pathology imperfectly mimics the human disease, but these models have become extremely important for the study of the mechanisms and modulators of human AD.

3. Anesthetic effects on the AD transgenic mouse models

3.1 APP mutation

The single amyloid mutation mouse model, which over expresses APP (APP_{swe}), has been used to test the hypothesis that anesthetic exposure alters pathologic and cognitive trajectory (Table 1). In the first such study (Bianchi et al., 2008), 12 month old Tg2576 mice were exposed to either sub MAC (minimum alveolar concentration) concentrations (0.8%) of isoflurane or halothane for 2h per day for 5 days (maintaining euthermia). Mouse learning and memory were tested prior to anesthetic exposure and then re-tested 2 days after the anesthetic exposures using the Morris Water Maze (Chen et al., 2000). No significant behavioral changes were detected in these transgenic mice that could be attributed to the anesthetic exposures, though significant impairment was detected in the aged-matched non-transgenic littermates exposed to isoflurane. The lack of an effect in the transgenic mice was attributed to a "floor effect" where the mice were already so cognitively impaired at this age that further decrements could not be detected. However, immunohistochemical examination of these mice revealed an increase in amyloidopathy in the halothane exposed transgenic mice, only 2 weeks after exposure. The poor association between amyloidopathy and cognition is now well appreciated in the Alzheimer community, but these early results were intriguing in that inhaled anesthetics alone produced changes in both cognition and amyloidopathy. Most interestingly, the two, otherwise similar anesthetics had differing effects, suggesting that optimization of anesthetic choice might be possible in vulnerable patients.

In order to address the floor effect problem, this same mouse model was then used to study the effects of isoflurane at an earlier, presymptomatic time point (Perucho et al., 2010), Tg2576 and wild type littermates, beginning at 7 months of age, were exposed to supra-MAC concentrations of isoflurane (2%), but for shorter duration (20–30 min), twice a week for 3 months. The authors reported increased mortality (especially during the 30 min exposures), decreased responsiveness after the exposures, reduced exploratory behavior in the Y-maze alternance test, increased apoptosis, increased amyloid aggregation and glial changes in the isoflurane exposed transgenic mice, all pointing to an accelerated AD outcome. These results suggest that a floor effect might exist in advanced Alzheimer's disease, and that a window of vulnerability exists in the presymptomatic period.

3.2 APP and PSEN mutations

Recent studies examined the effects of anesthetic exposures in neonatal mice containing transgenes with both the APP and PSEN-1 mutations (Lu et al., 2010; Zhang et al., 2011) (Table 1). They found that while both transgenic and non-transgenic neonates were significantly affected by exposure to 3% sevoflurane plus 60 % oxygen for 6 h, the APP/PSEN transgenic mice were more vulnerable than non-transgenic mice, including greater caspase-3 activation, apoptosis, as well as, increased amyloid beta 42 and pro-inflammatory TNF-α levels. Similar effects on capsase-3 activation were found in the same APP/PSEN transgenic 6-day old mice after exposure to 1.4% isoflurane but the effects were mitigated by pretreatment with propofol. Interestingly, while the isoflurane-induced caspase-3 activation was less pronounced in the age-matched wild type mice, propofol did not protect the wild type neonatal mice from the effects of isoflurane. These results suggest that vulnerability to anesthetic neurotoxicity exists even in a pre-pathology state but that propofol may be protective in the AD vulnerable brain.

3.3 Tau mutations

In addition to the above transgenic models of amyloidopathy, other investigators have studied anesthetic effects in transgenic mouse models of tauopathy (Planel et al., 2008; Planel et al., 2009) (Table 1). Pentobarbital –induced hypothermia was produced in both young (3–4 months) and old (18–20 months) hTau transgenic mice (Planel et al., 2008), and the brains were studied for changes in tau. They found that in the older mice, tau became hyperphosphorylated and detached from microtubules without changing microtubule stability. In a second study, exposures to isoflurane at clinically relevant concentrations (1.3 %) were carried out in pre-symptomatic JNPL3 mice (Planel et al., 2009). Immediately after exposure, anesthetic-induced hypothermia increased levels of phosphorylated aggregated forms of tau in somatodendritic areas in the brainstem that persisted for at least one week after exposure. Both of the tau mutation studies suggest that anesthetics might have disease targets in other than the amyloid pathway. This may have implications for a wide range of similar neurodegenerative diseases, such as frontotemporal dementia (Geser et al., 2010).

