Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2013 December ; 47: . doi:10.1016/j.pnpbp.2013.03.004.

Anesthesia and Tau Pathology

Robert A. Whittington[a,*], **Alexis Bretteville**[b], **Maya F. Dickler**[b], and **Emmanuel Planel**[b,c]

Robert A. Whittington: raw9@columbia.edu; Alexis Bretteville: alexisbretteville.pro@gmail.com; Maya F. Dickler: maya.dickler.1@ulaval.ca; Emmanuel Planel: emmanuel@planel.org

[a]Department of Anesthesiology, Columbia University, New York, NY 10032

[b]Centre de Recherche du CHU de Québec, Axe Neurosciences, Québec (QC), Canada, G1V 4G2

[c]Université Laval, Département de Psychiatrie et Neurosciences, Québec (QC), Canada, G1V 0A6

Abstract

Alzheimer's disease (AD) is the most common form of dementia and remains a growing worldwide health problem. As life expectancy continues to increase, the number of AD patients presenting for surgery and anesthesia will steadily rise. The etiology of sporadic AD is thought to be multifactorial, with environmental, biological and genetic factors interacting together to influence AD pathogenesis. Recent reports suggest that general anesthetics may be such a factor and may contribute to the development and exacerbation of this neurodegenerative disorder. Intra-neuronal neurofibrillary tangles (NFT), composed of hyperphosphorylated and aggregated tau protein are one of the main neuropathological hallmarks of AD. Tau pathology is important in AD as it correlates very well with cognitive dysfunction. Lately, several studies have begun to elucidate the mechanisms by which anesthetic exposure might affect the phosphorylation, aggregation and function of this microtubule-associated protein. Here, we specifically review the literature detailing the impact of anesthetic administration on aberrant tau hyperphosphorylation as well as the subsequent development of neurofibrillary pathology and degeneration.

Keywords

Anesthesia; Alzheimer's disease; Tau; Kinase; Phosphatase

Introduction

With a worldwide prevalence of 26.6 million cases as of 2006, Alzheimer's disease (AD) remains the most common form of dementia affecting the elderly population, and it is estimated that without a significant therapeutic breakthrough, the prevalence of this disorder will quadruple by the middle of this century (Brookmeyer et al., 2007). Advancing age is considered the major risk factor for the development of sporadic AD, which constitutes the majority of AD cases (~99%) (Harman, 2002; Bufill et al., 2009). AD pathology is considered to be multi-factorial, whereby a genetic predisposition interacts with

*Corresponding Author: Robert A. Whittington, MD, Columbia University, College of Physicians and Surgeons, Department of Anesthesiology, 622 West 168th Street PH 5, New York, NY 10032, Tel: 212-305-1567, Fax: 212-305-0777, raw9@columbia.edu.

environmental or biological factors, resulting in the development and/or acceleration of this neurodegenerative condition (Iqbal and Grundke-Iqbal, 2008; Papon et al., 2011).

The two histopathological hallmarks of AD are extracellular amyloid plaques, which are composed mainly of beta-amyloid (Aβ) peptide, and intra-neuronal neurofibrillary tangles (NFT), which are primarily composed of aberrantly hyperphosphorylated tau protein assembled into paired helical filaments (Grundke-Iqbal et al., 1986). Tau is normally enriched in the axonal compartment, but in AD and other tauopathies, it becomes hyperphosphorylated then subsequently relocalizes and aggregates in the somatodendritic compartment of affected neurons (Buee et al., 2000; Avila et al., 2004).

Recent studies have demonstrated that anesthetics can have an impact on the neuropathogenesis of AD, and even possibly accelerate the clinical progression of this neurodegenerative disorder (Eckenhoff et al., 2004; Xie et al., 2006; Planel et al., 2009; Run et al., 2009; Tan et al., 2010; Tang et al., 2011a; Le Freche et al., 2012). Furthermore, both pre-clinical and clinical studies have recently supported the notion that anesthesia has a significant impact on tau pathogenesis (Planel et al., 2007; Planel et al., 2008; Planel et al., 2009; Run et al., 2009; Run et al., 2010; Tang et al., 2011a; Tang et al., 2011b; Whittington et al., 2011; Le Freche et al., 2012). In this article, we specifically review the literature on reported changes in tau pathology and function following anesthetic exposure *in vivo*, and provide tables summarizing the anesthetics used in these articles (Table 1), as well as the results obtained from different groups (Table 2).

Anesthesia-Induced Tau Hyperphosphorylation: The Role of Hypothermia

Intracellular aggregates of abnormally hyperphosphorylated tau are present in a group of neurodegenerative diseases called tauopathies (Buee et al., 2000; Avila et al., 2004). Tau hyperphosphorylation can induce aggregation *in vitro* (Alonso et al., 2001; Sato et al., 2002), and is thought to induce NFT formation in the brain (Grundke-Iqbal et al., 1986; Trojanowski and Lee, 1994; Iqbal and Grundke-Iqbal, 2008). The distribution pattern of NFT in the brain of patients is highly hierarchical and has been divided into 6 histological stages (Braak and Braak, 1991, 1997; Braak et al., 2006) as well as 10 biochemical stages (Delacourte et al., 1999). Tau pathology correlates with dementia in AD as well as memory loss in normal aging and mild cognitive impairment (Wilcock and Esiri, 1982; Arriagada et al., 1992; Guillozet et al., 2003; Bretteville and Planel, 2008). In Alzheimer's disease, the accumulation of NFT in neurons is preceded by the appearance of hyperphosphorylated tau.

This disruption of tau phosphorylation homeostasis can result from the dysregulation of the activities of both tau-related kinases and phosphatases. Environmental factors can also be critical in the development of altered signal transduction, which then disrupts the balance of tau phosphorylation homeostasis, ultimately leading to the development of neurofibrillary degeneration and neuronal cell death observed in AD (Iqbal and Grundke-Iqbal, 2005; Iqbal and Grundke-Iqbal, 2008).

We previously demonstrated in the brains of 4 to 6 month-old non-transgenic C57BL/6J mice that both intravenous (chloral hydrate and sodium pentobarbital) and inhalational anesthetics (isoflurane) rapidly induce pronounced tau hyperphosphorylation at several phosphoepitopes including AT8 (Ser^{202}/Thr^{205}), PHF-1 (Ser^{396}/Ser^{404}), pS199 (Ser^{199}), TG3 (Thr^{231}), MC6 (Thr^{235}), pS262 (Ser262), and pS422 (Ser^{422}). This robust tau hyperphosphorylation was surprisingly reversed by the restoration of core body temperature to normal, thus demonstrating that anesthesia-induced hypothermia is a major mediator of tau hyperphosphorylation (Planel et al., 2007). The effect of hypothermia is very potent, with an 80% increase in tau phosphorylation for each degree Celsius below 37°C (Planel et al., 2004).

Tau phosphorylation is regulated by several protein kinases such as glycogen synthase kinase-3β (GSK-3β), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), calcium/calmodulin-dependent protein kinase II (CaMKII), c-Jun N-terminal kinase (JNK), cyclin-dependent kinase 5 (cdk5) and its specific activator p35, as well as AKT/PKB (protein kinase B) (Cross et al., 1995; Maccioni et al., 2001; Planel et al., 2002; Zhu et al., 2002; Tatebayashi et al., 2006; Sadik et al., 2009). Tau phosphorylation homeostasis is maintained through dephosphorylation mediated by protein phosphatase 2A (PP2A), protein phosphatase 2B (PP2B), and protein phosphatase 1 (PP1) (Goedert et al., 1992; Wang et al., 1996). PP2A is the major tau phosphatase in the brain, accounting for more than 70% of tau dephosphorylation (Liu et al., 2005). We determined that the hypothermia-induced tau hyperphosphorylation was not a consequence of tau kinase activation, but rather secondary to the direct inhibition of PP2A activity by the hypothermia itself (Planel et al., 2004; Planel et al., 2007).

