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Review Article

Do inhalational anesthetics cause cognitive dysfunction?

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ABSTRACT

Increasing evidence indicates that inhalational anesthetics may cause or increase the risk of developing postoperative cognitive dysfunction (POCD), especially in the elderly population. POCD may exist as a transient or long-term complication of surgery and anesthesia and is associated with reduced quality of life. There remains great discrepancy between clinical studies investigating the prevalence of POCD and inhalational anesthetics as many fail to show an association. However, numerous animal studies have suggested that inhalational anesthetics may alter cognitive function via amyloid β accumulation, modified neurotransmission, synaptic changes and dysregulated calcium homeostasis. Other factors such as neuroinflammation and pro-inflammatory cytokines may also play a role. This paper reviews the role of inhalational anesthetics in the etiology and underlying mechanisms that result in POCD.

1. Introduction

Surgical procedures and administration of anesthesia are associated with a transient or permanent state of cognitive decline. Many studies have documented the onset of postoperative cognitive dysfunction (POCD), which manifests subsequent to surgical procedures as a decline in brain function, typically resolving within 12 months. Extensive research has been conducted evaluating the effect of cardiopulmonary bypass during coronary artery bypass surgery (CABG), which is deemed to be the leading cause of POCD. The causal association between major surgical procedures, such as CABG, and cognitive decline has been well documented but it can also arise with minor surgery.[1] In examining the role of anesthesia and surgery on POCD it is extremely difficult to discriminate between the effects of the anesthetic agent and the effects of surgery and associated inflammation. However, animal models have suggested that inhalational anesthetic agents may precipitate a decline in cognitive function.[2,3] Some animal studies have suggested that surgery or anesthesia can increase amyloid β formation in the brain and impair memory.[4,5] Extensive deposition of amyloid β may result in synaptic loss and neuronal dysfunction, a central feature in the pathogenesis of Alzheimer's disease. It has been hypothesized that, perhaps through a build-up of amyloid β, inhalational anesthetics exert a neurotoxic effect on brain function. This review focuses on inhalational anesthesia and its role in the development of cognitive dysfunction. Determining the association between inhalational anesthesia and cognitive decline is essential in order to optimize postoperative outcomes in surgical patients and reduce the incidence of POCD.

2. POCD prevalence and incidence

In 1982, Savageau first described an association between cognitive dysfunction, surgery and anesthesia exposure.[6] The International Study of Postoperative Cognitive Dysfunction (ISPOCD) evaluating the prevalence and risk factors associated with POCD in the elderly population (mean age 68 years, range 60–-81 years) found a 26% incidence 1 week post-surgery with 10% of study participants exhibiting POCD 3 months post-surgery. Persistent POCD, as defined by 3 months after surgery, was associated with greater mortality than 1 week post-surgery. The authors concluded that age along with duration of anesthesia and poor education were significant risk factors in the development of POCD.[7] In a study comparing the effects of xenon, an inhalational anesthetic, to propofol, an intravenous anaesthetic, on development of POCD in elderly patients no significant difference in long-term cognitive function was observed.[8] Another study comparing these two types of anesthesia for supplementary general anesthesia for 35 patients undergoing knee surgery also found no difference in long-term cognitive function.[9] However, the authors acknowledged that a failure to find a significant difference might have been because of the small sample size as opposed to the absence of a true difference.

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The highest incidence of POCD occurs in elderly patients,[7] but it can develop in all age groups. The actual incidence of POCD varies greatly depending on how the condition is defined and the neuropsychological tests used in assessing cognitive function. As such the average incidence rates have been reported to be 53% at discharge, 30–80% a few weeks after surgery, 10–60% 3–6 months post-surgery and 30% at 1–2 years following surgery.[6,10–16] However, the mechanisms of POCD development remain largely unknown although the risk factors including old age, pre-operative medication, diabetes, type of surgery and atherosclerotic disease have been identified.[7,17–19] In this review, we will focus on the possible mechanisms of anesthesia-induced POCD development.

3. Anesthesia and cognitive decline

Several studies have been conducted with the aim of elucidating the mechanism underlying the cognitive dysfunction that follows anesthesia exposure; yet a clear mechanism remains to be defined. There is substantial evidence suggesting anesthesia has a role in cognitive decline, nevertheless a consensus remains to be reached between general opinion and accepted knowledge.