3.4 APP, PSEN and Tau mutations

The triple transgenic mouse model of AD (3xTgAD), which includes the human APP_{SWE}, tauP301L, and PS1M146V transgenes, has been used to study anesthetic effects (Table 1). Long-term cognitive and neuropathological effects after exposure to halothane or isoflurane were examined in pre-symptomatic (2, 4 and 6 months of age) 3xTgAD mice (Tang et al., 2011). The mice were given 5 h 1 MAC exposures, once a week for 4 weeks and hippocampal-dependent learning and memory measured in the Morris water maze 2 months later. Memory *improvement* was found in the halothane exposed mice, almost entirely attributable to the younger female mice, with no changes detectable in the isoflurane exposed mice. The improvement was attributed to preconditioning in a still plastic brain. However, phosphorylated tau levels were increased in the 3xTgAD mice after both anesthetic exposures, particularly in mice exposed at the 6 month time point. In a more recent study, both short-term and long-term effects of a brief 1.5 MAC desflurane exposure was examined in 8–11 month old 3xTgAD mice (Tang et al., 2012). Similar to the previous study in this mouse model, there were no behavioral or neuropathological effects found in either the 3xTgAD mice or C57BL/6 mice at 2 or 13 weeks after desflurane exposure, although there was a non-significant trend for a transient cognitive decline at 2 weeks post-exposure. The anti-inflammatory cytokine, IL-10, was increased 24 h after desflurane exposure in the wild type mice but not in the 3xTgAD mice. Taken together, both studies suggest that while anesthetic exposure does not accelerate the cognitive decline in presymptomatic 3xTgAD transgenic mice, the enhanced phosphorylated tau and altered anti-

inflammatory cytokine levels suggest a detrimental interaction with the underlying smoldering neuroinflammation presumed to underlie Alzheimer's disease.

3.5 Anesthetic Sensitivity

Anesthetic sensitivity varies considerably between mouse strains (Sonner et al., 1999), so in order to assure that these transgenic mice are being exposed to similar relative anesthetic concentrations as the wild type controls, two studies have examined anesthetic sensitivity in Alzheimer transgenic mouse models. In the first, minimum alveolar anesthetic concentration (MAC, essentially an EC_{50}) values were examined in another APP_{SWE} transgenic mouse model, APP23 (Eckel et al., 2010) (Table 1). Mac values for isoflurane in aged transgenic mice were significantly greater (~20%) compared to transgenic mice without the Swedish mutation, wild type mice, or young transgenic mice. In the second study, sensitivity to three inhaled anesthetics was examined in middle-aged (12–14 months) 3xTgAD mice (Bianchi et al., 2010) (Table 1). Similar to the Eckel et al study, a decrease in anesthetic sensitivity was found in the 3xTgAD mice compared with age-matched wild type controls. The finding that the AD vulnerable brain imparts a small degree of anesthetic resistance suggests that neuronal and synaptic dysfunction somehow reduces anesthetic sensitivity. Since these studies both suggest that transgenic animals are being relatively under-dosed with anesthetics relative to their wild type controls, observed enhancement in pathology or cognitive decline is likely to be real.

4. Conclusion

We have reviewed the various models used thus far to examine the effects of anesthetics alone on the progression of AD. While no one model fully recapitulates human AD, each model has its own unique properties which allow us to examine one or more of the pathological hallmarks of the disease, but it should be apparent that the data available to date are scarce. Anesthetics clearly have subtle effects on the AD vulnerable brain, and the AD brain also has effects on anesthetic sensitivity. There are many AD models that can be examined, which are continually updated on the Alzheimer Research Forum website (http://www.alzforum.org/res/com/tra/default.asp). It is important to understand the cognitive and neuropathological differences in the models before designing future studies. Finally, side-by-side comparisons of anesthetics will be helpful, not only to understand potential mechanistic underpinnings, but also to inform clinicians of the optimal choice of drug in vulnerable populations.

