

Are anaesthetics toxic to the brain?

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Editor's key points

- Alongside the desirable clinical effects, anaesthetic agents can be neurotoxic at the extremes of life.
- As reviewed by Hudson and Hemmings, the preclinical data are strong but reconciling this with the clinical picture produces a complicated and often conflicting picture.
- The authors underscore the need for robust prospective randomized clinical trials but highlight that these will be a challenge to the design; especially in standardizing the exposure and the measurement of outcome.

Summary. It has been assumed that anaesthetics have minimal or no persistent effects after emergence from anaesthesia. However, general anaesthetics act on multiple ion channels, receptors, and cell signalling systems in the central nervous system to produce anaesthesia, so it should come as no surprise that they also have non-anaesthetic actions that range from beneficial to detrimental. Accumulating evidence is forcing the anaesthesia community to question the safety of general anaesthesia at the extremes of age. Preclinical data suggest that inhaled anaesthetics can have profound and long-lasting effects during key neurodevelopmental periods in neonatal animals by increasing neuronal cell death (apoptosis) and reducing neurogenesis. Clinical data remain conflicting on the significance of these laboratory data to the paediatric population. At the opposite extreme in age, elderly patients are recognized to be at an increased risk of postoperative cognitive dysfunction (POCD) with a well-recognized decline in cognitive function after surgery. The underlying mechanisms and the contribution of anaesthesia in particular to POCD remain unclear. Laboratory models suggest anaesthetic interactions with neurodegenerative mechanisms, such as those linked to the onset and progression of Alzheimer's disease, but their clinical relevance remains inconclusive. Prospective randomized clinical trials are underway to address the clinical significance of these findings, but there are major challenges in designing, executing, and interpreting such trials. It is unlikely that definitive clinical studies absolving general anaesthetics of neurotoxicity will become available in the near future, requiring clinicians to use careful judgement when using these profound neurodepressants in vulnerable patients.

Keywords: anaesthesia, general; Alzheimer's disease; neurobehavioural manifestations; postoperative complications

General anaesthesia is a complex pharmacological response produced by a chemically heterogeneous class of drugs involving mechanisms that remain incompletely understood. Current concepts define anaesthesia by its core features of amnesia, unconsciousness, and immobility (in the order of decreasing potency), each mediated by pharmacological effects on specific neuronal networks in different regions of the central nervous system.¹ The molecular targets of these region- and dose-specific actions on neuronal network function have not been defined for most anaesthetics, although likely candidates have been identified and characterized. These include ligand-gated ion channels involved in inhibitory [receptors for γ -aminobutyric acid (GABA) and glycine] or excitatory [*N*-methyl-D-aspartate (NMDA) and AMPA subtype receptors for glutamate] synaptic transmission, ion channels conducting Na⁺, Ca²⁺, and K⁺ that regulate neuronal excitability and chemical transmission, and pleiotropic intracellular signalling pathways.² This diversity of potential targets increases the probability of both positive and negative non-anaesthetic effects (Table 1).

While the actions of the i.v. anaesthetics can often be ascribed primarily to one or a few targets, the potent inhaled anaesthetics (ethers and alkanes) appear to be particularly promiscuous, interacting with many functionally important targets, both in the nervous system and in other organs. As an example of the former, the anaesthetic effects of propofol and etomidate are mediated primarily through the potentiation of GABA_A receptors as demonstrated in the resistance to immobility of a knock-in mouse harbouring a mutant receptor engineered to be insensitive to these drugs.³ Analogous experiments have not been as conclusive for the inhaled anaesthetics, which are more than 100-fold less potent than i.v. anaesthetics and consequently are less selective in their target interactions. Nevertheless, i.v. and inhaled anaesthetics share overlapping effects on many targets including GABA_A and NMDA receptors. Actions on these two targets implicated in the desirable effects of anaesthetics, and other effects on unrelated targets, have come under renewed scrutiny for their potential roles in mediating potentially long-lasting detrimental effects on the developing and mature brain. A defining feature of

general anaesthetics is their ability to reversibly induce a coma-like state, but recent findings of changes in gene and protein expression persisting beyond emergence from anaesthesia provide a molecular basis for more durable effects.^{4 5} This brief review highlights some of the critical laboratory findings that have called attention to the neurotoxic effects of anaesthetics, and efforts to establish the clinical significance of potential effects of anaesthetics on neurodevelopmental outcome.