3.1. Neurocognitive dysfunction

Anesthetics exert their effect on consciousness at various levels in the central nervous system (CNS) and as such the phenomena witnessed subsequent to anesthetic administration prior to surgery is not the result of a single drug–target interaction. Anesthesia, even in low concentrations, can cause short-term amnesia, which is likely to be mediated through impairment of hippocampal function as the hippocampus is involved in short-term memory. Anesthetic agents also moderate function at various excitatory neurotransmitter-gated ion channels such as the ionotropic N-methyl-D-aspartic acid (NMDA) channel and inhibitory channels such as the γ-aminobutyric acid (GABA) channel. Actions at these sites may cause a modification in brain activity and can impair cognitive function.[20] In addition, a role for nicotinic acetylcholine receptors (nAChRs) in cognitive processes such as memory has been elucidated with dysfunction of the receptor linked to various CNS disorders such as Alzheimer's and Parkinson's diseases.[21] Thus it would appear, as has been suggested, that inhalational anesthetics modulate central nicotinic transmission despite nAChRs not directly influencing anesthesia-induced hypnosis.[19]

Long-term memory formation requires activation of NMDA receptors[22] with GABA receptors providing the major inhibitory stimulus on memory consolidation.[23] Both NMDA and GABA neurotransmitters are present within the hippocampus and thus subject to dysregulation by anesthetic agents. In 2004 Culley et al reported that in a rat model isoflurane-nitrous oxide general anesthesia produced impairment in the ability to acquire and perform a spatial memory task.[3] The authors inferred that the impairment in performance was caused by an anesthesia-induced alteration of structural and functional changes within the CNS. Importantly this deficit in performance occurred in both young and old mice, suggesting that it is not age dependent. Impaired hippocampal function and learning subsequent to isoflurane and nitrous oxide-induced anaesthesia has been well documented.[24,25] In a rat model of Pavlovian fear conditioning, isoflurane was found to cause anterograde amnesia.[26] Various volatile anesthetics have been shown to produce persistent detrimental effects on memory, learning and functional changes within the CNS.[19] From the body of evidence available it is clear that anesthesia-receptor interaction contributes to the clinical picture of neurocognitive dysfunction, yet the mechanisms underlying the resultant pathophysiology remains unclear.

3.2. Beta amyloid accumulation and deposition

The exact pathogenesis of POCD is complex and multifactorial; however it appears to share certain pathological markers with Alzheimer's disease including amyloid β deposition, astrocytic gliosis and tau phosphorylation.[4] Animal models have shown that anesthetics, particularly inhalational anesthetics, can increase the development of these pathological markers in the brain.[4,27,28]

The evidence implicating inhalational anesthesia exposure with increased amyloid β accumulation is considerable.[3,5,27] Isoflurane, in particular, has been shown to enhance amyloid β oligomerization and cytotoxicity.[29] *In vitro* studies have identified the inhalational anesthetic isoflurane as a neurotoxic agent promoting β-site amyloid precursor protein-cleaving enzyme (BACE) activity and amyloid β deposition,[30] and this has been replicated *in vivo* at clinical concentrations.[5] Given that isoflurane is known to be a significant cerebral metabolic depressant,[31] Xie et al hypothesized that isoflurane may alter amyloid precursor protein (APP) function and promote amyloid β production via energy inhibition.[5] Dong et al found that in wild-type mice sevoflurane elevated levels of BACE and amyloid β.[27] Bianchi et al showed that in the Tg2576 mouse model of APP overexpression amyloid β plaque formation increased, 1 week after anesthetic exposure.[32] Eckenhoff et al established that halothane produced a concentration-dependent enhancement of amyloid β oligomerization with anesthetic concentrations analogous to those used in the clinical setting.[29] These findings suggest a link between inhaled anesthetics and neurocognitive disease pathogenesis.