Other groups have subsequently confirmed this observation using various anesthetics in different *in vivo* models. Indeed, Tan *et al.* demonstrated in 6-month old Sprague-Dawley rats that 1.5% isoflurane anesthesia for 2h without temperature control leads to a 10- and 2.9-fold increase in hippocampal tau phosphorylation at the Thr^{205} and Ser^{396} phosphoepitopes, respectively (Tan et al., 2010). No increase in tau phosphorylation was observed in rats following isoflurane administration when normothermic conditions were maintained. These investigators also observed the inhibition of hippocampal PP2A activity following 2h of isoflurane administration under hypothermic conditions, thus confirming our previous findings. Run *et al.* also showed a higher degree of tau phosphorylation at the Thr^{181}, Thr^{205}, Thr^{212}, and 12E8 (Ser^{262}/$Ser^{356)}$ phosphoepitopes in 14–15 week-old C57BL/6J mice anesthetized for 1 hour with pentobarbital compared to mice sacrificed within 5 min of anesthetic administration. This observation correlated with the onset of hypothermia, which developed progressively during anesthesia (Run et al., 2009) and finally resulted in a drop in body temperature to a range of 26–30°C 1h after anesthesia.

Altogether, these data strongly suggest that anesthesia induced tau hyperphosphorylation is mediated through anesthesia-induced hypothermia and consequent inhibition of PP2A activity (Planel et al., 2004). They also suggest that hypothermia, which is common in the elderly, might enhance AD pathology (Whittington et al., 2010).

Anesthesia-Induced Hypothermia and Tau function

In the normal brain, tau is mainly found in the axonal compartment of neurons (Binder et al., 1985). In AD and other tauopathies, tau relocalizes to the somatodendritic compartment where classical NFT are located (Papasozomenos and Binder, 1987; Delacourte et al., 1990; Riederer and Binder, 1994). The appearance of hyperphosphorylated tau aggregates correlates with a loss of microtubules and the breakdown of normal axonal transport (Terry, 1996; Pollak et al., 2003). Thus, tau hyperphosphorylation has been proposed to impair its microtubule (MT) binding function, resulting in its detachment from MTs, which, in turn, destabilizes the MTs, disrupts MT-dependent axonal transport, and ultimately leads to the relocalization of tau to the somatodendritic compartment (Trojanowski and Lee, 1994; Mandelkow et al., 2003; Duff and Planel, 2005; Feinstein and Wilson, 2005; Mi and Johnson, 2006). However, it should be noted that it is still controversial whether tau hyperphosphorylation is the cause or consequence of MT collapse (Planel et al., 2008; Miyasaka et al., 2010).

The microtubule binding function of tau is regulated by two distinct mechanisms. The first level of regulation is assured by the establishment of a precise equilibrium between tau isoforms with 3 or 4 repeat binding domains: the inclusion of the alternatively spliced exon

10 leads to the presence of a fourth repeat domain and confers to the 4-repeat tau isoforms (4R) a higher capacity to bind and polymerize microtubules than tau isoforms containing only 3-repeat domains (3R) (Goedert and Jakes, 1990; Butner and Kirschner, 1991; Panda et al., 2003). The second level of regulation is by the homeostasis of tau phosphorylation levels established by a balance between tau kinases and phosphatases. Tau phosphorylation in and around the MT binding domain acts as a negative regulator of tau microtubule binding. Thus, dephosphorylated tau is more efficient to bind and polymerize microtubules than the phosphorylated form (Lindwall and Cole, 1984).

Recent work has begun to focus on the pathological consequences of aberrant tau hyperphosphorylation secondary to anesthesia-induced hypothermia. In non-transgenic mice, we observed that pentobarbital-induced hypothermia resulted in the robust hyperphosphorylation of microtubule (MT)-free tau, and the subsequent impairment of the ability of tau to bind and assemble MTs (Planel et al., 2008). In contrast to free tau, MT-bound tau was more resistant to hyperphosphorylation following pentobarbital-induced hypothermia, and MT detachment was not observed in non-transgenic mice. This lack of MT detachment is most likely secondary to the fact that murine adult tau solely consists of the 4-repeat (4R) tau isoforms (Janke et al., 1999), which are more tightly bound to microtubules than 3R tau and thus more resistant to detachment from MT. To verify this hypothesis, we used the htau transgenic mouse model (Andorfer et al., 2003) bearing a human tau minigene (Duff et al., 2000), which expresses both 3R and 4R human tau isoforms. This model also develops neurofibrillary pathology characterized by tau hyperphosphorylation, aggregation, somatodendritic relocalization, and cell death (Andorfer et al., 2005). Hence, in contrast to non-transgenic mice, a 4h exposure to pentobarbital-induced hypothermia resulted in detachment of 3R (but not 4R) tau isoforms associated with an accentuated relocalization of phosphorylated tau in the soma (Planel et al., 2008). However, this detachment of 3R tau did not result in the depolymerization of tubulin or dramatic reorganization of the axonal cytoskeleton (Planel et al., 2008), suggesting that, despite the pronounced hyperphosphorylation induced by anesthesia, tau isoforms residually bound to the MTs are sufficient for the maintenance of the MT network integrity.

Altogether, these data suggest that tau hyperphosphorylation induced by anesthesia affects negatively tau function by altering its capacity to properly bind and polymerize microtubules. However, anesthesia-induced tau hyperphosphorylation is not sufficient to detach enough tau from tubulin to result in the actual breakdown of the microtubule cytoskeleton (Planel et al., 2008).

Anesthesia-Induced Hypothermia and the Development of Tau Pathology

Based on our previous results showing that anesthesia-induced hypothermia could negatively impact tau's physiological function, we addressed the question of whether anesthetics could accelerate tau pathology in a mouse model of tauopathy (Planel et al., 2009). We took advantage of the JNPL3 mice, an aggressive mouse model of tauopathy overexpressing the pro-aggregative Tau_{P301L} mutation and consequently developing neurofibrillary degeneration (Lewis et al., 2000). We specifically observed that a single exposure to 1 minimum alveolar concentration (MAC) isoflurane (1.3%) for 4h produced significant hypothermia, which immediately resulted in pronounced tau hyperphosphorylation in the brainstem of 4 month-old female mice. This hyperphosphorylation was accompanied by an increase in insoluble tau levels 1 week after exposure. It should be noted that the increase in tau aggregation, observed 1 week following anesthesia, occurred at a time when the mice were no longer hypothermic. Repeated anesthesia (1 MAC isoflurane for 4h twice a week for 2 weeks) led to the same observations in 8 month-old JNPL3 males, which are known to develop tau pathology at a slower rate

than females. Of note, when the male JNPL3 mice were exposed to a similar dose of isoflurane with temperature control so as to avoid hypothermia, no increases in phosphorylated or insoluble tau were observed 1 week following exposure.

Other groups have further supported these findings. Indeed, using another transgenic mouse model overexpressing the same Tau_{P301L} mutation, following exposure to hypothermia induced by isoflurane, Menuet *et al.* have reported increased AT8 staining and tauopathy in several brainstem regions, including the nucleus ambiguus and Kolliker-Fuse nuclei, at 7 days post-exposure (Menuet et al., 2012). This mouse model of tauopathy has been previously shown to develop cognitive deficits as well as vocalization and respiratory abnormalities, the latter condition ultimately leading to premature death (Terwel et al., 2005; Dutschmann et al., 2010; Menuet et al., 2011b; Menuet et al., 2011a; Menuet et al., 2012). Moreover', these transgenic mice develop evidence of tauopathy within the pontine Kolliker-Fuse nucleus (Dutschmann et al., 2010). Interestingly, these investigators observed in 4 month old Tau P301L mice that a single exposure to 4h 1MAC isoflurane, under hypothermic conditions, resulted in the premature development of upper airway defects, which are normally observed in this mouse tauopathy model at later stages of life. Indeed, measurements of upper airway function revealed that the administration of isoflurane in a hypothermic environment resulted in the development of respiratory compromise at 4 months, which was comparable to the respiratory pathology typically observed in these mice at 8 months (Menuet et al., 2012). However, the administration of a similar dose of isoflurane to these Tau P301L mice with temperature control prevented the development of the ventilation abnormalities. Forced ventilation also prevented the exacerbation of upper airway pathology in these mice following isoflurane-induced hypothermia, suggesting that other physiological factors occurring during hypothermia (besides lower temperature) may play a role in mediating the development of airway pathology following isoflurane. Interestingly, the pretreatment with the NMDA receptor antagonist, memantine (20 mg/kg i.p., 1h prior to anesthesia), also prevented the development of upper airway pathology following the administration of isoflurane without temperature control, suggesting that the NMDA receptor pathway is involved in the development of airway defects following hypothermic isoflurane exposure. Moreover, the degree of tauopathy correlated well with the early onset of upper airway dysfunction and pretreatment with memantine reduced the development of the tauopathy observed 7 days following hypothermic isoflurane administration. However, the mechanism by which this NMDA-R antagonist is mediating its beneficial effects, in this mouse tauopathy model, remains unexplained.

