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anesthesia with bupivacaine decreases cerebral blood flow in former preterm infants. *Anesth Analg* 2004; 98:1280-3

References

1. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW: Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. *ANESTHESIOLOGY* 2010; 112:834-41
2. Creeley CE, Olney JW: The young: Neuroapoptosis induced by anesthetics and what to do about it. *Anesth Analg* 2010; 110:442-8
3. Hansen TG, Danish Registry Study Group, Flick R, Mayo Clinic Pediatric Anesthesia and Learning Disabilities Study Group: Anesthetic effects on the developing brain: Insights from epidemiology. *ANESTHESIOLOGY* 2009; 110:1-3

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Isoflurane-induced Neuroapoptosis in the Neonatal Rhesus Macaque Brain: Isoflurane or Ischemia-Reperfusion?

To the Editor:

We read with great interest the article by Brambrink and colleagues.¹ We want to raise a major point concerning their methodology and the ensuing interpretation of their results. The authors did not measure blood pressure in either the control group or at baseline in the treated animals. If we speculate that mean arterial pressure (MAP) measured at recovery time in their infant monkeys reflects MAP at baseline, a 35% decrease in MAP occurred during the entire procedure (see table 1 in their article). In infant animals as in infant humans, loss of autoregulation in preserved organs such as the central nervous system may rapidly occur, even when blood pressure moderately decreases. In a previous study, we observed that spinal cord blood flow was markedly decreased by epidural lidocaine in infant rabbits compared with adults and that the decrease in blood flow was correlated with a decrease in MAP.² Also, another study from our group performed in former premature infants showed that spinal anesthesia was accompanied by a decrease in cerebral blood flow parallel to the decrease in peripheral blood pressure.³ Then, it can not be ruled out that the neurodegeneration observed by the authors was simply related to the decrease in MAP observed during the 5-hour procedure.

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References

1. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW: Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. *ANESTHESIOLOGY* 2010; 112:834-41
2. Bouaziz H, Okubo N, Malinovsky JM, Benhamou D, Samii K, Mazoit JX: The age-related effects of epidural lidocaine, with and without epinephrine, on spinal cord blood flow in anesthetized rabbits. *Anesth Analg* 1999; 88:1302-7
3. Bonnet MP, Larousse E, Asehnoun K, Benhamou D: Spinal

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In Reply:

We thank Drs. Hansen and Henneberg as well as Drs. Mazoit, Roulleau, and Baujard for expressing interest in our recent publication on neuroapoptosis in the developing non-human primate brain after isoflurane anesthesia.¹ We appreciate the opportunity to discuss their valuable suggestions and concerns.

Before addressing Drs. Hansen and Henneberg's suggestions for the direction of future research, we would like to comment on their statement that 50-70% of all neurons die by natural apoptosis during development. As we have explained in a recent publication, this is a misconception.² Natural apoptosis deletes a high (but unknown) percentage of neuronal (and glial) precursor cells. However, after precursor cells differentiate into neurons and begin the synaptogenesis process, very few die by natural apoptosis, unless synaptogenesis is disrupted by some unnatural circumstance. Exposure to anesthetic drugs is an unnatural circumstance that disrupts synaptogenesis and deletes many neurons that would otherwise have survived and made a positive contribution to functions of the brain.

Drs. Hansen and Henneberg argue that further animal studies can serve no useful purpose, because there is no satisfactory way of extrapolating experimental findings from animals to humans. They express concern that more animal data will not clarify and may further confuse the issue of human susceptibility. Therefore, to move the field forward, they suggest that the research focus should now be on human research aimed at clarifying whether exposure of the developing human brain to anesthetic drugs is associated with long-term neurocognitive disturbances.

We agree that there is an urgent need for well designed human studies, but it does not logically follow that animal research is futile or should be halted. Rodent data served the very valuable purpose of alerting the medical profession and regulatory authorities to a neurotoxic action of anesthetic drugs. If it can be proven beyond reasonable doubt that anesthetic drugs, at clinically relevant doses, exert this neurotoxic action in the developing human brain, and that this results in neurodevelopmental disabilities, this would be a public health problem of considerable magnitude. Demonstrating that the nonhuman primate brain is susceptible to this neurotoxic action of anesthetic drugs when applied at clinically relevant doses does not provide definitive proof of human susceptibility, but it helps to close the translational gap and contributes new insight into the apparent species generality of this neurotoxic phenomenon.

A major benefit of the animal studies that have been performed is that they have spurred clinical researchers to conduct human studies. Several independent groups have now

reported preliminary findings that tentatively support the conclusion that brief exposure of human infants to anesthesia is associated with increased risk of long-term neurobehavioral disturbances.³⁻⁷ One study did not find an association, but anesthesia exposure was documented only by parental reporting.⁸ These studies and the tentative nature of their conclusions illustrate the difficulty of designing and conducting definitive clinical studies of anesthetic neurotoxicity. While prospective clinical studies are designed and conducted over the next several years, further animal research can provide insights into the mechanisms of anesthetic neurotoxicity and the identification of anesthetic regimens that are not neurotoxic in neonates.