3.3. Neuroinflammation and anesthesia

Neuroinflammation has been shown to play a role in the pathogenesis of neurodegenerative disorders[33–35] and cause cognitive impairment in humans and in animals.[36,37] Various pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-β (IL-β) are released into the bloodstream following surgery.[18] These cytokines can then go on to potentiate the inflammatory response by promoting the release of other cytokines from glial cells in the brain. Inflammation plays a pivotal role in the development of POCD.[38–40] Wu et al found that clinically relevant isoflurane anesthesia increased the production of TNF-α and IL-β and also IL-6 in the neurons of mice.[41] These findings support the current literature implicating a role for neurons in the production of pro-inflammatory cytokines which can lead to neuroinflammation.[35] Wu et al also showed that isoflurane elevated TNF-α levels to a greater degree in Alzheimer's disease transgenic mice, suggesting increased susceptibility to neuroinflammation in this study group;[41] this finding could have interesting correlates for the representative human demographic.

However, Schilling et al demonstrated that volatile anesthetics, in particular sevoflurane and desflurane, reduced pro-inflammatory cytokine release suggesting an alleviating effect on alveolar cytokine production in the ventilated lung after one-lung ventilation.[42] The findings from Schilling et al are based on cytokine release in the ventilated lung and therefore may not directly inform the debate on neuroinflammation, but do suggest that inhalational anesthetics may mediate an organ-dependent alteration of cytokine induction and release.

The exact mechanism by which inhalational anesthetic agents mediate an increase in TNF-α and other pro-inflammatory cytokines has yet to be elucidated. However, it has been shown that nuclear factor kappa B-dependent (NF-κB-dependent) pathways and the receptor for advanced glycation end products (RAGE) play a role in transcription and cytokine production.[43,44]

3.4. Neuroinflammation and surgery

In the operating room, anesthesia and surgery affect the patient concomitantly. Surgical trauma and its consequences most likely play a greater role than anesthesia on the development of POCD. For example, surgery has been shown to cause a transient neurocognitive decline associated with a hippocampal inflammatory response and activation of glial cells.[2,4,45] Pro-inflammatory cytokines released in the periphery exert their effect on the central nervous system either directly, by traversing the somewhat permeable blood–brain barrier, or indirectly by altering vagal afferent nerve function. The glial cells can be activated within the CNS by either means and once activated go on to release a variety of inflammatory mediators such as TNF-α and IL-1β[46,47] and neurotoxins such as amyloid β.[48] These cytokines released within the hippocampus interfere with cognition and cause a resultant decline in cognitive function. A 2010 study by Wan et al found that the microgliosis induced by surgery was prevented by the prior administration of celastrol, a potent anti-oxidant and anti-inflammatory compound.[2] Similarly Cibelli et al also demonstrated in 2010 that attenuation of the pro-inflammatory cytokine response to surgery is possible by the administration of an anti-inflammatory agent.[45] In addition to this, fluctuations in hormone levels following surgical trauma may affect neurotransmitter synthesis thereby disturbing cognitive function.[49] The neuroinflammatory response to surgery appears to be a significant contributor to the pathogenesis of POCD.

3.5. Synaptic changes following anesthesia

The consequences of amyloid β accumulation in neuroinflammation and Alzheimer's disease pathogenesis has been implicated with many deleterious effects; one of these is the ability of aggregates of amyloid β to initiate a cascade of events resulting in synaptic dysfunction and thus neuronal impairment.[18] Abnormalities in hippocampal synaptic neurotransmission following anesthesia have also been reported.[25]

Several studies have shown inhalational anesthetics to decrease synaptic transmission.[50–52] A possible method by which this happens was explored in a study by Fütterer et al in which rats were anesthetized with 5.7% desflurane and brains removed and examined at 0, 24 and 72 hours; cytosolic proteins were examined and a proteome-wide study conducted.[53] Dynamin-1 was found to be decreased directly and 72 hours after anesthesia. Dynamin-1 mediates the clathrin-dependent endocytosis of membrane proteins by which synaptic function is regulated,[54] and therefore the authors suggested that through a reduction in this rate-limiting protein various ion channels and receptors could be moved from the neuronal cell membrane thus altering synaptic neurotransmission. The authors of this study also showed that the protein expression induced by inhalational anesthetics persists for much longer than has previously been reported. Evidence from Fütterer et al and other studies provides yet another paradigm from which to evaluate the molecular mechanisms and resultant pathophysiological changes that have been so heavily studied and examined in the discourse on POCD.

