Beyond Anesthesia Apoptosis

Wiring and Communication Matter!

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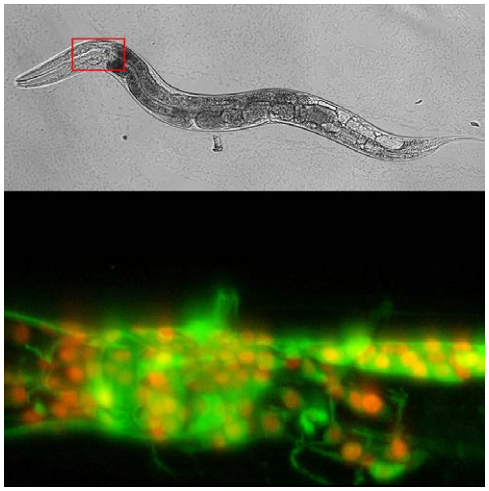
Although the potential human relevance remains controversial, animal data—from nematodes to nonhuman primates—published during the past two decades revealed that a wide assortment of general anesthetics can induce an extensive array of morphological and functional changes in the developing brain.[1] Among the multitude of cellular responses triggered by general anesthetics, apoptosis or programmed cell death received the most attention. This entity is a commonly used endpoint of laboratory studies in the field of developmental anesthesia neurotoxicity, and its presence is often thought to be responsible for behavioral and cognitive dysfunctions later in life. Indeed, the prevailing view is that the initial neuronal destruction, as assessed by widespread neuroapoptotic activation, leads to ongoing disturbances in neuronal connectivity, synaptic plasticity, and interneuron dynamics, suggesting that the sequence of detrimental experimental outcomes stems from massive and widespread neuronal cell death.[2] However, as of today, no causal relationship has been convincingly demonstrated between anesthesia-induced apoptosis and neural dysfunction. Therefore, an emerging plausible alternative is that early life anesthesia exposure–associated cognitive alterations, observed in a wide range of laboratory animals, may result from more subtle, yet long-lasting, changes in neuronal architecture and synaptic communication.



"Since we continue to grapple with the issue of human relevance for developmental anesthesia neurotoxicity [in animals], why do we celebrate 'yet another' experimental neurotoxicity study…?"

In this issue of Anesthesiology, an elegant experimental work conducted on the nematode *Caenorhabditis elegans* seems to emphasize this latter possibility.[3] *C. elegans* is an appealing model for studying the mechanistic and functional neuronal correlates to anesthesia-induced behavioral impairments since morphological, genetic, and functional characteristics of neuronal networks are well-characterized in this species. An additional advantage of the model is that, since this nematode does not have a cardiovascular system, systemic hemodynamic effects of anesthetic drugs need not to be considered as potential confounding factors. In a carefully designed series of experiments, Wirak *et al.* report lasting changes in food searching–associated locomotor behavior patterns in *C. elegans* after exposure to isoflurane during the neurodevelopmentally critical L1 larval stage. Most importantly, by being able to image the neuronal circuitries as they get selectively activated during locomotion, the authors were able to establish a correlation between isoflurane-induced impairment of locomotion patterns and modified premotor interneuron dynamics responsible for that behavior. Last but not least, genetic dissection of mechanistic pathways underlying these behavioral alterations revealed a potential role for the lasting activation of neuronal stress response pathways in response to anesthetic exposure.

What do these results teach us? At first, they provide us with reasonable functional evidence that cell death may not be the most important or even a necessary initial step leading to long-lasting neurodevelopmental abnormalities observed in numerous laboratory animal models. More likely, ongoing maladaptive changes in neuronal morphology and synapsing could be the culprit when rapidly developing, and hence vulnerable, neurons are exposed to unphysiological conditions brought upon by general

Image: C. Connor, Brigham and Women's Hospital/Harvard Medical School.

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anesthetics. If so, assessment of apoptosis in experimental studies—although perhaps a useful initial screening tool—may be of limited value. Based on our current understanding, it is reasonable to suggest that a greater focus should be placed on other morphofunctional parameters designed to examine the synapse formation and function of neuronal networks. Unfortunately, assessment of such experimental outcome parameters, including the state-of-the art imaging technology applied in the work of Wirak *et al.*, requires tremendous technological investment that may not be within the reach of most research groups working in the field.