The young brain

Brain development, synaptogenesis, GABAergic transmission, and apoptosis

The developing brain has several significant differences from the adult brain that provide a physiological basis for enhanced vulnerability to anaesthetics. Early in development the number of neurones formed is significantly greater than in adult mammals. At the same time, there is an exuberant burst of synapse formation (synaptogenesis) before synapses are eventually pruned to establish behaviourally relevant connections between neurones. Programmed cell death, or apoptosis, is responsible for the elimination of 50–70% of developing neurones under normal circumstances.^{6 7} Apoptosis is a highly regulated mechanism of controlled cell involution and death that has both physiological and pathological roles. This apoptotic pruning of brain cells establishes normal cortical architecture and function. Apoptosis also serves to remove neurones after pathological insults, such as ischaemia or hypoxia, after withdrawal of neurotrophic factors, and after exposure to anaesthesia in early development.⁸ However, it is difficult to determine the extent to which apoptosis after anaesthesia involves cells that were already destined to die, or whether anaesthesia induces excessive apoptosis in viable cells that might negatively impact maturation of the nervous system.

One significant difference between immature and mature mammalian brain with neuropharmacological implications is the developmentally regulated reversal of the transmembrane chloride gradient. This is relevant to anaesthetic effects as many anaesthetic agents enhance the activity of GABA_A and glycine receptors, both of which are coupled to intrinsic chloride-conducting ion pores to increase the permeability of the cell membrane to chloride ions. In adults, expression of the KCC2 K⁺/Cl⁻ cotransporter produces an inward electrochemical chloride gradient that results in inward chloride flux after enhanced chloride permeability of the GABA-gated ion channel. This leads to hyperpolarization of the neurone and resulting suppression of neuronal activity. However, early in development before KCC2 expression the gradient for chloride is reversed such that the increase in chloride permeability associated with GABA_A or glycine receptor activation leads to depolarization of the neurone, with resultant excitation. Hyperexcitation in human neonates evident by electroencephalography has been reported with sevoflurane,^{9 10} isoflurane,¹¹ and propofol¹² anaesthesia, and might be related to the developmental switch from

N⁺-K⁺-2Cl⁻ cotransporter 1 (NKCC1) to KCC2 expression and the associated reversal of the chloride electrochemical potential that occurs perinatally in humans.¹³

Developmental neurotoxicity in young animal models

At least in immature rodents, exposure to either NMDA-type glutamate receptor antagonists or positive modulators of GABA_A receptors can lead to increased apoptosis. Blockade of NMDA receptors by ketamine in the developing rodent brain causes excessive apoptosis.^{14 15} These early observations of ketamine neurotoxicity were of concern but were considered agent-specific. Evidence that more commonly used anaesthetics also produced neurodegeneration in neonatal animals elevated concerns. One particularly compelling study designed to model paediatric anaesthesia exposed rat pups on postnatal day P7 to a cocktail of isoflurane, midazolam, and nitrous oxide at levels sufficient to maintain a surgical plane of anaesthesia for 6 h.¹⁶ Immediately after exposure, the rat pups developed excessive neuronal apoptosis throughout the brain, including the hippocampus and cerebral cortex. This apoptotic effect was significant both physiologically, with impairment of hippocampal long-term potentiation (an *in vitro* model of synaptic plasticity relevant to learning and memory), and behaviourally, with impairment of spatial reference memory as juveniles that persisted into adulthood. Isoflurane exposure alone led to significant apoptosis, but the addition of other agents to the cocktail substantially increased the degree of apoptosis.