Overall, these data demonstrate that the capacity of isoflurane to exacerbate neurofibrillary pathology in Tau_{P301L} mouse models is dependent on physiological changes occurring during anesthesia-induced hypothermia, and not directly on this volatile anesthetic *per se*.

Anesthesia-Induced Hypothermia and cognitive deficits

It has been well established that hypothermia leads to memory disruption in numerous organisms including rodents (Riccio et al., 1968; Hamm, 1981; Richardson et al., 1983; Santucci et al., 1987). However, the mechanisms by which hypothermia produces memory disruption are not well understood. Some studies suggest that a reduction of protein synthesis resulting from a general decrease in energy-dependent cellular processes plays a role, whereas others, including our own studies, suggest a disruption of cellular signaling events positioned upstream of transcription or translation (Fulton et al., 2008; Whittington et al., 2013).

However, few studies have addressed the cognitive impact of changes in tau pathology following anesthesia-induced hypothermia. Recently, Tan *et al.*, observed that the increase

in phosphorylated tau following the administration of 1.5% isoflurane anesthesia for 2h without temperature control in 6 month old Sprague Dawley rats was associated with the impairment of working and reference memory as measured using the Y-maze test (Tan et al., 2010). However, it is very important to note that a direct, causal relationship between the changes in tau phosphorylation observed following anesthesia-induced hypothermia and memory impairment was not established in this study. In 18-month old Sprague Dawley rats, 1.4% isoflurane for 2h with temperature control resulted in the impairment of memory and learning as measured with the Morris Water Maze (Liu et al., 2012). However, these cognitive changes were not associated with any changes in total tau or tau phosphorylated at the Thr^{231} and Ser^{396} phosphoepitopes. Hence, the restoration of normal body temperature can prevent the increase in tau phosphorylation observed following isoflurane anesthesia; however, this does not necessarily eliminate the cognitive impairment observed in aged rodents following exposure to this anesthetic (Culley et al., 2003; Liu et al., 2012). Of note, thus far, the studies examining the relationship between tau pathology and cognitive function following isoflurane-induced hypothermia have been somewhat limited by the fact that, in these studies, only a few phosphoepitopes have been analyzed for aberrant phosphorylation, they solely have examined non-transgenic animals without preexisting AD pathology, and they have been designed such that no causal relationship between pathological tau burden and the degree of cognitive decline has ever been definitively established.

In summary, anesthesia-induced hypothermia results in pronounced tau hyperphosphorylation, and the acceleration of tau pathology in transgenic mouse tauopathy models. With isoflurane, the maintenance of normothermia appears to mitigate the negative effects of this anesthetic on tau phosphorylation; however, cognitive impairment still has been reported under these conditions. Studies with memantine in a mouse tauopathy model suggest that the NMDA-R pathway may play a role in the development of tau pathology observed following isoflurane-induced hypothermia; however, other receptor pathways cannot be excluded at the present time. Furthermore, the mechanism by which memantine antagonizes the negative effects of isoflurane-induced hypothermia on tau pathology remains unclear and warrants further investigation. Although the impairment of memory observed following isoflurane-induced hypothermia has been associated with increases in tau phosphorylation in rodents, a true causal link between tau hyperphosphorylation and impaired cognition has not yet been established. Hence, future studies are required to address this potential relationship.

Anesthesia-Induced Tau Pathology and Normothermia

Although there is ample evidence suggesting that anesthetic-induced hypothermia possesses the capacity to produce aberrant tau hyperphosphorylation and even accelerate neurofibrillary pathology, recent studies suggest that certain anesthetics can induce tau hyperphosphorylation in the absence of hypothermia. For example, Run *et al.* demonstrated in C57BL/6J mice that following exposure to either 30 sec of ether vapor or 5 min after an intraperitoneal pentobarbital injection, an increase in tau phosphorylation was observed at multiple phosphoepitopes (Run et al., 2009), including Thr^{181}, Ser^{199}, Thr^{205}, Ser^{262}, Ser^{404}, and Thr^{212}. In terms of the mechanism underlying this normothermic tau hyperphosphorylation, these investigators also observed that this increased tau phosphorylation was associated with the activation of the stress-induced kinases mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK), suggesting that these specific protein kinases may a play a role under these conditions.

We recently examined the impact of the administration of propofol (2,6 diisopropylphenol), an intravenous sedative-hypnotic anesthetic commonly used in humans to provide general

anesthesia as well as conscious sedation, on tau phosphorylation under normothermic conditions (Whittington et al., 2011). Compared to hypothermic propofol administration, normothermic propofol administration produced a lower degree of hippocampal tau phosphorylation; nevertheless, hyperphosphorylation still occurred in the absence of hypothermia. Specifically, 30 min following the administration of propofol 250 mg/kg i.p. to C57BL/6 mice, significant increases in hippocampal tau phosphorylation were observed at the AT8 (Ser^{202}/Thr^{205}), CP13 (Ser^{202}), and PHF-1 (Ser^{396}/Ser^{404}) phosphoepitopes (Whittington et al., 2011). Interestingly, tau hyperphosphorylation persisted at the AT8 phosphoepitope 2h after propofol anesthesia, despite the recovery of the righting reflex in all of the mice. In the cortex, propofol also increased tau phosphorylation at the AT8, PHF-1, $pSer^{262}$, MC6, and $pSer^{422}$ phosphoepitopes 30 min following administration, and again this increase persisted at AT8 2h following propofol administration. Moreover, the mechanism of tau phosphorylation following normothermic propofol administration *in vivo*, was found to be similar to that observed during hypothermia-induced tau phosphorylation (Planel et al., 2007), in that the tau hyperphosphorylation under normothermic conditions was associated with a decrease in PP2A activity (to 77 ± 9%).

We also have determined that the tau hyperphosphorylation observed after normothermic propofol administration *in vivo* is not, in essence, a function of an anesthetic-induced physiologic change. To establish this, we examined tau hyperphosphorylation under normothermic condition *in vitro* using SH-SY5Y human neuroblastoma cells that were stably transfected to constitutively express human tau with 3 MT-binding domains (Tau-SH-SY5Y cells) (Mailliot et al., 2000; Delobel et al., 2002; Hamdane et al., 2003). We observed that a 1h exposure of a physiologic dose of propofol, 3 μg/ml (16.8 μM) at 37°C, in these Tau-SH-SY5Y cells resulted in increased phosphorylated tau levels at the AT8, CP13, and PHF-1 phosphoepitopes. Thus, tau phosphorylation following normothermic propofol administration is not the consequence of an anesthetic-induced physiologic change such as hypothermia, hypercarbia, or hypotension, but is indeed the consequence of a direct, pharmacologic effect.

Although propofol has the capacity to increase tau phosphorylation in the absence of hypothermia (Whittington et al., 2011), it is unclear whether this ability to induce tau hyperphosphorylation is specific to propofol, or a property shared by other commonly used intravenous anesthetics. Thus, we investigated the impact of a sedative dose of dexmedetomidine (300 μg/kg i.p), a commonly used sedative-analgesic agent, on levels of phosphorylated tau in non-transgenic mouse hippocampus under normothermic conditions (Whittington *et al.* personal communication). Thirty min following its administration, Dex significantly increased hippocampal tau phosphorylation at the AT8 (182 ± 36%), PHF-1 (183 ± 27%), and CP13 (170 ± 68%) phosphoepitopes. Interestingly, at 2h, Dex treatment was still associated with significant increases in hippocampal phosphorylated tau levels at all three phosphoepitopes, despite the return of the righting reflex in all of the mice at this time point. Furthermore, 6h post-dexmedetomidine this increase still persisted at AT8. Thus, these data demonstrate that, in terms of intravenous anesthetics, the ability to induce tau hyperphosphorylation under normothermic conditions is not a property unique to propofol. However, the mechanism by which two pharmacologically diverse anesthetics produce similar changes in tau phosphorylation remains to be determined.