3.6. Neurotransmission affected by inhalational anesthetics

It has been suggested that exposure to inhalational anaesthetics can cause neurotoxicity via activation of GABA receptors resulting in neuronal apoptosis.[25,55,56] Various studies have shown that enhancement of GABAergic activity in the neonatal brain can indeed result in excitotoxicity and neurodegenration in immature neurons.[56,57] Another key site of action of anesthetics is the NMDA receptor; antagonism of this receptor by inhalational anesthetics such as isoflurane may result in neuronal degeneration and apoptosis thus suppressing the neurotrophic support glutamate affords the brain.[25,56] Anesthetics exert their therapeutic effect at various sites with which they have affinity. Receptor site interactions via agonistic or antagonistic actions, as apparent by the ability of inhalational anesthetics to increase activity at the GABA receptor site[58] and some NMDA antagonizing inhalational anesthetics such as isoflurane and nitrous oxide to cause neurotoxicity,[3,59] suggest that anesthetic–receptor interplay modulates neurotransmission which preludes neurocognitive decline as witnessed postoperatively.

3.7. Neuronal calcium homeostasis affected by anesthetics

Another site where anesthetics may modulate function is within the neuronal cytoplasm and organelles; mounting evidence suggests that inhalational anesthetics may alter intracellular calcium homeostasis which may contribute to the molecular mechanisms behind the pathogenesis of neurodegenerative disorders such as POCD and Alzheimer's disease.[20,60,61] It has been hypothesized that anesthesia-mediated activation of inositol triphospate (IP_3) or ryanodine receptors on the endoplasmic reticulum (ER) membrane causes the alteration in calcium concentrations.[62,63] Recent investigations have proved this hypothesis by showing that, in both tissue culture and animal studies, inhalational anesthetics induce neurodegeneration and apoptosis via a disruption of intracellular calcium homeostasis, specifically by causing excessive activation of IP_3 receptors, resulting in increased calcium release from the ER.[60,64,65] However this phenomenom was found to occur inconsistently between different inhalational anesthetics; isoflurane being the most potent inducer of calcium dysregulation and subsequent neurodegenration.[60] In addition, another study found that rat pheochromocytoma neurosecretory cells (PC12), a cell type with elevated IP_3 receptor activity, transfected with an Alzheimer's presenilin-1 mutation rendered neurons more vulnerable to isoflurane toxicity.[66] Considerable evidence here points to a role for calcium homeostasis as a major regulator in the neurodegeneration pathway. Calcium also plays a role in the release of neurotransmitters and thus its dysregulation may also exert a passive effect on neurotransmission via this indirect route.

3.8. Nitric oxide changes following anesthesia

Inhalational anesthetics have also been shown to increase synthesis of nitric oxide (NO)[67] and decrease activity of nitric oxide synthase (NOS).[68] In a study by Tobin et al NOS inhibitors were shown to block the increase in NO synthesis suggesting that inhalational anesthetics increase NO by enhancing NOS activity.[68] Nitric oxide has been indentified as having a role in learning and memory processes.[69] Since NO is known to relax blood vessels and thus facilitate blood flow to the brain,[70] it had been suggested that it may augment neuronal activity in this context. However, several studies have shown that the NOS inhibitor 7-nitroindazole (7-NI) results in impaired memory and learning processes in various animal studies,[71–73] but does not affect cerebral blood flow.[74] These findings suggest that direct impairment of neuronal action as opposed to alteration of cerebral blood flow is the cause of the cognitive deficits observed by NOS inhibitors.[69]

3.9. Physiology and anesthesia

A less well-explored area of research is the physiological changes that take place with aging and how these may alter the ability of the body to process anesthetics. POCD is most common in

the elderly population and normal physiological changes associated with senescence may explain the apparent greater extent of cognitive decline in this age group. The changes in pharmacodynamics and pharmacokinetics that occur with aging, coupled with the presence of possible co-morbidities, may affect the clinical picture of cognitive dysfunction in this group of the population following surgery and exposure to anesthesia. These various factors may affect the dose−response relationship of anesthetics and thus the incidence of POCD in the elderly.[17]

4. Clinical implications of POCD

Currently there is no treatment for POCD and therefore patients face a variable clinical outcome that may range from short-term cognitive decline to long-term dysfunction. POCD is a potentially traumatizing experience resulting in diminished quality of life, recurrent hospital admissions and increased hospital costs. The use of inhalational anesthetics is of considerable importance in patients who may undergo multiple procedures and thus increase their exposure to anesthesia. The pathogenesis of POCD is poorly understand and much needs to be done to elucidate the mechanism behind it with a view to developing novel therapeutic interventions or altering the delivery of currently used regimens to prevent the devastating consequences, particularly for the elderly population, that are currently encountered.