The increased neuronal death with additional agents suggests that the significant event might be the pharmacologically induced coma itself rather than the particular agent used to achieve the anaesthetic state. Indeed, equipotent exposure of neonatal mice to desflurane, isoflurane, and sevoflurane produced similar increases in apoptotic cell death.¹⁷ In addition to the data for ketamine and volatile anaesthetics, *in vivo* or *in vitro* data suggest increased neuronal cell death after neonatal animal exposure to midazolam,¹⁸ diazepam,^{19 20} clonazepam,^{19 20} propofol,^{21 22} pentobarbital,²⁰ nitrous oxide,²³ and xenon.²⁴ However, conflicting reports also exist showing no adverse effects after exposure to midazolam, ketamine, thiopental, propofol, nitrous oxide, isoflurane, sevoflurane, and xenon. Indeed, under some circumstances, xenon appears to rescue neurones from isoflurane-induced apoptosis.²³ Although concerns that derangements of physiological homeostasis secondary to anaesthesia might contribute to neurodegeneration are valid, a number of well-controlled studies have implicated the anaesthetic exposure itself as the cause. Collectively, these studies illustrate the significance of experimental details such as dosage, duration, timing, species, and outcome studied. Given evidence for developmental neurodegeneration in response to exposure to all major classes of anaesthetics, further studies are essential to determine the relative toxicity of specific agents and the possibility of concomitant administration of neuroprotective drugs to counteract the pro-apoptotic effects of anaesthetics.

Since, at least under some conditions, essentially every anaesthetic agent has the potential to induce apoptosis in neonatal neurones, it is important to consider whether the anaesthetic state itself promotes apoptosis in the neonatal period. It has been proposed that anaesthetic suppression of spontaneous neuronal activity might lead to insufficient neurotrophic factor secretion in the developing nervous system.²⁵ If anaesthetic-induced suppression of electrophysiological activity occurs during critical developmental periods, neurones that are pharmacologically 'disconnected' from the network might be pruned through apoptotic mechanisms. However, at ages relevant to anaesthetic neurodegeneration (P4–8 rats), a significant number of rats have evidence of epileptic seizures with sevoflurane anaesthesia, and both seizure activity and apoptosis could be mitigated by co-administration of bumetanide, an NKCC1 inhibitor. These findings, suggest that apoptosis after anaesthesia could be secondary to excitotoxicity rather than to the withdrawal of trophic factors.²⁶ It remains to be seen whether perturbation of the neonatal chloride gradient can rescue neurones from apoptosis under other conditions, but the idea that pharmacological prophylaxis for long-term cognitive deficits after neonatal anaesthesia might be possible is provocative (Table 1).

Neurogenesis

Neurogenesis, or the creation of neurones, depends upon coordinated neuronal progenitor stem cell proliferation, neuronal differentiation, migration, and ultimately integration into active networks to ensure neuronal survival and appropriate function. Because increased neurogenesis could theoretically compensate for neuronal loss during the perinatal period, it has been hypothesized that persistent effects of perinatal anaesthetic exposure implies that perinatal exposure to anaesthesia also suppresses neurogenesis. Consistent with this hypothesis, rats exposed to isoflurane on P7 showed decreased neuronal progenitor proliferation with delayed-onset deficits in fear conditioning and spatial reference tasks.²⁷ In a separate study, P14 rats exposed to

isoflurane for 35 min daily for 4 days showed a decrease in hippocampal neuronal progenitor cells, decreased neurogenesis, and impaired object recognition and reversal learning compared with controls. Intriguingly, P60 rats (adults) exposed to isoflurane showed no cell death after exposure and had increased neuronal differentiation with an associated improvement in neurocognitive function on testing 8 weeks later, again highlighting the often contradictory effects of exposure to anaesthesia during different developmental windows.²⁸