Interestingly, tau phosphorylation under normothermic conditions does not appear to be a phenomenon solely observed with intravenous anesthetics. Indeed, Le Freche *et al.* have recently observed that acute exposure to the inhalational anesthetic sevoflurane resulted in significant, dose-dependent tau hyperphosphorylation in the hippocampus of nontransgenic mice (Le Freche et al., 2012). These same investigators have also examined the long-term effects of repeated exposure to sevoflurane on spatial memory and tau phosphorylation in

mice. Specifically, starting at 6 months of age, the nontransgenic mice were repeatedly exposed to low-dose (1.5%) or high dose (2.5%) sevoflurane for 1h, under normothermic conditions, and this exposure was repeated monthly until 10 months of age (5 exposures in total). At 9 months of age, spatial learning and memory testing, as assessed using the Morris Water Maze (MWM), revealed significant impairment of acute memory retention following exposure to both doses of sevoflurane. One month following the last sevoflurane exposure, hippocampal tau phosphorylation was increased at the Ser^{396}/Ser^{404} and Thr^{181} phosphoepitopes, without evidence of tau aggregation. Mechanistically, these same investigators concluded that repeated exposure to sevoflurane might involve the activation of AKT and ERK kinases as well as inactivation of GSK-3, suggesting that normothermic sevoflurane exposure may lead to the dysregulation of signaling along the MAPK and AKT/GSK3 pathways. The finding that tau kinases may be involved in the hyperphosphorylation observed following normothermic anesthesia exposure are consistent with the findings of Run *et al.* and suggest that PP2A inhibition may not be the dominant mechanism by which hyperphosphorylation occurs following this type of normothermic anesthesia exposure (Run et al., 2009). In summary, the findings of Le Freche *et al.* are critical in that they demonstrate clearly that repeated normothermic exposure to a volatile anesthetic can result in aberrant tau hyperphosphorylation, which is associated with memory impairment. Nevertheless, a causal relationship between the phosphorylated tau burden and cognitive impairment, under these same conditions, remains to be established, and further studies are thus indicated.

The findings that exposure to a volatile anesthetic under normothermic conditions leads to remote tau hyperphosphorylation, has been further supported by recent work in a triple-transgenic (3xTg-AD) mouse model (Oddo et al., 2003), which harbors 3 mutant genes: human beta-amyloid precursor protein (APP_{Swe}), presenilin-1 ($PS\text{-}1_{M146V}$), and tau (tau_{P301L}) and develops Aβ and tau pathology as well as cognitive impairment (Filali et al., 2012). Using quantitative immunostaining, Tang *et al.* (Tang et al., 2011b) observed that repeated normothermic exposure to halothane or isoflurane (5h once a week for 4 weeks), at 6–8 months of age, was associated with significantly increased hippocampal tau phosphorylation at the Thr^{231} phosphoepitope in the 3xTg-AD mice group. Furthermore, similar increases in hippocampal tau phosphorylation were observed following either halothane or isoflurane. Dong *et al.* have also recently shown that 2h exposure to 1.4% isoflurane in 5 to 8 month-old APPswe/PS1dE9 line 85 mice (Jankowsky et al., 2004), led to persistent phosphorylation at pS262 up to 24h after anesthesia (Dong et al., 2012).

Hence, repeated volatile anesthetic exposure possesses the potential to induce persistent tau hyperphosphorylation even in the absence of anesthesia-induce hypothermia. However, the mechanisms involved in mediating this effect and the long-term neuropathological and functional sequelae stemming from this aberrant hyperphosphorylation have yet to be fully elucidated. Furthermore, as previous studies with isoflurane have not observed such negative effects on tau pathology in a normothermic setting (Planel et al., 2009; Menuet et al., 2012), these recent studies by Le Freche *et al.* and Tang *et al.,* which indeed demonstrate a pathological change in tau following normothermic volatile anesthetic exposure, strongly suggest that whether an anesthesia-induced detrimental effect on tau pathology will become manifest is possibly dependent on several factors: the anesthetic exposure paradigm, mouse strain and genotype, tau phenotype, and the actual time point at which the animal is examined for tau pathology.

Tau, anesthesia and synaptic plasticity

In addition to the potential degradation of normal cytoskeletal structure and the disruption of axonal transport, there is the possibility that the tau hyperphosphorylation, insolubility, as

well as the impaired tau binding and assembly observed following anesthesia might ultimately impair processes such as synaptic plasticity, learning and memory. Although there is considerable evidence suggesting that Aβ plays a significant role in mediating synaptic dysfunction and neurotoxicity in AD (Kamenetz et al., 2003; Haass and Selkoe, 2007), the precise mechanisms by which hyperphosphorylated tau species and other tau-related pathologic changes result in synaptic dysfunction and cognitive impairment are unclear.

Nevertheless, recent studies have suggested that tau pathology may indeed impair hippocampal synaptic transmission. For example, Hoover *et al.* have shown that the relocalization of hyperphosphorylated tau to dendritic spines was associated with synaptic dysfunction *via* a mechanism involving the impairment of glutamate receptor trafficking (Hoover et al., 2010). Furthermore, Burnouf *et al.*, demonstrated in hippocampal slices from THY-Tau22 mice, a transgenic mouse model associated with hippocampal tau pathology and concomitant memory impairment, that the enhanced synaptic transmission normally induced by brain-derived neurotrophic factor (BDNF) was impaired, and this change was associated with cognitive impairment (Burnouf et al., 2013). Mechanistically, this impaired response to exogenous BDNF was the consequence of N-methyl D-aspartate receptor (NMDA-R) dysfunction, which appears to be secondary to an abnormal interaction between tau pathology (hyperphosphorylated and insoluble tau forms) and the NR2B subunit as well as Src protein kinase, a major kinase regulating NR2B expression. As Src inhibition has been associated with decreased NR2B expression and synaptic plasticity (Sinai et al., 2010), the potential for pathological tau species to interact with this kinase, could theoretically contribute to memory impairment.

While the relationship between glutamatergic receptor and synaptic plasticity has been extensively studied, GABAergic (γ-aminobutyric acid) synapse development has been less scrutinized (Kuzirian and Paradis, 2011). Since many anesthetics bind GABA receptors (Fig. 1), their effects on tau could be mediated by this interaction. Indeed, it has been shown that $GABA_A$ receptor activation could enhance tau phosphorylation through reduced binding of PP2A to tau, and with the involvement of cdk5 but not GSK-3β (Nykanen et al., 2012). Moreover, there might be a feedback loop between tau pathology and GABAergic synapses since it was recently discovered in Tau_{P301L} mutant mice that GABAergic neurons were in a hypermetabolic state leading to increased GABA levels (Hege Nilsen et al., 2013).

Despite these findings, further studies are definitely warranted to elucidate the precise mechanisms by which tau hyperphosphorylation and aggregation lead to synaptic dysfunction and neurotoxicity, and whether anesthetics can exacerbate such systems.

Clinical Implications

There is a paucity of information examining the impact of the clinical administration of anesthesia on tau pathology in humans. This is partly due to the fact that, unfortunately, in actual clinical practice, it is often difficult to separate the impact of anesthesia from surgery, when determining the effect of anesthesia on changes in AD-associated biomarkers. Also, these studies have been somewhat limited in that they have lacked proper control groups. Nevertheless, there are some studies that have examined changes in the levels of total and phosphorylated tau in the postoperative period. Palotás *et al.* found that levels of total tau were significantly elevated at 6 months in patients who underwent coronary bypass surgery without cardiopulmonary bypass (Palotas et al., 2010). Although the patients were no longer on sedative medication at the time of CSF sampling, given the remote changes in tau pathology observed in rodents following anesthesia (Planel et al., 2009; Tang et al., 2011b; Le Freche et al., 2012), a potential contributory effect of anesthesia on the increases in total

tau observed in these patients could not be excluded. Hitherto, Tang *et al.* have published the only human study to date that has examined tau phosphorylation in otherwise healthy individuals following anesthesia for routine surgery in which the anesthesia type was actually taken into consideration (Tang et al., 2011a). These investigators measured levels of total tau and tau phosphorylated at Thr^{181} in patients undergoing surgery for idiopathic cerebrospinal fluid leak correction, and observed that both total tau and phospho-Thr^{181} steadily increased until at least 48h, which was the last sampling time point. As the authors noted, the increase in phospho-Thr^{181} postoperatively is particularly interesting, as increased levels of phosphorylation at this epitope in CSF has been observed to be the most sensitive indicator of cognitive decline in normal patients (Tang et al., 2011a).

As noted above, it is not possible to dissociate the effects of anesthesia and surgery in patients. However, a recent preclinical study in 3xTG-AD mice has attempted to tackle this problem by comparing desflurane alone *versus* desflurane and cecal ligation and found that surgery *per se* led to memory impairment, enhanced tau pathology and neuroinflammation (Tang et al., 2012). However, the study was not conclusive in terms of a causative link between cognitive impairment and tau pathology.

