Anesthesia Kills Brain Cells, but What Does It Mean?

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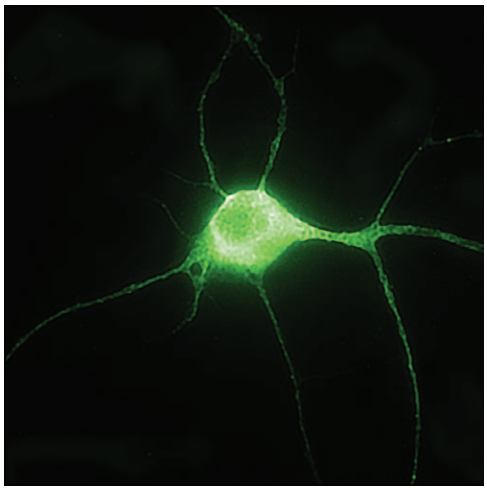
THE possibility of neurocognitive dysfunction after early exposure to anesthesia is an area of concern for anesthesiologists. Two recent clinical trials ("General Anaesthesia and Awake-Regional Anaesthesia in Infancy" [GAS] and "Pediatric Anesthesia Neurodevelopment Assessment" [PANDA]) suggest that shorter exposures to anesthesia do not lead to severe deficits in young children; however, it remains less clear whether longer exposures are safe and whether examination of children at an older age using tools specific for other cognitive domains might reveal deficits like those reported in previous retrospective studies. The mechanism that leads to deficits with longer exposures and the age range in which animals (and possibly children) are susceptible is an active area of both preclinical and clinical research. The article by Jiang *et al.*[1] in this issue of ANESTHESIOLOGY builds on excellent work they have published previously to take a more in-depth look at one of the most common outcomes reported after early anesthesia exposure—brain cell death.



"...brain cell death [after isoflurane] occurs in both neonatal and adult animals (albeit at different rates), but cognitive dysfunction only follows exposure in young animals..."

It has long been known that a single exposure to anesthesia leads to widespread neuronal cell death throughout the brain in very young animals. Previous work by the same team[2] demonstrated beautifully that not just any neurons die but rather neurons of a specific age. Susceptibility of a particular cell is based on its own developmental birth date and not the age of the animal. During early development, different brain regions are populated by new neurons at different times, which likely leads to the varying susceptibility of these regions to early anesthetic exposure. The lack of neurogenesis later on is also why it was initially believed that little or no brain cell death occurred in adult animals exposed to anesthesia. However, with a very careful analysis, this same research group determined that brain cell death does occur in adults but only in regions with ongoing neurogenesis such as the hippocampus and olfactory bulbs. The much lower rates of neurogenesis during adulthood even in these neurogenic regions is likely why it was overlooked in previous investigations.

In the research reported here, Jiang *et al.*[1] used genetic tools to label a small cohort of developing hippocampal neurons and then exposed the animals to isoflurane anesthesia 2 weeks later when those young neurons are most susceptible to anesthetic-mediated cell death. The results confirm their previous findings that isoflurane exposure greatly increases caspase expression and cell death in these immature, developing neurons. They also found that both 14 and 60 days later, there is no difference in the total number of neurons derived from this population of labeled cells and no difference in the rate that these cells continue to undergo cell division. In other words, both the pool of progenitors and the total number of adult neurons are equivalent in anesthetized and control animals weeks after anesthetic exposure.

This well-done and interesting study answers some questions and raises a number of possibilities that will require further research. It is already established that the same anesthetic in a 1-week-old rodent and an adult rodent leads to a cognitive deficit in the younger animal only. Anesthetic exposure in the experiments by Jiang *et al.*[1] was performed on 21-day-old rodents—in between the early and late time points explored previously. It is unknown whether exposure at this age leads to a cognitive deficit or not. The precise age window in which rodents are susceptible remains poorly defined at this time, and human studies that report a deficit have used subjects with a wide exposure age range but have not included a negative control group that is older or younger. If the animals in the study by Jiang *et al.*[1] do not have a deficit, it would suggest that they have reached an "adult-like" stage in which some developing neurons found in neurogenic regions are indeed susceptible to cell death but that does not yield a detectable change in the total number

Image: Photomicrograph courtesy of D. Culley, Brigham and Women's Hospital/Harvard Medical School.

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of neurons or progenitors and does not produce a lasting cognitive deficit. Additional studies will have to be done to determine the age range of susceptibility so that important outcomes such as cognitive function can be more closely tied to observations such as brain cell death. Because brain cell death occurs in both neonatal and adult animals (albeit at different rates), but cognitive dysfunction only follows exposure in young animals, the importance of hippocampal brain cell death in this key outcome remains ambiguous.

Adults are not susceptible to the same cognitive deficit found in neonates for a number of possible reasons. One suggested by the authors and supported by their data is that the hippocampal dentate gyrus is a neurogenic region and can recover from the brain cell death that occurs. Compensation for lost neurons in the dentate could arise from a brief increased rate of neurogenesis or a decreased rate of pruning of newly developed cells that fail to make appropriate connections. Both of these would result in equivalent numbers of neurons and stem cells detected at a later time point, as Jiang *et al.*[1] have reported. By contrast, in young animals, the widespread neurogenesis that takes place during early development leads many brain areas to be susceptible to this type of cell death. Cells in some regions of the brain will remain vulnerable for days to weeks after neuronal cell division has been completed. Once developmental neurogenesis ends, it becomes difficult to replace those cells, and even if new neurons are available, access to pathways connecting different regions of the brain may no longer be open. The result could be equivalent total neuron numbers but differences in regional connectivity when compared to animals anesthetized as adults. This will be an important area of exploration in future studies since even after early anesthesia exposure, adult differences in total neuron count are rarely observed.[3] Finally, it is possible that the neuronal loss observed after anesthesia exposure is not responsible for the cognitive deficit at all, and some other mechanism is to blame. Brain cell death is nearly always observed after neonatal anesthesia exposure in rodents but does not reliably correlate with changes in cognitive function.[3–5] Altered connectivity could be reflected by a loss of spines or synapses that occurs only in neonates and persists into adulthood[6] or a change in white-matter tracts that connect these regions. Comparison of cell loss and connectivity is also potentially measurable in humans where the volume and density of a particular region (cell number) and robustness of white-matter tracts can be assessed by modalities of magnetic resonance imaging.

Jiang *et al.*[1] have precisely defined the population of brain cells at risk of dying after exposure to a volatile anesthetic like isoflurane. In these 21-day-old rodents, like in adults, the brain seems capable of recovering or replacing the lost cells, so the total number of neurons does not change in the long term. Understanding the transition in cognitive outcome from neonates, where brain cell death is widespread, to adults, where it is limited to neurogenic regions, will require cognitive studies of animals at this intermediate age. Clearly pinpointing the overlap between anesthetic-mediated brain cell death and later cognitive dysfunction is critical to understanding how the two are connected, if indeed they are at all. The article by Jiang *et al.*[1] is an excellent step toward that goal.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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