Are Epigenetic Changes the Key to the Elusive Mechanism for the Long-lasting Effects of Anesthetic Drugs that Persist after Emergence?

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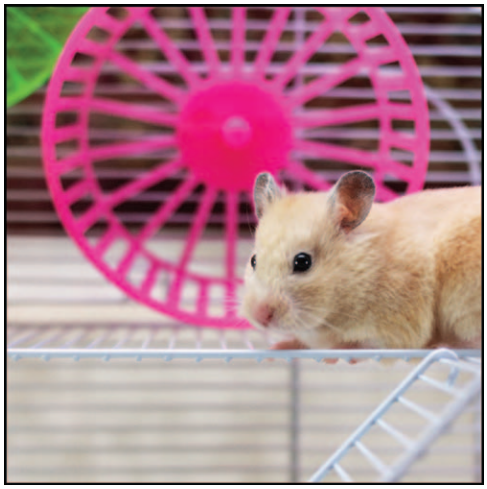
IN this issue of Anesthesiology, Wu *et al.*[1] provide strong experimental evidence that long-term cognitive effects of isoflurane exposure are directly linked to epigenetic modulation of brain-derived neurotrophic factor (BDNF) expression in the developing mouse brain. Epigenetic means "outside of the genetic code" or changes in the transcription and translation of genes that do not occur *via* alteration of the DNA sequence itself. Epigenetic changes induced by the environment can be mediated through control of DNA transcription factors (such as BDNF) that upregulate or downregulate the transcription of genomic DNA. BDNF is well known as an important mediator in pain plasticity and memory.[2] In the hippocampus, BDNF is important for the induction and maintenance of late-phase long-term potentiation, substrates for memory formation, and preservation.[2]



"…isoflurane-induced epigenetic modulation of BDNF that was sustained [in adulthood] could still be reversed by exposure to an enriched environment."

In the current study, hippocampal BDNF expression was found to be reduced in adult animals treated with isoflurane as neonates. By using sophisticated molecular, imaging, and behavioral tools, the authors showed that the BDNF downregulation was associated with reduced mRNA translation of proteins important for synaptic transmission, a reduction in hippocampal synapse number, with electrophysiological changes in the hippocampus thought to be important for memory formation, and with behavioral evidence of learning deficits. One of the most exciting findings from the current study is that exposure of the animals to an enriched environment after birth appeared to mitigate this injury through upregulation of BDNF. Animals in the environmental enrichment group had access to an ever changing variety of toys, running wheels for exercise, and social activity with other animals. BDNF deficiency induced by other factors such as prenatal opioid exposure is known to be mitigated through interaction with an enriched environment.[3] Mechanisms that upregulate this important trophic factor are interesting targets for translational research.

Evidence linking exposure to various types of general anesthetics to long-term cognitive deficit in neonatal animals has been available for almost 20 yr. It is remarkable that anesthesia can generate a long-lasting biological footprint even while the desired hypnotic activity resolves according to the expected rapid reduction in drug concentration in species from rodents to primates.[4] A plausible mechanism for this long-lasting effect has been long in coming and is provided in these studies. Despite the clear evidence for injury in preclinical studies, it has been difficult to demonstrate a consistent causal link between anesthesia and cognitive dysfunction in humans. The mismatch between the very high level of experimental and now mechanistic clarity in animals and the weakness of findings in the clinical literature has resulted in continuing controversy about how we should consider these findings in clinical care.[4] Part of the difficulty in translating these findings is that truly definitive study designs are impossible in human infants. It is ethically unfeasible to study human infants under anesthesia without surgical intervention or causative disease, as such all clinical studies are observational and have the potential for associated confounding and bias.

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These findings from this study may help to clarify the difficulty in translation of these potentially important findings into clinical practice. The demonstration of a tractable mechanism for anesthetic-induced damage in rodents provides both new avenues for evaluation of changes in human infants and a potential explanation for the difficulty in translating these concerning findings. Evaluation of acute effects of volatile anesthetics on BDNF expression in children would provide an important link to this putative mechanism. There is a conflicting literature on whether epigenetic changes in circulating cells may reflect epigenetic changes in local areas of the brain; however, it is conceivable that a blood test may in the future tell us something about BDNF regulation. One of the major results of this neonatal murine study is the demonstration that isoflurane-induced epigenetic modulation of BDNF that was sustained at adult stage could still be reversed by exposure to an enriched environment. Even if the reduction in BDNF expression were found in serum or cerebrospinal fluid in infants after surgery, the impact of the future environment may overshadow any deleterious effect in humans or restrict such effects to a subset of environmentally disadvantaged children. This may also be part of the reason that these findings have been difficult to translate in clinical studies. The enriched environment described for the mice would be a typical environment for most human children. The richness of an infant's environment cannot be compared with that of a rat in a cage, even one with a few toys and access to daily exercise.

A weakness in this study that is common to many recovery studies involving anesthesia in rodents is that the animals were not ventilated, and in the experimental group, the anesthetic was delivered in 100% oxygen, whereas the control group breathed room air. Hyperoxia has variable effects on BDNF expression in different tissues over different time courses in young rodents.[5] Some of the retrospective clinical trials looking at behavioral outcomes of anesthetized children involved cohorts from the 70s and 80s when protocols for airway control and monitoring were less advanced. As such, an interaction between hyperoxia, hypercarbia, and anesthetic effect must be considered.

In conclusion, we find in the current study a compelling mechanism to explain the long-term neurological and behavioral changes that have been found in rodents exposed to volatile anesthetics. This is the first but likely not the only demonstration of anesthetic-induced epigenetic changes as these mechanisms have been found to be pivotal in key processes in the development and maintenance of neurons and other cell types. In every drug that we apply to the human (or other animal) body, we need to remain mindful that our understanding of the complex physiology that makes us self-assemble and function is yet in its infancy, and unexpected consequences will be routine.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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