Clinical significance of development neurotoxicity

The clinical significance of these observations remains controversial. The most robust neurotoxicity data available in primates were obtained by exposure of rhesus monkey fetuses and newborns to 24 h of ketamine anaesthesia. This produced neurodegeneration assessed using biomarkers for apoptosis both at day 122 of gestation and at P5, but not at P35, while a smaller exposure of 3 h on P5 demonstrated no neurodegeneration.²⁹ A shortcoming of this study, specifically that demonstration of biomarkers for apoptosis does not equate to a behaviourally significant lesion, was addressed by a follow-up work from the same group,³⁰ which documented long-lasting cognitive deficits in rhesus monkeys after exposure to 24 h of ketamine anaesthesia at P5–6. The animals were longitudinally assessed with the Operant Test Battery from the National Center for Toxicological Research, a test battery for which monkey and human child performance is similar.³¹ Beginning at 10 months of age, control animals outperformed ketamine-exposed animals in accuracy and response speed for a learning task and a colour and position discrimination task; this effect persisted for at least 10 months. While the study by Paule and colleagues is very suggestive, it did not attempt to define a dose–response curve for anaesthetic exposure effect on cognitive performance and it made no attempt to define the temporal boundaries of the critical developmental period for exposure. Nonetheless, a primate model has now demonstrated that a single, albeit prolonged, exposure to an

Table 1 Putative anaesthetic, neurotoxic, and neuroprotective targets of general anaesthetics

Target	Anaesthesia	Neurotoxicity	Neuroprotection
Synaptic transmission			
GABA _A receptors	+	+	+
NMDA receptors	+	+	+
Neuronal nicotinic acetylcholine receptors	+	+	
Excitability			
Na ⁺ channels	+	+	+
Ca ²⁺ channels	+	+	+
K ⁺ channels	+	+	+
Intracellular signalling			
Protein kinase pathways	?		+
Alzheimer precursor protein (APP) processing		+	+
Tau phosphorylation		+	+

anaesthetic during a critical neurodevelopmental period can have profound and long-lasting effects on cognitive performance.

Demonstration of anaesthetic toxicity in animal models requires substantial exposure, both in dosage and duration. Some estimate of the minimum required exposure for a significant effect on neurodevelopment comes from studies that have demonstrated significant apoptotic and necrotic cell death in neonatal monkeys exposed to ketamine for 9 h²⁹ or isoflurane for 5 h.³² Ketamine exposure for 3 h was not sufficient to induce massive cell death,³³ so it is possible that there is an exposure threshold, or minimum dose time exposure time, for neurodegeneration. Information regarding the minimal neurotoxic dose and duration in humans would be extremely useful in defining the margin of neurological safety for specific anaesthetics. But it will be impossible to reliably obtain such data until specific non-invasive biomarkers for apoptotic neurodegeneration are developed.

Anaesthetic exposure must occur during the critical period of neurogenesis and synaptogenesis to have significant apoptotic sequelae. It is difficult to compare data from rodents, which are altricial species that have a late postnatal brain growth spurt, to primates, which are precocial species with exuberant *in utero* brain growth spurts. Further complicating the translation of animal studies to humans are species differences in developmental timelines. The rat critical period for anaesthesia exposure resulting in neurotoxicity [(P0–P14) approximates the 20th week of gestation in humans], while the rhesus monkey critical period for anaesthetic neurodegeneration approximates the 26th week of gestation in humans.³⁴ Thus, anaesthetic neurotoxicity is probably most significant for the premature human fetus rather than term neonates or infants. However, there is a paucity of human data to support or refute the clinical extrapolation of these animal data.

While it is likely that early exposure to anaesthesia can, under certain circumstances, lead to long-term cognitive deficits in humans, the only data that can be directly levelled at the problem at this time is necessarily retrospective. In one case series, children exposed to multiple anaesthetics before the age of 4 yr had twice the incidence of learning disability diagnoses later in life compared with age-matched birth cohort controls.³⁵ Another retrospective cohort study examining enrollees of the New York State Medicaid system found that children who underwent hernia repair before 3 yr of age were more than twice as likely than age-matched controls to have a developmental or behavioural disorder diagnosis.³⁶ Of course, these data cannot distinguish the relative roles of surgery, anaesthesia, or comorbid conditions, and hence remain suggestive but inconclusive. A twin study conducted by Bartels and colleagues that attempted to eliminate genetic confounders by comparing learning disabilities in identical twins concordant or not for early anaesthetic exposure did not support a role for anaesthesia in the development of subsequent learning disabilities.³⁷ The long-term cognitive effects of early anaesthetic exposure consequently remain an area of active enquiry, supported by the US Food

and Drug Administration in collaboration with the International Anesthesia Research Society through the SmartTots programme (www.smarttots.org).

