General Anesthetic Neurotoxicity

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General anesthesia is one of the great advances of medicine and allows ever more complicated surgery to be performed safely, including on patients at the extremes of age. However miraculous, general anesthesia is not without risk, a fact we and our patients acknowledge and accept to enjoy its benefits. But, is central nervous system toxicity one of those risks? Our clinical experience says "no" but accumulating laboratory data say "yes." Here we address the reality and myth of general anesthetic-induced neurotoxicity and put it into perspective for the practicing clinician.

Neurotoxicity is usually defined as a structural change or functional alteration of the nervous system resulting from exposure to a chemical, biological, or physical agent (1). It can be acute, subacute, or silent (i.e., evident only months to years after exposure), with the latter form being most controversial and difficult to prove. Vulnerability to neurotoxicity is especially high during development, when the blood brain barrier is not fully developed, neurogenesis and synaptogenesis are occurring at high rates, and neurotransmitters have different effects than they do in adult brain (e.g., GABA is excitatory) and perform functions besides neurotransmission (e.g., regulate stem cell proliferation and differentiation). Well-known examples of agents highly toxic to the developing central nervous system include lead and ethanol. At the other extreme, the old brain may be vulnerable to neurotoxicity for different reasons. The mature brain, like the developing brain, contains immature cells that develop into neurons and get incorporated into functional neuronal circuits. It also has regions constantly remodeling synaptic connections in a rapid, highly dynamic process known as synaptic plasticity, which is the foundation of learning and memory and fundamental to healthy brain function. However, the old brain suffers from the ravages of age, including shrinkage of neurons, loss of various neurotransmitters and receptors, a markedly lower rate of neurogenesis and synaptogenesis, and accumulation of potentially toxic byproducts such as the Alzheimer's disease peptide, β amyloid (Aβ). Thus, the old brain has reduced reserve, meaning that, because of its limited ability to compensate, insults that would go unnoticed at a younger age may become evident in the form of functional impairments (e.g., cognitive decline). In this sense, the old brain is also vulnerable to neurotoxicity.

So, are general anesthetics neurotoxins during development and/or aging? General anesthetics are obviously chemical and biological agents; indeed, they are among the most potent centrally acting drugs in common clinical use. They share the property of interfering with neurotransmission to the point of producing coma and do this largely by either positively modulating inhibitory GABA neurotransmission or antagonizing glutamate-mediated excitatory neurotransmission (2). In this respect, general anesthetics share features with known developmental neurotoxins such as ethanol and antiepileptic agents (3), making a good story—or a scary one—for anesthetic-induced neurotoxicity. But, do the data support it?

The phenomenon has been best studied in cell culture and the developing rodent brain. In these models, several classes of general anesthetics kill cells and produce neurodegeneration. Thus, at concentrations within the range used for human anesthesia, ketamine, nitrous oxide, midazolam, barbiturates, and isoflurane cause death of cultured postnatal hippocampal neurons and/or trigger massive apoptosis, or programmed cell death, in the developing brain (particularly cortex and anterior thalamus) (4–10). Importantly, in animal models, exposure to general anesthesia *in utero* or in the early neonatal period is associated with delayed behavioral development, functional impairment in the hippocampus, and learning disability in adulthood (7,11,12). Exposure need not be chronic; behavioral changes have been reported in the adult offspring of pregnant dams anesthetized briefly (2–6 h) with clinically relevant dosages of halothane or nitrous oxide, in adult mice that were anesthetized on the second day of life, and in adult rats given a single dose of ketamine in the neonatal period (7,13,14). In some ways, this recapitulates the situation with ethanol, where binge exposure is more harmful than continuous exposure to low-dosages and even a single low-dose exposure is neurotoxic (1,15). In fact, as noted above, the similarity in receptor mechanisms of action and neurotoxic potential of general anesthetics, antiepileptic agents, and ethanol, an established fetal neurotoxin suggests a common mechanism for the developmental neurotoxicity may be an unbalancing of NMDA receptor mediated excitatory and GABA mediated inhibitory neurotransmission (4).

A key point is that vulnerability to general-anesthetic-induced neurotoxicity is not uniform throughout development. Vulnerability is maximal during the period of intense synaptogenesis, otherwise referred to as the brain growth spurt (4,5,16). This occurs at different times in different species. In humans, synaptogenesis and the brain growth spurt begin around midgestation and continue through the 2nd year of life (17), meaning that this issue potentially has broad implications for patients requiring obstetrical or pediatric anesthesia and surgery during these critical times.

Not surprisingly, therefore, there is quite a bit of controversy and concern about it (18–20). Some dispute that it is due to the anesthetic agents at all. It is not easy to measure and control systemic physiology in a creature that weighs just a few grams and many studies in neonatal rodents have not done so, leaving open the possibility that abnormal systemic physiology explains the results. However, when blood pressure, blood gases, and serum glucose are measured in pregnant or neonatal animals under anesthetic conditions that produce neurodegenerative changes, it turns out that systemic physiology is reasonably normal (16,21). In addition, in a hippocampal culture model, where systemic physiology becomes irrelevant, isoflurane is neurotoxic (22). Another criticism is that some studies used supraclinical dosages or an anesthetic "cocktail" with limited relevance to the clinical situation. However, neurotoxicity is observed when agents are used alone and when clinically relevant, or even subanesthetic, dosages are administered for a clinically relevant interval. As such, the neurotoxic effects of general anesthetics on the developing rodent brain are not easily explained away by abnormal systemic physiology, unusual drug combinations, or excessive dosages.