Drs. Mazoit, Roulleau, and Baujard raise an important question: is it possible that the reported findings¹ may be caused by some mechanism other than a direct action of the anesthetic drug? Specifically, they postulate that hypoxia/ischemia, secondary to reduced blood pressure, can explain the neuroapoptosis response in our isoflurane-treated infant monkeys. It is important to recognize that there is no evidence for the claim that reduced blood pressure, even to an extreme degree, can trigger acute neuroapoptosis in the developing brain of any species. In contrast, there are more than 50 published reports from multiple independent laboratories showing that alcohol and anesthetic or anticonvulsant drugs do trigger acute neuroapoptosis in the developing rodent and monkey brain. Moreover, we have shown previously that hypoxia/ischemia causes an acute *excitotoxic* cell death response in the developing rodent brain that is not accompanied in the acute period by any evidence of apoptotic neurodegeneration.⁹⁻¹¹ In contrast, anesthetic drugs cause an acute *apoptotic* cell death response in the developing brain that is not accompanied by any evidence of excitotoxic neurodegeneration.^{1,12-15} Evidence that intentional induction of profound hypoxia/ischemia does not trigger an acute apoptosis response in the developing brain signifies that it is highly unlikely that a decrease in blood pressure to a modest nonischemic degree will trigger acute neuroapoptosis.

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References

1. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW: Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. *ANESTHESIOLOGY* 2010; 112:834-41
2. Creeley CE, Olney JW: The young: Neuroapoptosis induced by anesthetics and what to do about it. *Anesth Analg* 2010; 110:442-8
3. DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G: A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. *J Neurosurg Anesthesiol* 2009; 21:286-91
4. Kalkman CJ, Peelen L, Moons KG, Veenhuizen M, Bruens M, Sinnema G, de Jong T: Behavior and development in

children and age at the time of first anesthetic exposure. *ANESTHESIOLOGY* 2009; 110:805-12

5. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO: Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *ANESTHESIOLOGY* 2009; 110:796-804
6. DiMaggio C, Sun LS, Li G: Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a birth cohort of 5824 twin pairs (abstract). Presented at: The IARS and SAFEKIDS International Science Symposium: Anesthetic-Induced Neonatal Neuronal Injury, Honolulu, HI, March 20, 2010 (ISS-A1)
7. Thomas JJ, Choi JW, Bayman EO, Kimble KK, Todd MM, Block RI: Does anesthesia exposure in infancy affect academic performance in childhood (abstract ISS-A1)? Presented at: The IARS and SAFEKIDS International Science Symposium: Anesthetic-Induced Neonatal Neuronal Injury, Honolulu, HI, March 20, 2010
8. Bartels M, Althoff RR, Boomsma DI: Anesthesia and cognitive performance in children: No evidence for a causal relationship. *Twin Res Hum Genet* 2009; 12:246-53
9. Ikonomidou C, Price MT, Mosinger JL, Friedrich G, Labruyere J, Shahid Salles KS, Olney JW: Hypobaric-ischemic conditions produce glutamate-like cytopathology in infant rat brain. *J Neurosci* 1989; 9:1693-700
10. Ishimaru MJ, Ikonomidou C, Tenkova TI, Der TC, Dikranian K, Sesma MA, Olney JW: Distinguishing excitotoxic from apoptotic neurodegeneration in the developing rat brain. *J Comp Neurol* 1999; 408:461-76
11. Young C, Tenkova T, Dikranian K, Olney JW: Excitotoxic *versus* apoptotic mechanisms of neuronal cell death in perinatal hypoxia/ischemia. *Curr Mol Med* 2004; 4:77-85
12. Ikonomidou C, Bittigau P, Ishimaru MJ, Wozniak DF, Koch C, Genz K, Price MT, Stefovskaya V, Hörster F, Tenkova T, Dikranian K, Olney JW: Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. *Science* 2000; 287:1056-60
13. Dikranian K, Ishimaru MJ, Tenkova T, Labruyere J, Qin YQ, Ikonomidou C, Olney JW: Apoptosis in the *in vivo* mammalian forebrain. *Neurobiol Dis* 2001; 8:359-79
14. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF: Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003; 23:876-82
15. Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Wang H, Labruyere J, Olney JW: Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. *Br J Pharmacol* 2005; 146:189-97

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Postoperative Cognitive Decline: The Unsubstantiated Phenotype

To the Editor:

Correlation of a clinical outcome (phenotype) with a biomarker or genotype requires accurate phenotyping and genotyping. We question the accuracy and reliability of phenotyping (determination of postoperative cognitive dysfunction [POCD] at 1 yr) by McDonagh *et al.*¹ POCD lacks consensus diagnostic criteria, and disparate methods have been employed for its detection.² There are several method-