Nevertheless, although it is difficult to clinically dissociate the impact of anesthesia from surgery in studies designed to determine the impact of anesthesia on tau pathology in humans, there are instances in which patients receive anesthetics without undergoing a surgical procedure. For example, many of the intravenous anesthetics used during surgery are often used for sedative purposes in patients requiring mechanical ventilation in an intensive care unit setting. Furthermore, as opposed to a transient exposure for a surgical procedure, many of these patients are exposed to some of these anesthetics for days and, in some instances, for weeks. Given that there is preclinical evidence suggesting that the ability of anesthetics to exacerbate and accelerate tau pathology may indeed be a dose-dependent phenomenon and/or a consequence of repeated exposure, clearly future studies focusing on the impact of prolonged or repeated anesthesia exposure in humans, particularly those with or at risk for AD, are necessary.

Conclusion

In summary, both pre-clinical and early clinical studies suggest that anesthetics can accelerate tau pathology. Furthermore, the presence of hypothermia during anesthesia administration, a common clinical occurrence, appears to exacerbate the degree of phosphorylation and accelerate the development of neurofibrillary pathology in models of pre-existing tau pathology. However, although it may accelerate the process, hypothermia appears not to be an absolute requisite for the development of tau pathology following anesthesia exposure, as changes in tau pathology have been described during normothermic anesthesia administration.

Hence, the potential clinical impact of anesthesia on the development of tau pathology, and on AD pathology in general, should not be underestimated as recently it is estimated that 234.2 million people undergo surgery and thus anesthesia each year (Weiser et al., 2008). Furthermore, as life expectancy continues to increase and with estimates predicting that, without a significant therapeutic breakthrough, the number AD cases is expected to significantly increase (Brookmeyer et al., 2007), the potential impact of this exposure on patients with or at risk for AD should not be discounted or ignored. This is particularly true given the fact that patients with AD are at higher risk for an exacerbation of their pre-existing cognitive impairment post-operatively, a condition associated with significant medical costs (Xie and Tanzi, 2006).

Acknowledgments

This work was supported by National Institute of General Medical Sciences grants K08GM00681 and R01GM101698 (to R.A.W.), grants from Canadian Institutes for Health Research (MOP-106423, PCN-102993), Natural Sciences and Engineering Research Council (354722), Alzheimer Society of Canada, Canada Foundation for Innovation (23905), and a Research Scholar Career Awards (16205, 20048) from the Fonds de la Recherche en Santé du Québec (to E.P.).

Abbreviations

3R	3-repeat tau isoforms
4R	4-repeat tau isoforms
3xTg-AD	triple transgenic Alzheimer's disease mouse model
AD	Alzheimer's disease
AKT/PKB	protein kinase B
APP	amyloid-β precursor protein
Aβ	amyloid-β
BDNF	brain-derived neurotrophic factor
CaMKII	calcium/calmodulin-dependent protein kinase II
cdk5	cyclin-dependent kinase 5
CSF	cerebrospinal fluid
Dex	dexmedetomidine
ERK	extracellular signal-regulated kinase
GABA	γ-aminobutyric acid
GSK-3β	glycogen synthase kinase-3β
i.p	intra peritoneal
JNK	c-Jun N-terminal kinase
MAC	minimum alveolar concentration
MAPK	mitogen-activated protein kinase
MT	microtubule
MWM	Morris water maze
NFT	neurofibrillary tangles
NMDA-R	N-methyl D-aspartate receptor
NR2B	subunit 2B of NMDA receptor
PP1	protein phosphatase 1
PP2A	protein phosphatase 2A
PP2B	protein phosphatase 2B
PS-1	presenilin-1
-Ser	serine
Src	short for sarcoma, a non-receptor tyrosine kinase

Tau-SH-SY5Y cells	human neuroblastoma cells constitutively expressing human tau with 3 microtubule-binding domains
Thr	threonine

References

Alonso AC, Zaidi T, Novak M, Grundke-Iqbal I, Iqbal K. Hyperphosphorylation induces self-assembly of tau into tangles of paired helical filaments / straight filaments. Proc Natl Acad Sci U S A. 2001; 98:6923–6928. [PubMed: 11381127]

Andorfer C, Acker CM, Kress Y, Hof PR, Duff K, Davies P. Cell-cycle reentry and cell death in transgenic mice expressing nonmutant human tau isoforms. J Neurosci. 2005; 25:5446–5454. [PubMed: 15930395]

Andorfer C, Kress Y, Espinoza M, de Silva R, Tucker KL, Barde Y-AA, Duff K, Davies P. Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms. J Neurochem. 2003; 86:582–590. [PubMed: 12859672]

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology. 1992; 42:631–639. [PubMed: 1549228]

Avila J, Lucas JJ, Perez M, Hernandez F. Role of tau protein in both physiological and pathological conditions. Physiol Rev. 2004; 84:361–384. [PubMed: 15044677]

Binder LI, Frankfurter A, Rebhun LI. The distribution of tau in the mammalian central nervous system. J Cell Biol. 1985; 101:1371–1378. [PubMed: 3930508]

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991; 82:239–259. [PubMed: 1759558]

Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging. 1997; 18:351–357. [PubMed: 9330961]

Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol. 2006; 112:389–404. [PubMed: 16906426]

Bretteville A, Planel E. Tau aggregates: toxic, inert, or protective species? J Alzheimers Dis. 2008; 14:431–436. [PubMed: 18688094]

Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007; 3:186–191. [PubMed: 19595937]

Buee L, Bussiere T, Buee-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res Brain Res Rev. 2000; 33:95–130. [PubMed: 10967355]

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]

Burnouf S, Martire A, Derisbourg M, Laurent C, Belarbi K, Leboucher A, Fernandez-Gomez FJ, Troquier L, Eddarkaoui S, Grosjean ME, Demeyer D, Muhr-Tailleux A, Buisson A, Sergeant N, Hamdane M, Humez S, Popoli P, Buee L, Blum D. NMDA receptor dysfunction contributes to impaired brain-derived neurotrophic factor-induced facilitation of hippocampal synaptic transmission in a Tau transgenic model. Aging Cell. 2013; 12:11–23. [PubMed: 23082852]

Butner KA, Kirschner MW. Tau protein binds to microtubules through a flexible array of distributed weak sites. The Journal of Cell Biology. 1991; 115:717–730. [PubMed: 1918161]

Cross DA, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature. 1995; 378:785–789. [PubMed: 8524413]

Culley DJ, Baxter M, Yukhananov R, Crosby G. The memory effects of general anesthesia persist for weeks in young and aged rats. Anesthesia and analgesia. 2003; 96:1004–1009. table of contents. [PubMed: 12651650]

Delacourte A, Flament S, Dibe EM, Hublau P, Sablonniere B, Hemon B, Sherrer V, Defossez A. Pathological proteins Tau 64 and 69 are specifically expressed in the somatodendritic domain of the degenerating cortical neurons during Alzheimer's disease. Demonstration with a panel of antibodies against Tau proteins. Acta Neuropathol. 1990; 80:111–117. [PubMed: 2117840]

Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, Ghozali F, Fallet-Bianco C, Pasquier F, Lebert F, Petit H, Di Menza C. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology. 1999; 52:1158–1165. [PubMed: 10214737]

Delobel P, Flament S, Hamdane M, Delacourte A, Vilain JP, Buee L. Modelling Alzheimer-specific abnormal Tau phosphorylation independently of GSK3b and PKA kinase activities. FEBS Lett. 2002; 516:151–155. [PubMed: 11959122]

Dong Y, Wu X, Xu Z, Zhang Y, Xie Z. Anesthetic isoflurane increases phosphorylated tau levels mediated by caspase activation and Abeta generation. PloS one. 2012; 7:e39386. [PubMed: 22745746]

Duff K, Planel E. Untangling memory deficits. Nat Med. 2005; 11:826–827. [PubMed: 16079873]

Duff K, Knight H, Refolo LM, Sanders S, Yu X, Picciano M, Malester B, Hutton M, Adamson J, Goedert M, Burki K, Davies P. Characterization of pathology in transgenic mice over-expressing human genomic and cDNA tau transgenes. Neurobiology of Disease. 2000; 7:87–98. [PubMed: 10783293]