5. Future study

Drug interventions that target the body's molecular mechanisms for processing anesthesia may help to overcome the deleterious effects of volatile anesthetics. Future research should be directed towards exploring inhalational anesthetics with neuroprotective effects; such as xenon which affords neuroprotection via its antagonism of the NMDA receptor.[75] Barbiturates have also been proposed as neuroprotective agents and may play a role in the future of POCD prevention and management.[76] However the nature of volatile anesthetics is such that they can affect many physiological systems and antagonism of some central or peripheral effects may also prove a viable therapeutic pursuit.

6. Conclusion

With life expectancy on the increase, the burden of disease and illness necessitating surgical intervention in the elderly population is likely to also increase. It is paramount that a thorough understanding of the effects of surgery and anesthesia on cognitive function is developed, and in particular the role of inhalational anesthetics on cognitive decline.

References

1. Canet J, Raeder J, Rasmussen LS, Enlund M, Kuipers HM, Hanning CD, et al. Cognitive dysfunction after minor surgery in the elderly. *Acta Anaesthesiol Scand* 2003;**47**:1204−10.
2. Wan Y, Xu J, Ma D, Zeng Y, Cibelli M, Maze M. Postoperative impairment of cognitive function in rats − a possible role for cytokine-mediated inflammation in the hippocampus. *Anesthesiol* 2007;**106**:436−43.
3. Culley DJ, Baxter MG, Yukhananov R, Crosby G. Long-term impairment of acquisition of a spatial memory task following isoflurane-nitrous oxide anesthesia in rats. *Anesthesiol* 2004;**100**:309−14.
4. Wan Y, Xu J, Meng F, Bao Y, Ge Y, Lobo N, et al. Cognitive decline following major surgery is associated with gliosis, beta-amyloid accumulation, and tau phosphorylation in old mice. *Crit Care Med* 2010;**38**:190−8.
5. Xie Z, Culley DJ, Dong Y, Zhang G, Zhang B, Moir RD, et al. The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid beta-protein level in vivo. *Ann Neurol* 2008;**64**:618−27.
6. Savageau JA, Stanton BA, Jenkins CD, Klein MD. Neuropsychological dysfunction following elective cardiac operation. 1. Early assessment. *J Thorac Cardiovasc Surg* 1982;**84**:585−94.
7. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *Lancet* 1998;**351**:857−61.
8. Hoecker J, Stapelfeldt C, Leiendecker J, Meybohm P, Hanss R, Scholz J, et al. Postoperative neurocognitive dysfunction in elderly patients after xenon versus propofol anesthesia for major noncardiac surgery. A double-blinded randomized controlled pilot study. *Anesthesiol* 2009;**110**:1068−76.
9. Rasmussen LS, Schmehl W, Jakobsson J. Comparison of xenon with propofol for supplementary general anaesthesia for knee replacement: a randomized study. *Br J Anaesth* 2006;**97**:154−9.
10. Savageau JA, Stanton BA, Jenkins CD, Frater RWM. Neuropsychological dysfunction following elective cardiac operation. 2. A 6-month reassessment. *J Thorac Cardiovasc Surg* 1982;**84**:595−600.
11. Shaw PJ, Bates D, Cartlidge NEF, French JM, Heaviside D, Julian DG, et al. Long-term intellectual dysfunction following coronary-artery bypass graft-surgery − A 6-month follow-up study. *Quart J Med* 1987;**62**:259−68.
12. Hammeke TA, Hastings JE. Neuropsychologic alterations after cardiac operation. *J Thorac Cardiovasc Surg* 1988;**96**:326−31.
13. Treasure T, Smith PL, Newman S, Schneidau A, Joseph P, Ell P, et al. Impairment of cerebral function following cardiac and other major surgery. *Eur J Cardiothorac Surg* 1989;**3**:216−21.
14. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *New Engl J Med* 2001;**344**:395−402.
15. Van Dijk D, Jansen EWL, Hijman R, Nierich AP, Diephuis JC, Moons KGM, et al. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery − A randomized trial. *J Am Med Assoc* 2002;**287**:1405−12.
16. van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EWL, et al. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *J Am Med Assoc* 2007;**297**:701−8.
17. Bekker AY, Weeks EJ. Cognitive function after anaesthesia in the elderly. Best practice & research. *Clin Anaesthesiol* 2003;**17**:259−72.
18. Vanderweyde T, Bednar MM, Forman SA, Wolozin B. Iatrogenic risk factors for Alzheimer's disease: surgery and anesthesia. *J Alzheimer Dis* 2010;**22**(Suppl. 3):91−104.
19. Mandal PK, Schifilliti D, Mafrica F, Fadale V. Inhaled anesthesia and cognitive performance. *Drugs Today* 2009;**45**:47−54.
20. Wei H, Xie Z. Anesthesia, calcium homeostasis and Alzheimer's disease. *Curr Alzheimer Res* 2009;**6**:30−5.
21. Hogg RC, Raggenbass M, Bertrand D. Nicotinic acetylcholine receptors: from structure to brain function. *Rev Physiol Biochem Pharmacol* 2003;**147**:1−46.
22. McGaugh JL. Neuroscience − memory − a century of consolidation. *Science* 2000;**287**:248−51.
23. McGaugh JL, Izquierdo I. The contribution of pharmacology to research on the mechanisms of memory formation. *Trends Pharmacol Sci* 2000;**21**:208−10.
24. Olney JW, Wozniak DF, Jevtovic-Todorovic V, Farber NB, Bittigau P, Ikonomidou C. Drug-induced apoptotic neurodegeneration in the developing brain. *Brain Pathol* 2002;**12**:488−98.
25. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003;**23**:876−82.
26. Dutton RC, Maurer AJ, Sonner JM, Fanselow MS, Laster MJ, Eger EI. Isoflurane causes anterograde but not retrograde amnesia for Pavlovian fear conditioning. *Anesthesiol* 2002;**96**:1223−9.
27. Dong Y, Zhang G, Zhang B, Moir RD, Xia W, Marcantonio ER, et al. The common inhalational anesthetic sevoflurane induces apoptosis and increases betaaA-myloid protein levels. *Arch Neurol* 2009;**66**:620−31.
28. Run X, Liang Z, Gong C- X. Anesthetics and tau protein: animal model studies. *J Alzheimer Dis* 2010;**22**:S49−55.
29. Eckenhoff RG, Johansson JS, Wei HF, Carnini A, Kang BB, Wei WL, et al. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiol* 2004;**101**:703−9.
30. Xie Z, Dong Y, Maeda U, Moir RD, Xia W, Culley DJ, et al. The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid beta-protein accumulation. *J Neurosci* 2007;**27**:1247−54.
31. Maekawa T, Tommasino C, Shapiro HM, Keifergoodman J, Kohlenberger RW. Local cerebral blood-flow and glucose-utilization during isoflurane anesthesia in the rat. *Anesthesiol* 1986;**65**:144−51.
32. Bianchi SL, Tran T, Liu C, Lin S, Li Y, Keller JM, et al. Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics. *Neurobiol Aging* 2008;**29**:1002−10.
33. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. *Neurobiol Aging* 2000;**21**:383−421.
34. Sastre M, Klockgether T, Heneka MT. Contribution of inflammatory processes to Alzheimer's disease: molecular mechanisms. *Int J Development Neurosci* 2006;**24**:167−76.
35. Cameron B, Landreth GE. Inflammation, microglia, and Alzheimer's disease. *Neurobiol Dis* 2010;**37**:503−9.
36. Hoogman M, van de Beek D, Weisfelt M, de Gans J, Schmand B. Cognitive outcome in adults after bacterial meningitis. *J Neurol Neurosurg Psychiatr* 2007;**78**:1092−6.
37. Schmidt H, Heimann B, Djukic M, Mazurek C, Fels C, Wallesch CW, et al. Neuropsychological sequelae of bacterial and viral meningitis. *Brain* 2006;**129**: 333−45.

38. Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition — The case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc* 2002;**50**:2041–56.
39. McGeer PL, McGeer EG. The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res Rev* 1995;**21**:195–218.
40. Buvanendran A, Kroin JS, Berger RA, Hallab NJ, Saha C, Negrescu C, et al. Upregulation of prostaglandin E-2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. *Anesthesiol* 2006;**104**:403–10.
41. Wu X, Yan L, Dong Y, Zhang G, Zhang Y, Xu Z, et al. The inhalation anesthetic isoflurane increases levels of proinflammatory TNF-α, IL-6, and IL-1β. *Neurobiol Aging*, in press
42. Schilling T, Kozian A, Senturk M, Huth C, Reinhold A, Hedenstierna G, et al. Effects of volatile and intravenous anesthesia on the alveolar and systemic inflammatory response in thoracic surgical patients. *Anesthesiol* 2011;**115**: 65–74.
43. Fang F, Lue L-F, Yan S, Xu H, Luddy JS, Chen D, et al. RAGE-dependent signaling in microglia contributes to neuroinflammation, Aβ accumulation, and impaired learning/memory in a mouse model of Alzheimer's disease. *FASEB J* 2010;**24**: 1043–55.
44. Combs CK, Karlo JC, Kao SC, Landreth GE. beta-Amyloid stimulation of microglia and monocytes results in TNF alpha-dependent expression of inducible nitric oxide synthase and neuronal apoptosis. *J Neurosci* 2001;**21**:1179–88.
45. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, et al. Role of interleukin-1 beta in postoperative cognitive dysfunction. *Ann Neurol* 2010;**68**: 360–8.
46. Giulian D, Baker TJ, Shih LCN, Lachman LB. Interleukin-1 of the central nervous system is produced by ameboid microglia. *J Exp Med* 1986;**164**:594–604.
47. Lieberman AP, Pitha PM, Shin HS, Shin ML. Production of tumor necrosis factor and other cytokines by astrocytes stimulated with lipopolysaccharide or a neurotropic virus. *Proc Nat Acad Sci USA* 1989;**86**:6348–52.
48. Butterfield DA, Reed T, Newman SF, Sultana R. Roles of amyloid beta-peptide-associated oxidative stress and brain protein modifications in the pathogenesis of Alzheimer's disease and mild cognitive impairment. *Free Radical Biol Med* 2007;**43**:658–77.
49. Stoudemire A, Anfinson T, Edwards J. Corticosteroid-induced delirium and dependency. *Gen Hosp Psychiatr* 1996;**18**:196–202.
50. Pearce RA, Stringer JL, Lothman EW. Effect of volatile anesthetics on synaptic transmission in the rat hippocampus. *Anesthesiol* 1989;**71**:591–8.
51. Nishikawa K, MacIver MB. Excitatory synaptic transmission mediated by NMDA receptors is more sensitive to isoflurane than are non-NMDA receptor-mediated responses. *Anesthesiol* 2000;**92**:228–36.
52. MacIver MB, Mikulec AA, Amagasu SM, Monroe FA. Volatile anesthetics depress glutamate transmission via presynaptic actions. *Anesthesiol* 1996;**85**:823–34.
53. Futterer CD, Maurer MH, Schmitt A, Feldmann RE, Kuschinsky W, Waschke KF. Alterations in rat brain proteins after desflurane anesthesia. *Anesthesiol* 2004; **100**:302–8.
54. Blanpied TA, Scott DB, Ehlers MD. Dynamics and regulation of clathrin coats at specialized endocytic zones of dendrites and spines. *Neuron* 2002;**36**:435–49.
55. Ikonomidou C, Bittigau P, Koch C, Genz K, Hoerster F, Felderhoff-Mueser U, et al. Neurotransmitters and apoptosis in the developing brain. *Biochem Pharmacol* 2001;**62**:401–5.
56. Olney JW, Young C, Wozniak DF, Jevtovic-Todorovic V, Ikonomidou C. Do pediatric drugs cause developing neurons to commit suicide? *Trends Pharmacol Sci* 2004;**25**:135–9.