Prospective randomized studies are clearly required to help clarify these issues of long-term cognitive effects of early anaesthetic exposure in humans given the limitations inherent in retrospective studies. But the design and execution of prospective studies is non-trivial and years will be required to obtain useful neurodevelopmental data (Table 2). It will be extremely challenging for a single study to resolve the interactions between genetic factors, environment, anaesthesia, surgery, etc., on long-term neurocognitive outcome, which is already a difficult endpoint to assess. Challenges in designing such trials include selecting the best comparison group and the resulting ethics of randomization; choice of the anaesthetic used in the treatment group and its timing, dosing and duration; ensuring adherence to protocols through careful design and execution; and selection of sensitive endpoints that can achieve significance within a reasonable time and with a minimum of subjects. Resolving the effects of surgery, anaesthesia and co-morbid conditions alone are a particular challenge as it is ethically impossible to perform surgery without anaesthesia and anaesthesia is rarely given alone without a surgical procedure.

An ongoing study that will attempt to separate the effects of general anaesthesia from the surgical procedure is the GAS study (A Multi-site Randomized Controlled Trial Comparing Regional and General Anesthesia for Effects on Neurodevelopmental Outcome and Apnoea in Infants) of infants requiring inguinal herniorrhaphy.³⁸ Infants will be randomized to receive either general anaesthesia with sevoflurane or spinal anaesthesia without sedation followed by neurocognitive testing at ages 2 and 5 yr (clinicaltrials.gov/ct2/show/NCT00756600). A second study [Pediatric Anesthesia

Table 2 Factors in assessing clinical trial evidence of anaesthetic effects on neurocognitive development

Retrospective vs prospective design
Age-matched controls vs twin study
Dose and duration of anaesthetic exposure
Choice of anaesthetic agents
Differentiating effects of surgery and anaesthesia
Impact of comorbidities, genetics, and environment
Control of confounding factors
Sedation
Other drugs
Temperature
Hypoxaemia
Hypotension
Ischaemia
Age-appropriate and validated assessments of neurocognitive function
Clinical relevance of small but measurable effects

NeuroDevelopmental Assessment Study (PANDAS)] has undergone a feasibility study (clinicaltrials.gov/ct2/show/NCT00754897) and is currently in the late planning stages to compare a retrospective cohort of children who received anaesthesia at less than 3 yr of age with unanaesthetized siblings in a prospective assessment of neurocognitive outcome in an attempt to reduce genetic and environmental contributions to cognitive performance.³⁹ This combined prospective assessment of a retrospective exposed cohort has advantages in terms of subject recruitment and study efficiency.

The old brain

Ageing and postoperative cognitive dysfunction

The elderly appear to be at increased risk of prolonged cognitive dysfunction after surgery and anaesthesia. The existence and prevalence of postoperative cognitive dysfunction (POCD) in the elderly were established in the International Study of Postoperative Cognitive Dysfunction.⁴⁰ While short-term cognitive dysfunction was associated with multiple comorbid medical conditions, the predominant risk factor for prolonged cognitive decline was advanced age.⁴¹

Loss of cognitive reserve, inflammation, and neurodegeneration

The underlying mechanisms for the association of POCD with surgery, anaesthesia, or both in the elderly remain unclear, but could reflect altered drug responses, loss of functional reserve, or the cumulative effects on chronic disease over time. With ageing, rates of neurogenesis and synaptogenesis decrease, the total number of neurones decline, and potentially toxic by-products accumulate. These processes lead to a gradual loss of reserve, increasing the vulnerability of the brain to insults, including exposure to perioperative stressors. Current theories for anaesthetic contributions to POCD include direct toxic effects, such as alterations in calcium homeostasis,⁴² systemic inflammatory effects secondary to the surgical insult,⁴³ age-sensitive suppression of neuronal stem cell function,^{27 44} and acceleration of ongoing endogenous neurodegenerative processes.^{45 46}