Dutschmann M, Menuet C, Stettner GM, Gestreau C, Borghgraef P, Devijver H, Gielis L, Hilaire G, Van Leuven F. Upper airway dysfunction of Tau-P301L mice correlates with tauopathy in midbrain and ponto-medullary brainstem nuclei. J Neurosci. 2010; 30:1810–1821. [PubMed: 20130190]

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]

Feinstein SC, Wilson L. Inability of tau to properly regulate neuronal microtubule dynamics: a loss-of-function mechanism by which tau might mediate neuronal cell death. Biochimica et biophysica acta. 2005; 1739:268–279. [PubMed: 15615645]

Filali M, Lalonde R, Theriault P, Julien C, Calon F, Planel E. Cognitive and non-cognitive behaviors in the triple transgenic mouse model of Alzheimer's disease expressing mutated APP, PS1, and Mapt (3xTg-AD). Behav Brain Res. 2012; 234:334–342. [PubMed: 22796601]

Fulton D, Kemenes I, Andrew RJ, Benjamin PR. Time-window for sensitivity to cooling distinguishes the effects of hypothermia and protein synthesis inhibition on the consolidation of long-term memory. Neurobiol Learn Mem. 2008; 90:651–654. [PubMed: 18793738]

Goedert M, Jakes R. Expression of separate isoforms of human tau protein: correlation with the tau pattern in brain and effects on tubulin polymerization. EMBO J. 1990; 9:4225–4230. [PubMed: 2124967]

Goedert M, Cohen ES, Jakes R, Cohen P. p42 MAP kinase phosphorylation sites in microtubule-associated protein tau are dephosphorylated by protein phosphatase 2A1. Implications for Alzheimer's disease [corrected] [published erratum appears in FEBS Lett 1992 Nov 23;313(2): 203]. FEBS Lett. 1992; 312:95–99. [PubMed: 1330687]

Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, Wisniewski HM. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. J Biol Chem. 1986; 261:6084–6089. [PubMed: 3084478]

Guillozet AL, Weintraub S, Mash DC, Mesulam MM. Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. Arch Neurol. 2003; 60:729–736. [PubMed: 12756137]

Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol. 2007; 8:101–112. [PubMed: 17245412]

Hamdane M, Sambo A-VVA-V, Delobel P, Bégard S, Violleau A, Delacourte AA, Bertrand P, Benavides J, Buée L, Begard S, Buee L. Mitotic-like tau phosphorylation by p25-Cdk5 kinase complex. The Journal of biological chemistry. 2003; 278:34026–34034. [PubMed: 12826674]

Hamm RJ. Hypothermia-induced retrograde amnesia in mature and aged rats. Dev Psychobiol. 1981; 14:357–364. [PubMed: 7250524]

Harman D. Alzheimer's disease: role of aging in pathogenesis. Ann N Y Acad Sci. 2002; 959:384–385. [PubMed: 11976212]

Hege Nilsen L, Rae C, Ittner LM, Gotz J, Sonnewald U. Glutamate metabolism is impaired in transgenic mice with tau hyperphosphorylation. J Cereb Blood Flow Metab. 2013

Hoover BR, Reed MN, Su J, Penrod RD, Kotilinek LA, Grant MK, Pitstick R, Carlson GA, Lanier LM, Yuan LL, Ashe KH, Liao D. Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. Neuron. 2010; 68:1067–1081. [PubMed: 21172610]

Iqbal K, Grundke-Iqbal I. Metabolic/signal transduction hypothesis of Alzheimer's disease and other tauopathies. Acta Neuropathologica. 2005; 109:25–31. [PubMed: 15645264]

Iqbal K, Grundke-Iqbal I. Alzheimer neurofibrillary degeneration: significance, etiopathogenesis, therapeutics and prevention. J Cell Mol Med. 2008; 12:38–55. [PubMed: 18194444]

Janke C, Beck M, Stahl T, Holzer M, Brauer K, Bigl V, Arendt T. Phylogenetic diversity of the expression of the microtubule-associated protein tau: implications for neurodegenerative disorders. Brain Res Mol Brain Res. 1999; 68:119–128. [PubMed: 10320789]

Jankowsky JL, Fadale DJ, Anderson J, Xu GM, Gonzales V, Jenkins NA, Copeland NG, Lee MK, Younkin LH, Wagner SL, Younkin SG, Borchelt DR. Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: evidence for augmentation of a 42-specific gamma secretase. Hum Mol Genet. 2004; 13:159–170. [PubMed: 14645205]

Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S, Malinow R. APP processing and synaptic function. Neuron. 2003; 37:925–937. [PubMed: 12670422]

Kuzirian MS, Paradis S. Emerging themes in GABAergic synapse development. Prog Neurobiol. 2011; 95:68–87. [PubMed: 21798307]

Le Freche H, Brouillette J, Fernandez-Gomez FJ, Patin P, Caillierez R, Zommer N, Sergeant N, Buee-Scherrer V, Lebuffe G, Blum D, Buee L. Tau Phosphorylation and Sevoflurane Anesthesia: An Association to Postoperative Cognitive Impairment. Anesthesiology. 2012

Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van Slegtenhorst M, Gwinn-Hardy K, Paul Murphy M, Baker M, Yu X, Duff K, Hardy J, Corral A, Lin WL, Yen SH, Dickson DW, Davies P, Hutton M. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. Nat Genet. 2000; 25:402–405. [PubMed: 10932182]

Lindwall G, Cole RD. Phosphorylation affects the ability of tau protein to promote microtubule assembly. J Biol Chem. 1984; 259:5301–5305. [PubMed: 6425287]

Liu F, Grundke-Iqbal I, Iqbal K, Gong CX. Contributions of protein phosphatases PP1, PP2A, PP2B and PP5 to the regulation of tau phosphorylation. Eur J Neurosci. 2005; 22:1942–1950. [PubMed: 16262633]

Liu W, Xu J, Wang H, Xu C, Ji C, Wang Y, Feng C, Zhang X, Xu Z, Wu A, Xie Z, Yue Y. Isoflurane-induced spatial memory impairment by a mechanism independent of amyloid-beta levels and tau protein phosphorylation changes in aged rats. Neurological research. 2012; 34:3–10. [PubMed: 22196855]

Maccioni RB, Otth CC II, Munoz JP. The protein kinase Cdk5. Structural aspects, roles in neurogenesis and involvement in Alzheimer's pathology. Eur J Biochem. 2001; 268:1518–1527. [PubMed: 11248668]

Mailliot C, Bussiere T, Hamdane M, Sergeant N, Caillet ML, Delacourte A, Buee L. Pathological tau phenotypes. The weight of mutations, polymorphisms, and differential neuronal vulnerabilities. Ann N Y Acad Sci. 2000; 920:107–114. [PubMed: 11193138]

Mandelkow EM, Stamer K, Vogel R, Thies E, Mandelkow E. Clogging of axons by tau, inhibition of axonal traffic and starvation of synapses. Neurobiology of aging. 2003; 24:1079–1085. [PubMed: 14643379]

Menuet C, Cazals Y, Gestreau C, Borghgraef P, Gielis L, Dutschmann M, Van Leuven F, Hilaire G. Age-related impairment of ultrasonic vocalization in Tau.P301L mice: possible implication for progressive language disorders. PLoS ONE. 2011a; 6:e25770. [PubMed: 22022446]

Menuet C, Borghgraef P, Voituron N, Gestreau C, Gielis L, Devijver H, Dutschmann M, Van Leuven F, Hilaire G. Isoflurane anesthesia precipitates tauopathy and upper airways dysfunction in pre-symptomatic Tau.P301L mice: Possible implication for neurodegenerative diseases. Neurobiol Dis. 2012

Menuet C, Borghgraef P, Matarazzo V, Gielis L, Lajard AM, Voituron N, Gestreau C, Dutschmann M, Van Leuven F, Hilaire G. Raphe tauopathy alters serotonin metabolism and breathing activity in terminal Tau.P301L mice: possible implications for tauopathies and Alzheimer's disease. Respir Physiol Neurobiol. 2011b; 178:290–303. [PubMed: 21763469]

Mi K, Johnson GV. The role of tau phosphorylation in the pathogenesis of Alzheimer's disease. Current Alzheimer research. 2006; 3:449–463. [PubMed: 17168644]

Miyasaka T, Sato S, Tatebayashi Y, Takashima A. Microtubule destruction induces tau liberation and its subsequent phosphorylation. FEBS Lett. 2010; 584:3227–3232. [PubMed: 20561519]