Acknowledgments

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Abbreviations

AD	Alzheimer's disease
Aβ	amyloid beta
APP	amyloid precursor protein
APPswe	amyloid precursor protein with the Swedish mutation
FAD	familial Alzheimer's disease
MAC	minimum alveolar concentration
PSEN1	presenilin-1

PSEN2	Presenilin-2
NFTs	neurofibrillary tangles
3xTgAD	triple transgenic AD mouse model

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Table 1

Alzheimer Transgenic Mouse Models used in Anesthetic Exposure Studies

Transgenic AD Model	Mutation	Cognitive decline	Aβ Plaque	NFTs	Anesthetic Exposure	Age Gender	Results	References
Tg2576 (Hsiao et al., 1996)	APP_{SWE} (APP695)	9 mo	11–12 mo	No	Isoflurane Halothane (0.8–1% in 30% oxygen) 2h/day for 5 days	12 mo females	No effect behavior 2 days post-exposure, Halothane increased Aβ plaque	(Bianchi et al., 2008)
Tg2576 (Hsiao et al., 1996)	APP_{SWE} (APP695)	9 mo	11–12 mo	No	Isoflurane (2% in 98% oxygen) 20–30 min, 2x/week, for 3 months	7 mo males	increased mortality, less responsiveness, reduced exploratory behavior, increased apoptosis, reduced astroglia, increased microglia, increased Aβ aggregates, reduced autophagy	(Perucho et al., 2010)
APP23 (Sturchler-Pierrat et al., 1997)	APP_{SWE} (APP751)	3 mo	6 mo	No	Isoflurane (0.5–2% in 100% oxygen) Dose-response	4 & 18 mo males	Increased MAC in 18 mo Tg mice	(Eckel et al., 2010)
APP + PS1 (Jankow sky et al., 2001)	APP_{SWE}, PSEN1d E9	7 mo	6–7 mo	No	Sevoflurane (2.1%/3% in 60% oxygen) 6 h One exposure	6 days males & females	Increased caspase-3, increased apoptosis, increased Aβ levels, increased TNF-α	(Lu et al., 2010)
APP + PS1 (Jankow sky et al., 2001)	APP_{SWE}, PSEN1d E9	7 mo	6–7 mo	No	isoflurane (1.4% in 100% oxygen) with/with out propofol pretreatment (i.p. 200 mg/kg) 6 h One exposure	6 days males & females	Increased caspase-3 Propofol pretreatment attenuates isofluraneinduced caspase-3 activation	(Zhang et al, 2011)
hTau (Andorfer et al., 2003)	Human PAC, H1 haplotype	No	No	Somatic 3–6 mo Somato-dendritic 9–12 mo	Pentobarbital (100 mg/kg) room temp 1–4 h One injection	3–4 mo & 18–20 mo males & females	Anesthesia-induced hypothermia, increased tau hyperphosphorylation, detachment of tau from microtubules in old mice	(Planel et al., 2008)
JNPL3 (Lewis et al., 2000)	P301L	No	No	10–12 mo	Isoflurane (1.3% in 30% oxygen) room temp 4 h (females), 4 h, 2x/week for 2 weeks (males)	4 mo females, 8 mo males	Anesthesia-induced hypothermia, detachment of tau from microtubules, accelerated tauopathy during anesthetic exposure and 1 week post-exposure	(Planel et al., 2009)
3xTg-AD (Oddo et al., 2003)	APP_{SWE}, tauP301 L, PS1M146V	9–15 mo	Intraneuronal 4 mo plaque 10–12 mo	12–15 mo	Isoflurane (0.59–1.05%), Halothane (0.61–1.22%), Sevoflurane (0.94–2.08% in 100% oxygen) Dose-response 3 exposures	12–14 mo males & females	Mild resistance to anesthetics, emergence unaltered	(Bianchi et al., 2010)

Transgenic AD Model	Mutation	Cognitive decline	Aβ Plaque	NFTs	Anesthetic Exposure	Age Gender	Results	References
3xTg-AD (Oddo et al., 2003)	APP_{SWE}, tauP301 L, PS1M146V	9–15 mo	Intraneuronal 4 mo plaque 10–12 mo	12–15 mo	Isoflurane Halothane (0.9–1% in 30% oxygen) 5 h/week for 4 weeks	2,4, 6 mo males & females	Halothane improved cognition 2 mo post-exposure in 2 mo females, Isoflurane increased tau in 6 mo mice at 3 mo post-exposure	(Tang et al., 2011)
3xTgAD (Oddo et al., 2003)	APP_{SWE}, tauP301 L, PS1M146V	9–15 mo	Intraneuronal 4 mo plaque 10–12 mo	12–15 mo	Desflurane (9 % in 40% oxygen) 30 min One exposure	8–11 mo males & females	No long-term behavioral effects, altered IL-10 at 24h	(Tang et al., 2012)