Alzheimer's disease and neurodegeneration

Alzheimer's disease is a chronic neurodegenerative process associated with diffuse atrophy of the cerebral cortex, deposition of characteristic plaques of amyloid β ($A\beta$) peptide, and accumulation of neurofibrillary tangles made up of hyperphosphorylated tau protein.⁴⁷ Theories of neurodegeneration in Alzheimer's disease largely focus on the toxic effects of aggregated $A\beta$ peptide oligomers that result from intramembrane proteolysis of the transmembrane protein amyloid precursor protein (APP).⁴⁸ APP mutations that favour cleavage of APP by γ -secretase to $A\beta_{42}$ are associated with Alzheimer's disease. Similar synthetic peptides demonstrate toxicity to hippocampal and cortical neurones *in vitro*. Accumulation of insoluble protein aggregates is emerging as a common phenomenon in many

neurodegenerative diseases, although their role in pathogenesis or as mechanisms to sequester toxic aggregates is controversial.⁴⁹

Anaesthetics and neurodegenerative mechanisms

Experiments performed in cell culture models of neurodegeneration have shown that isoflurane,⁵⁰ isoflurane with nitrous oxide,⁵¹ sevoflurane,⁵² and desflurane with hypoxia⁵³ induce apoptosis and increase $A\beta$ formation, though several of these studies were performed in tumour cells rather than neurones. In a study of mice exposed to 2 h of isoflurane anaesthesia, increased neocortical and hippocampal expression of the apoptotic marker caspase 3 was observed at 6 h post exposure, and elevated $A\beta$ was detected at 24 h post exposure.⁴⁶ Volatile anaesthetics can enhance aggregation of $A\beta$ *in vitro*,^{54 55} providing another potential interaction between anaesthesia and Alzheimer's disease pathology.

However, not all data favour an $A\beta$ mechanism for neurodegenerative anaesthetic effects as a possible aetiology of POCD. A transgenic mouse model of Alzheimer's disease demonstrated increased production of amyloid plaque without associated cognitive deficits after daily exposure to halothane or isoflurane, while wild-type mice developed cognitive impairment after repeated isoflurane exposure.⁵⁶ Additional complications exist, in that choice of drug, exposure duration, dose, and interval to testing might all matter. Several studies suggest a potential neuroprotective preconditioning effect with lower exposures.^{57–59} Findings that anaesthetics can have both protective and toxic effects on neuronal survival demonstrate the complexities in anaesthetic mechanisms and the importance of conducting studies *in vivo* to determine overall effects on survival and behaviour.

Multiple anaesthetic agents can also promote hyperphosphorylation of the microtubule-associated protein tau when associated with hypothermia, which does not occur if normothermia is maintained.⁶⁰ A subsequent study, however, found that a propofol anaesthetic that maintained normothermia still increased tau phosphorylation.⁶¹ Hyperphosphorylated tau tends to self-assemble into neurofibrillary tangles⁴⁷ found abundantly in Alzheimer's disease and Parkinson's disease.

Neuroinflammation and neurogenesis

Several studies have attempted to study the effect of systemic inflammation from a surgical insult on neuroinflammation, neurogenesis, and postoperative cognitive function. In one study, adult rats given neuroleptanaesthesia that underwent splenectomy showed impaired cognitive function on postoperative days 1 and 3 compared with rats that were anaesthetized without surgery; performance of anaesthetized rats that did not undergo surgery was indistinguishable from non-anaesthetized controls.⁴³ Increases in expression of interleukin-1 β (IL-1 β) mRNA and protein in hippocampus suggested that cognitive impairment resulted from