Nykanen NP, Kysenius K, Sakha P, Tammela P, Huttunen HJ. gamma-Aminobutyric acid type A (GABAA) receptor activation modulates tau phosphorylation. The Journal of biological chemistry. 2012; 287:6743–6752. [PubMed: 22235112]

Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron. 2003; 39:409–421. [PubMed: 12895417]

Palotas A, Reis HJ, Bogats G, Babik B, Racsmany M, Engvau L, Kecskemeti E, Juhasz A, Vieira LB, Teixeira AL, Mukhamedyarovi MA, Rizvanov AA, Yalvac ME, Guimaraes MM, Ferreira CN, Zefirov AL, Kiyasov AP, Wang L, Janka Z, Kalman J. Coronary artery bypass surgery provokes Alzheimer's disease-like changes in the cerebrospinal fluid. J Alzheimers Dis. 2010; 21:1153–1164. [PubMed: 21504113]

Panda D, Samuel JC, Massie M, Feinstein SC, Wilson L. Differential regulation of microtubule dynamics by three- and four-repeat tau: implications for the onset of neurodegenerative disease. Proceedings of the National Academy of Sciences of the United States of America. 2003; 100:9548–9553. [PubMed: 12886013]

Papasozomenos SC, Binder LI. Phosphorylation determines two distinct species of Tau in the central nervous system. Cell Motil Cytoskeleton. 1987; 8:210–226. [PubMed: 2446784]

Papon M-A, Whittington RA, El-Khoury NB, Planel E. Alzheimer's disease and anesthesia. Frontiers in neuroscience. 2011; 4:272. [PubMed: 21344011]

Planel E, Sun X, Takashima A. Role of GSK-3 beta in Alzheimer's disease pathology. Drug Development Research. 2002; 56:491–510.

Planel E, Bretteville A, Liu L, Virag L, Du ALL, Yu WHH, Dickson DWW, Whittington RAA, Duff KEE. Acceleration and persistence of neurofibrillary pathology in a mouse model of tauopathy following anesthesia. The FASEB Journal. 2009; 23:2595.

Planel E, Richter KEG, Nolan CE, Finley JE, Liu L, Wen Y, Krishnamurthy P, Herman M, Wang L, Schachter JB, Nelson RB, Lau L-FL-FF, Duff KE. Anesthesia leads to tau hyperphosphorylation through inhibition of phosphatase activity by hypothermia. J Neurosci. 2007; 27:3090–3097. [PubMed: 17376970]

Planel E, Krishnamurthy P, Miyasaka T, Liu L, Herman M, Kumar A, Bretteville A, Figueroa HY, Yu WH, Whittington Ra, Davies P, Takashima A, Nixon RA, Duff KE. Anesthesia-induced hyperphosphorylation detaches 3-repeat tau from microtubules without affecting their stability in vivo. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2008; 28:12798–12807. [PubMed: 19036972]

Planel E, et al. Alterations in glucose metabolism induce hypothermia leading to tau hyperphosphorylation through differential inhibition of kinase and phosphatase activities: implications for Alzheimer's disease. J Neurosci. 2004; 24:2401–2411. [PubMed: 15014115]

Pollak D, Cairns N, Lubec G. Cytoskeleton derangement in brain of patients with Down syndrome, Alzheimer's disease and Pick's disease. Journal of neural transmission. 2003:149–158. [PubMed: 15068247]

Riccio DC, Hodges LA, Randall PK. Retrograde amnesia produced by hypothermia in rats. J Comp Physiol Psychol. 1968; 66:618–622. [PubMed: 4305622]

Richardson R, Riccio DC, Morilak D. Anterograde memory loss induced by hypothermia in rats. Behav Neural Biol. 1983; 37:76–88. [PubMed: 6882343]

Riederer BM, Binder LI. Differential distribution of tau proteins in developing cat cerebellum. Brain Res Bull. 1994; 33:155–161. [PubMed: 8275333]

Run X, Liang Z, Gong CX. Anesthetics and tau protein: animal model studies. J Alzheimers Dis. 2010; 22(Suppl 3):49–55. [PubMed: 20858970]

Run X, Liang Z, Zhang L, Iqbal K, Grundke-Iqbal I, Gong CX. Anesthesia induces phosphorylation of tau. J Alzheimers Dis. 2009; 16:619–626. [PubMed: 19276556]

Sadik G, Tanaka T, Kato K, Yamamori H, Nessa BN, Morihara T, Takeda M. Phosphorylation of tau at Ser214 mediates its interaction with 14-3-3 protein: implications for the mechanism of tau aggregation. J Neurochem. 2009; 108:33–43. [PubMed: 19014373]

Santucci AC, Kasenow PM, Riccio DC, Richardson R. Hypothermia-induced anterograde amnesia: is memory loss attributable to impaired acquisition? Behav Neural Biol. 1987; 48:13–23. [PubMed: 3632548]

Sato S, Tatebayashi Y, Akagi T, Chui DH, Murayama M, Miyasaka T, Planel E, Tanemura K, Sun X, Hashikawa T, Yoshioka K, Ishiguro K, Takashima A. Aberrant tau phosphorylation by glycogen synthase kinase-3beta and JNK3 induces oligomeric tau fibrils in COS-7 cells. J Biol Chem. 2002; 277:42060–42065. [PubMed: 12191990]

Sinai L, Duffy S, Roder JC. Src inhibition reduces NR2B surface expression and synaptic plasticity in the amygdala. Learn Mem. 2010; 17:364–371. [PubMed: 20660101]

Tan W, Cao X, Wang J, Lv H, Wu B, Ma H. Tau hyperphosphorylation is associated with memory impairment after exposure to 1.5% isoflurane without temperature maintenance in rats. Eur J Anaesthesiol. 2010; 27:835–841. [PubMed: 20485178]

Tang JX, Baranov D, Hammond M, Shaw LM, Eckenhoff MF, Eckenhoff RG. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. Anesthesiology. 2011a; 115:727–732. [PubMed: 21857497]

Tang JX, Mardini F, Janik LS, Garrity ST, Li RQ, Bachlani G, Eckenhoff RG, Eckenhoff MF. Modulation of Murine Alzheimer Pathogenesis and Behavior by Surgery. Ann Surg. 2012

Tang JX, Mardini F, Caltagarone BM, Garrity ST, Li RQ, Bianchi SL, Gomes O, Laferla FM, Eckenhoff RG, Eckenhoff MF. Anesthesia in presymptomatic Alzheimer's disease: a study using the triple-transgenic mouse model. Alzheimers Dement. 2011b; 7:521–531. e521. [PubMed: 21745760]

Tatebayashi Y, Planel E, Chui DH, Sato S, Miyasaka T, Sahara N, Murayama M, Kikuchi N, Yoshioka K, Rivka R, Takashima A. c-jun N-terminal kinase hyperphosphorylates R406W tau at the PHF-1 site during mitosis. Faseb J. 2006; 20:762–764. [PubMed: 16478768]

Terry RD. The pathogenesis of Alzheimer disease: an alternative to the amyloid hypothesis. Journal of neuropathology and experimental neurology. 1996; 55:1023–1025. [PubMed: 8857998]

Terwel D, Lasrado R, Snauwaert J, Vandeweert E, Haesendonck CV, Borghgraef P, Leuven FV, Van Haesendonck C, Van Leuven F. Changed conformation of mutant Tau-P301L underlies the moribund tauopathy, absent in progressive, nonlethal axonopathy of Tau-4R/2N transgenic mice. The Journal of biological chemistry. 2005; 280:3963–3973. [PubMed: 15509565]

Trojanowski JQ, Lee VM. Paired helical filament tau in Alzheimer's disease. The kinase connection. Am J Pathol. 1994; 144:449–453. [PubMed: 8129030]

Wang JZ, Grundke-Iqbal I, Iqbal K. Restoration of biological activity of Alzheimer abnormally phosphorylated tau by dephosphorylation with protein phosphatase-2A, -2B and -1. Brain Res Mol Brain Res. 1996; 38:200–208. [PubMed: 8793108]

Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008; 372:139–144. [PubMed: 18582931]

Whittington RA, Papon MA, Chouinard F, Planel E. Hypothermia and Alzheimer's disease neuropathogenic pathways. Current Alzheimer research. 2010; 7:717–725. [PubMed: 20678067]

Whittington RA, Bretteville A, Virag L, Emala CW, Maurin TO, Marcouiller F, Julien C, Petry FR, El Khoury NB, Morin F, Charron J, Planel E. Anesthesia-induced hypothermia mediates decreased ARC gene and protein expression through ERK/MAPK inactivation. Scientific Reports. 2013 In press.