Considering that the developing brain is fundamentally different from the mature brain in a myriad of ways, there is likely to be more to it. Two of these differences are especially relevant to this discussion. First, neurogenesis, gliogenesis, and synaptogenesis are much more robust in the developing than mature brain. In fact, an excess of cells is produced and those that are unsuccessful in making synaptic contacts are eliminated via the natural pruning process of apoptosis (23). Second, whereas activation of GABA receptors mediates inhibition in the mature CNS, the opposite effect—depolarization and excitation—occurs in developing neurons (24). Accordingly, one can hypothesize that general anesthetics delivered at a critical time might trigger neuroapoptosis by unbalancing the normal relationship between excitation and depression, possibly interfering with neurotrophin-dependent survival (21) and signaling the brain that vast numbers of cells are unnecessary and should be eliminated. If this is true, it implies properties fundamental to general anesthetic action may be the signals for millions of nerve cells to commit suicide in the developing brain.

Is the old brain similarly vulnerable? Probably not in the same way; for reasons given earlier, the adult brain is, in general, less vulnerable to environmental toxins than the developing brain. But, like the developing brain, the old brain makes new neurons (25,26) and has neurons constantly in the process of active remodeling and synaptogenesis (27,28). These may be points of vulnerability but few studies have addressed the impact of general anesthesia on these processes in the old brain. There are still reasons to worry. The brain loses the capacity for plasticity and neurogenesis over time, leaving the aged brain with less "reserve," meaning that small toxic events could have greater impact on brain function. In terms of acute neurotoxicity, ketamine and nitrous oxide, alone or in combination, produce vacuolization in cerebrocortical neurons (which corresponds to swelling of mitochondria and endoplasmic reticulum) of adult and aged animals, with the aged brain being more sensitive to ketamine and a nitrous oxide-ketamine drug combination (29). The old brain also becomes susceptible to neurodegeneration over time. Alzheimer's disease (AD), a dementing, neurodegenerative disorder, is a good example; AD becomes more common with age, afflicting about 50% of elders aged 80–85 years. The pathophysiology of AD is hotly debated but the prevailing view is that β amyloid (Aβ), a small protein formed by cleavage of a larger precursor, amyloid precursor protein (APP), is a major player (30). Soluble Aβ inhibits neurotransmission and is implicated in cognitive impairment that develops before the full blown disease (31); if the Aβ burden is sufficiently large, as it is in AD, it deposits, forming amyloid plaques, induces a neuroinflammatory response, and kills neurons (30). It is therefore of considerable interest that some general anesthetic agents affect the properties and processing of Aβ. Isoflurane and halothane at clinically relevant concentrations increase the oligomerization of Aβ in cultured nonneural cells and also increase its toxicity (32). Likewise, isoflurane increases activity of β-secretase (BACE), the enzyme that forms Aβ, and induces Aβ-dependent apoptosis in cultured neural cells overexpressing APP (33). As such, it is clear that that isoflurane and halothane can affect Aβ processing, change its physical properties, and augment its neurotoxic qualities, at least *in vitro*. To date, however, no studies have examined whether the same events occur *in vivo*, so the clinical relevance of these results are uncertain.

Indeed, talk of general anesthetic-mediated neurotoxicity is alarming to those of us who administer general anesthesia for a living—not to mention to our patients and their families. But let's be clear on what the data don't say. They don't say that general anesthetics produce neurotoxicity in patients. No studies have demonstrated general anesthetic-induced neurotoxicity in non-human primates, let alone humans, either neonatal or old, at clinically relevant dosages or durations of exposure. Given existing data, however, studies in nonhuman primates are urgently needed and are currently underway. Deciphering the impact of a

general anesthetic administered to a human fetus or neonate on subsequent brain development and function will be extremely difficult. Childhood is a time of remarkable brain growth and experience that profoundly influence cognitive capacity as an adult and the obvious confounder introduced by a concurrent illness serious enough for general anesthesia and surgery to be required will be difficult to eliminate or handle. Elders are a different story and there are some data that pertain to this issue. A large percentage of elderly patients suffer from difficulties with concentration and attention long after surgery and anesthesia and careful studies reveal a 10%–15% incidence of postoperative cognitive deterioration in this group (34). The relationship between general anesthesia and these mild cognitive changes is unsettled. In old rats, general anesthesia with isoflurane, nitrous oxide, or isoflurane-nitrous oxide produces an enduring deficit in spatial working memory and persistent changes in hippocampal gene expression (35–37) but, in patients, the incidence of postoperative cognitive impairment is similar after general or regional anesthesia (38). As for general anesthesia and Alzheimer's disease, retrospective epidemiological studies reveal an inverse relationship between cumulative exposure to general anesthesia and age of onset of AD but no difference in its incidence (39,40).

Therefore, despite the persuasive nature of what is known, one must remember that much is unknown. Cells, mice, and rats are not the same as children, women, and men. What's more, we have no idea what to change or whether it would be better in this regard or worse. Much more work is needed in the laboratory and the clinic to determine whether general anesthetic-induced neurotoxicity is a myth or a reality in patients. Whatever the outcome, general anesthesia is nothing short of miraculous and no one will elect to return to the days of swigging whiskey and biting a bullet when facing a surgical procedure. There may soon come a day, however, when concerns about general anesthetic-induced neurotoxicity will change the drugs we use, how we use them, and who we use them on. We're not there yet—but stay tuned.

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