systemically triggered neuroinflammation. In a similar model, postsurgical memory dysfunction was mitigated both by non-specific immunosuppression with minocycline and by pretreatment with an IL-1 receptor antagonist, and was less prominent in IL-1 receptor knockout mice.⁶² The IL-1 response to surgery appears to be mediated by tumour necrosis factor- α (TNF- α). Peripheral TNF- α blockade attenuates the IL-1 β -mediated neuroinflammatory response and the associated postoperative cognitive decline,⁶³ suggesting the possibility of pretreatment with an anti-TNF antibody to ameliorate POCD. This inflammatory response appears to be more prominent in older mice, consistent with age-related POCD in humans.⁶⁴ However, surgery might not be the only culprit in a neuroinflammatory response as increased levels of TNF- α , IL-6, and IL-1 β have been reported after isoflurane anaesthesia alone. Moreover, the increase in TNF- α was more marked in Alzheimer's disease transgenic mice than in wild-type mice, suggesting that some of the increase in neurodegenerative markers after anaesthetic exposure is because of neuroinflammation.⁶⁵ This is an evolving area clearly requiring further investigation.

Clinical evidence of an association between anaesthesia and POCD

Data linking Alzheimer's disease pathophysiology to anaesthesia exposure in humans are contradictory. In one case-controlled study, Bohnen and colleagues⁴⁵ demonstrated no significant difference in mean cumulative duration of general anaesthesia between unaffected controls and Alzheimer's patients. In another case-controlled study, Gasparini and colleagues⁶⁶ did not find an association between the number of surgical operations and risk of Alzheimer's disease, or between exposures to anaesthesia in a 1–5 yr window preceding the onset of Alzheimer's disease. Yet, a separate study by Bohnen and colleagues⁶⁷ found a relationship between cumulative anaesthesia exposure before age 50 yr and earlier onset of Alzheimer's disease, suggesting that the time horizon for accumulating effects is longer than one might think. This might be explained by an acceleration of a steady rate of accumulation of neurotoxic A β oligomers by exposure to anaesthetics that would manifest as a critical threshold is reached earlier than in the absence of prior anaesthetic exposure.

Recent evidence suggests that the severity of POCD might have been overestimated. A relatively recent retrospective cohort study by Avidan and colleagues found no long-term cognitive decline in annual assessments that could be independently attributed to illness or surgery, and neither illness nor surgery appeared to speed progression to dementia, although patients who had initial dementia declined more rapidly over the course of the study than those who did not.⁶⁸ This study attributed the difference between their results and results from prior studies to methodological limitations in earlier studies owing to the lack of relevant control groups, lack of information about the trajectory of cognitive

status before surgery, and poor controls for repeated exposure to cognitive tests leading to training effects. However, the study by Avidan and colleagues is retrospective and used a dementia rating scale rather than more traditional methods to assess POCD. If POCD were to resolve within 1 yr, it could easily be missed with annual assessments, despite potentially significant medical and socioeconomic consequences. All of which argues for multicentre prospective clinical trials to determine the contributions of anaesthesia, surgery, and illness on cognitive dysfunction in the elderly.

Conclusions

Accumulating evidence from animal studies justifies recent concerns regarding the neurotoxic potential of anaesthetic drugs, particularly at the extremes of age. In the young brain, neurodevelopmental factors predispose to anaesthetic excitotoxicity and effects on neurogenesis and synaptogenesis that can impair neurocognitive performance after early anaesthetic exposure. In the old brain, progressive neurodegenerative disease pathways can be exacerbated by anaesthetics in laboratory studies. The clinical impact of these preclinical findings has not been established owing to difficulties in designing definitive studies and the significant delay between exposure and testing. Clearly further investigations, both experimental and epidemiological, are warranted to establish the clinical relevance and possible neuroprotective strategies for these untoward effects. Alternatives to surgery and general anaesthesia are usually not available and pain itself can cause long-term neurodevelopmental deficits.⁶⁹ As current data do not support significant changes in practice other than avoiding purely elective procedures, anaesthesiologists should strive to minimize unnecessary exposure to general anaesthetic agents and other factors that might potentiate toxicity in susceptible patients.

Conflict of interest

H.C.H. is an editor of the *British Journal of Anaesthesia* and *Anesthesiology*, and has received research funding from the US National Institutes of Health and departmental sources. A.E.H. has no conflicts to declare.

Funding

Preparation of this review was funded by departmental resources.

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