Whittington RA, Virág L, Marcouiller F, Papon M-AA, El Khoury NB, Julien C, Morin F, Emala CW, Planel E, Virag L, Marcouiller F, Papon M-AA, Khoury NB, Julien C, Morin F, Emala CW, Planel E. Propofol directly increases tau phosphorylation. PLoS ONE. 2011; 6:e16648. [PubMed: 21304998]

Wilcock GK, Esiri MM. Plaques, tangles and dementia. A quantitative study. J Neurol Sci. 1982; 56:343–356. [PubMed: 7175555]

Xie Z, Tanzi RE. Alzheimer's disease and post-operative cognitive dysfunction. Exp Gerontol. 2006; 41:346–359. [PubMed: 16564662]

Xie Z, Dong Y, Maeda U, Moir R, Inouye SK, Culley DJ, Crosby G, Tanzi RE. Isoflurane-induced apoptosis: a potential pathogenic link between delirium and dementia. The journals of gerontology Series A, Biological sciences and medical sciences. 2006; 61:1300–1306.

Zhu X, Lee HG, Raina AK, Perry G, Smith MA. The role of mitogen-activated protein kinase pathways in Alzheimer's disease. Neurosignals. 2002; 11:270–281. [PubMed: 12566928]

Highlights

- Exposure to anesthetics might enhance the risk of Alzheimer's disease
- Alzheimer's disease brains contain intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau; tau pathology correlates with dementia
- Here we review evidences showing that anesthesia can enhance tau pathology

Table 1

List of anesthetics known to induce tau hyperphosphorylation *in vivo*, either directly or indirectly.

ANESTHETICS	NAME	FAMILY	ADMINISTRATION	PRIMARY MECHANISM	USAGE
Isoflurane	1-chloro-2,2,2-trifluoroethyl difluoromethyl ether	Halogenated ether	Volatile	Not well understood. Binds to GABA, glutamate and glycine receptors	• Maintenance of general anesthesia
Sevoflurane	1,1,1,3,3,3-hexafluoro-2- (fluoromethoxy)propane	Halogenated ether	Volatile	Not well understood. Binds to GABA, glutamates and glycine receptors	• Induction and maintenance of general anesthesia
Halothane	2-bromo-2-chloro-1,1,1- trifluorethane)	Halogenated ether	Volatile	Not well understood. Binds to GABA, glutamates and glycine receptors	• Induction and maintenance of general anesthesia
Propofol	2,6-diisopropylphenol	Alkyl phenol	Intravenous	Potentiation of GABAA receptor activity	• Induction and maintenance of general anesthesia • Sedation for mechanical ventilation • Procedural sedation
Pentobarbital	5-Ethyl-5-(1-methylbutyl)- 2,4,6(1H,3H,5H)-pyrimidinetrione	Barbiturate	Intravenous	Positive allosteric modulation of GABAA receptors, binding site is located in the Beta subunit. Also, targets glutamate, adenosine, and nicotinic acetylcholine receptors	• Anesthetic in veterinary medicine
Dexmedetomidine	(S)-4-[1-(2,3-dimethylphenyl)ethyl]-3H-imidazole	α2-adrenergic receptor agonist	Intravenous	Agonist of α2-adrenergic receptors	• Sedation without causing respiratory depression
Chloral hydrate	2,2,2-trichloroethane-1,1-diol	NA	Intravenous, oral	Enhances the GABA receptor complex.	• Sedative, hypnotic drug

Table 2

List of studies demonstrating *in vivo* tau hyperphosphorylation after anesthesia.

REFERENCE	ANESTHETICS USED	DOSES USED	MODEL USED	EFFECT OF HYPOTHERMIA	EFFECT OF NORMOTHERMIA	MICROTUBULE BINDING	COGNITIVE IMPAIRMENT	MECHANISMS	NOTES
Planel (2007)	Isoflurane Pentobarbital Chloral hydrate	• Exposure to vapors • 100mg/kg i.p. • 500mg/kg i.p	• C57BL/6 male mice	• AT8, PHF-1, pS^{199}, TG3, MC6, pS^{262}, pS^{422} (+++)	• Rescued	• NA	• NA	• Inhibition of PP2A activity under hypothermic conditions	• 80% increase in tau phosphorylation for every degree Celsius drop below 37°C.
Planel (2008)	Pentobarbital	• 100 mg/kg i.p • 100 mg/kg i.p.	• C57BL/6J female and male mice • hTau female and male mice	• (MT)-free Tau (+++) • (MT)-free Tau (+++)	• NA • NA	• Impaired • Impaired	• NA	• NA	• No MT detachment or relocalization in non-transgenic mice • Relocalization of 3R tau in the soma
Planel (2009)	Isoflurane	• 1.3% (1.0 MAC, 30% O_2) for 4h	• JNLP3 female mice	• AT8, CP13, MC-6, PHF-1 (+++) • Increase in insoluble tau levels	• Rescued	• NA	• NA	• Anesthesia-induced hypothermia inhibited PP2AC	• Same results with repeated anesthesia in JNLP3 male mice
Run (2009)	Pentobarbital	• 50mg/kg i.p for 1h	• C57BL/6J female mice	• Thr^{181}, Thr^{205}, Thr^{212}, 12E8 (+++)	• Thr^{181}, Ser^{199}, Thr205, Thr^{212}, Ser^{262}, Ser^{404} (++)	• NA	• NA	• Anesthesia-induced hypothermia leading to PP2AC inhibition • Normothermic effect due to activation of MAPK and JNK	.
Tan (2010)	Isoflurane	• 1.5% (1.0 MAC, 30% O_2) for 2h	• Sprague-Dawley rats	• Thr^{205}, Ser^{396} (+++)	• Rescued	• NA	• NA	• Inhibition of PP2A under hypothermic conditions, rescued by normothermic conditions.	
Whittington (2011)	Propofol	• 250 mg/kg i.p. (0.5h, 2h & 6h) • 3μg/ml	• C57BL/6 male mice • Tau-SH-SY5Y cells	• AT8, CP13, PHF-1 (+++) • NA	• AT8, CP13, PHF-1 (+) • AT8, CP13, PHF-1 (+)	• NA	• NA	• Normothermic effect likely due to PP2A inhibition.	• Effect persisted up to 2h at AT8
Tang (2011)	Halothane or Isoflurane	• 0.9–1.1% (1.0 MAC, 40% O_2),	• 3xTg-AD mice	• NA	• Thr^{231} (+++)	• NA	• NA	• NA	

REFERENCE	ANESTHETICS USED	DOSES USED	MODEL USED	EFFECT OF HYPOTHERMIA	EFFECT OF NORMOTHERMIA	MICROTUBULE BINDING	COGNITIVE IMPAIRMENT	MECHANISMS	NOTES
		repeated exposure							
Menuet (2012)	isoflurane	• 1.5% (1.0 MAC, 30% O2) for 4h	• Tau P301L mice	• AT8 (+++)	• NA	• NA	• NA	• NA	• Upper airway dysfunction under hypothermic conditions, rescue effect by normothermia.
Liu (2012)	isoflurane	• 1.4% (1.0 MAC, 30% O2) for 2h	• Sprague-Dawley rats	• Thr231, Ser396 (+++),	• Rescued	• NA	• YES	• NA	• Cognitive impairment not rescued by normorthermic conditions
Le Freche (2012)	Sevoflurane	• 1.5 or 2.5% (repeated exposure)	• C57BL/6 female mice	• NA	• PHF-1, Thr181 (+++)	• NA	• YES	• Normothermic effect likely due to activation of AKT and ERK kinases and inactivation of GSK-3.	
Dong (2012)	isoflurane	• 1.4% for 2h	• AD transgenic mice [B6.Cg-Tg (APPswe, PSEN1dE9) 85Dbo/J]	• NA	• PS262 (+++)	• NA	• NA	• Normothermic effect may result from the isoflurane-induced caspase activation and Aβ generation	• Effect persisted up to 24h after exposure
Whittington (personal communication)	Dexmedetomidine	• 300μg/kg i.p. (0.5h, 2h & 6h)	• C57BL/6 male mice • Tau-SH-SY5Y cells	• NA	• AT8, PHF-1, CP13 (+++)	• NA	• NA	• NA	• Effect persisted 2h later for all three epitopes and up to 6h at AT8