57. Represa A, Ben-Ari Y. Trophic actions of GABA on neuronal development. *Trends Neurosci* 2005;**28**:278–83.
58. Franks NP. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nature Rev Neurosci* 2008;**9**:370–86.
59. Culley DJ, Baxter M, Yukhananov R, Crosby G. The memory effects of general anesthesia persist for weeks in young and aged rats. *Anesthes Analges* 2003;**96**: 1004–9.
60. Yang H, Liang G, Hawkins BJ, Madesh M, Pierwola A, Wei H. Inhalational anesthetics induce cell damage by disruption of intracellular calcium homeostasis with different potencies. *Anesthesiol* 2008;**109**:243–50.
61. Kindler CH, Eilers H, Donohoe P, Ozer S, Bickler PE. Volatile anesthetics increase intracellular calcium in cerebrocortical and hippocampal neurons. *Anesthesiol* 1999;**90**:1137–45.
62. Lindholm D, Wootz H, Korhonen L. ER stress and neurodegenerative diseases. *Cell Death Differentiation* 2006;**13**:385–92.
63. Hanson CJ, Bootman MD, Roderick HL. Cell signalling: IP3 receptors channel calcium into cell death. *Curr Biol* 2004;**14**:R933–5.
64. Liang G, Ward C, Peng J, Zhao Y, Huang B, Wei H. Isoflurane causes greater neurodegeneration than an equivalent exposure of sevoflurane in the developing brain of neonatal mice. *Anesthesiol* 2010;**112**:1325–34.
65. Wei H, Liang G, Yang H, Wang Q, Hawkins B, Madesh M, et al. The common inhalational anesthetic isoflurane induces apoptosis via activation of inositol 1,4,5-trisphosphate receptors. *Anesthesiol* 2008;**108**:251–60.
66. Liang G, Wang Q, Li Y, Kang B, Eckenhoff MF, Eckenhoff RG, et al. A presenilin-1 mutation renders neurons vulnerable to isoflurane toxicity. *Anesthes Analges* 2008;**106**:492–500.
67. Baumane L, Dzintare M, Zvejniece L, Meirena D, Lauberte L, Sile V, et al. Increased synthesis of nitric oxide in rat brain cortex due to halogenated volatile anesthetics confirmed by EPR spectroscopy. *Acta Anaesthesiol Scand* 2002;**46**:378–83.
68. Tobin JR, Martin LD, Breslow MJ, Traystman RJ. Selective anesthetic inhibition of brain nitric-oxide synthase. *Anesthesiol* 1994;**81**:1264–9.
69. Paul V, Ekambaram P. Involvement of nitric oxide in learning & memory processes. *Indian J Med Res* 2011;**133**:471–8.
70. Garthwaite J, Boulton CL. Nitric-oxide signaling in the central nervous system. *Ann Rev Physiol* 1995;**57**:683–706.
71. Prickaerts J, Steinbusch HWM, Smits JFM, de Vente J. Possible role of nitric oxide cyclic GMP pathway in object recognition memory: effects of 7-nitroindazole and zaprinast. *Eur J Pharmacol* 1997;**337**:125–36.
72. Vanaja P, Ekambaram P. Demonstrating the dose- and time-related effects of 7-nitroindazole on picrotoxin-induced convulsions, memory formation, brain nitric oxide synthase activity, and nitric oxide concentration in rats. *Pharmacol Biochem Behav* 2004;**77**:1–8.
73. Kendrick KM, Guevara-Guzman R, Zorrilla J, Hinton MR, Broad KD, Mimmack M, et al. Formation of olfactory memories mediated by nitric oxide. *Nature* 1997;**388**:670–4.
74. Akar FY, Ulak G, Tanyeri P, Erden F, Utkan T, Gacar N. 7-Nitroindazole, a neuronal nitric oxide synthase inhibitor, impairs passive-avoidance and elevated plus-maze memory performance in rats. *Pharmacol Biochem Behav* 2007;**87**:434–43.
75. Ma D, Williamson P, Januszewski A, Nogaro M-C, Hossain M, Ong LP, et al. Xenon mitigates isoflurane-induced neuronal apoptosis in the developing rodent brain. *Anesthesiol* 2007;**106**:746–53.
76. Fodale V, Santamaria LB. Drugs of anesthesia, central nicotinic receptors and post-operative cognitive dysfunction. *Acta Anaesthesiol Scand* 2003;**47**:1180.