A second important take home point stems from the genetic investigations in the study suggesting anesthetics-induced activation of stress response pathways. Although a direct comparison to higher mammalian species is fraught with many pitfalls, it is noteworthy that various disturbances in stress response and socioemotional development have also been described in rodents and non-human primates when the exposure to general anesthesia occurred during the critical stages of their brain development.[1] For example, Raper *et al.* has shown that the exposure of neonatal monkeys to the inhaled general anesthetic sevoflurane during critical stages of their brain development results in an anxious phenotype characterized by maladaptive responses to unavoidable stress and social challenges resulting in the disturbances in emotional development later in life.[4] This would reemphasize that anesthesia-induced developmental impairment in behaviors is not only cognitive in nature, but importantly, it seems to affect many types of behaviors, with emotional, stress-related behaviors being very much targeted.

Since we continue to grapple with the issue of human relevance for developmental anesthesia neurotoxicity, why do we celebrate "yet another" experimental neurotoxicity study in our journal? The answer to this question is that the study from Wirak *et al.* also ignites thoughts for future research directions in anesthetics-induced modulation of neural circuitry. As such, this line of research maybe of fundamental relevance that is beyond the issue of developmental anesthesia neurotoxicity. For example, an important question would be whether or not the effects of isoflurane, and possibly other anesthetics, on neuronal dynamics observed by the authors are restricted to critical developmental periods or can also be observed, albeit to a limited extent, at later stages of life. Another interesting issue to investigate would be how repeated exposure to anesthetics may modify neuronal dynamics and, thereby, metaplasticity (*i.e.*, activity-dependent changes in neural functions that modulate subsequent synaptic plasticity). While research in this domain is not directly related to perioperative care, the fact that anesthetics are powerful modulators of neuronal activity makes these drugs excellent tools to study fundamental tenets of synaptic plasticity. In this regard, the data from Wirak *et al.*, add to the accumulating knowledge in the field of fundamental neuroscience, teaching us that even short-term interference with physiologic patterns of neuronal homeostasis can trigger context-dependent long-term alterations in neural circuitry function. At least some clinical data seem to support these fundamental tenets. Indeed, mounting evidence suggest that exposure to a wide variety of anesthetic drugs can trigger therapeutic effects, lasting for weeks, in patients with major depressive disorders.[5] On the other hand, and more controversially, the role of general anesthetics in postoperative cognitive dysfunction and neurodevelopment is also currently under intense scrutiny. Mechanistic understanding of how these context-dependent effects operate will deepen our knowledge of anesthesia mechanisms of actions and, potentially, could also contribute to fuel future research on neuromodulation—a concept that extends beyond our current simplistic view of general anesthesia.

Competing Interests

Dr. Jevtovic-Todorovic is an Associate Editor of Anesthesiology. Dr. Vutskits is an Editor of Anesthesiology.

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References

1. Jevtovic-Todorovic V: Exposure of developing brain to general anesthesia: What is the animal evidence? Anesthesiology 2018; 128:832–9
2. Woodward TJ, Timic Stamenic T, Todorovic SM: Neonatal general anesthesia causes lasting alterations in excitatory and inhibitory synaptic transmission in the ventrobasal thalamus of adolescent female rats. Neurobiol Dis 2019; 127:472–81
3. Wirak GS, Gabel CV, Connor CW: Isoflurane exposure in juvenile *Caenorhabditis elegans* causes persistent changes in neuron dynamics. Anesthesiology 2020; 133:569–82
4. Raper J, Alvarado MC, Murphy KL, Baxter MG: Multiple anesthetic exposure in infant monkeys alters emotional reactivity to an acute stressor. Anesthesiology 2015; 123:1084–92
5. Vutskits L: General anesthetics to treat major depressive disorder: Clinical relevance and underlying mechanisms. Anesth Analg 2018; 126:208–16