Abstract # 140

Early Gestational Exposure to Isoflurane Results in Granule Cell Loss in the Dentate Gyrus in Adulthood

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Arvind Palanisamy, M.B., B.S., M.D., FRCA; Deirdre M. McCarthy, B.S.; Pradeep G. Bhide, Ph.D.; Gregory Crosby, M.D.; Deborah J. Culley, M.D.
Brigham and Women’s Hospital/ Harvard Medical School; Massachusetts General Hospital/Harvard Medical School

Introduction: Commonly used general anesthetic agents have adverse effects on neurodevelopment in rodents and primates. Vulnerability is high during synaptogenesis, with anesthetic exposure leading to neuronal loss and behavioral deficits in adulthood. Whether the brain is similarly vulnerable during earlier stages of neurodevelopment is unclear and could be important because approximately 0.5-1.0% of pregnant women receive general anesthesia for non-obstetric surgeries and fetal surgical interventions. In this regard, we have demonstrated that 4 h of maternal anesthesia with isoflurane during early gestation leads to a deficit in spatial memory of male offspring in adulthood. Because spatial memory is mediated by the hippocampus, we performed this study to test the hypothesis that early gestational exposure to isoflurane causes cell loss in the hippocampus.

Methods: Timed, pregnant Sprague-Dawley rats were assigned randomly to 4 h of general anesthesia with 1.4% isoflurane in 100% oxygen or 100% oxygen alone on gestational day 14, which corresponds to the 2nd trimester in humans. The dams were recovered and monitored until delivery on day 22. Following delivery, the female pups were culled and the male pups were allowed to grow to adulthood. At 4 months of age, adult male rats (N = 10 and 13, control and isoflurane groups, respectively) were sacrificed for quantitative histology of hippocampal subregions. Sections were stained with cresyl violet and the total number of cells in the granular layer of the dentate gyrus and the pyramidal cell layer in the CA1 region were determined by a blinded observer using stereology and the optical fractionator method. Data were analyzed using two-way ANOVA with Bonferroni’s correction; P < 0.05 was accorded statistical significance.

Results: Isoflurane anesthesia was physiologically well tolerated by the dams. There were no differences in the birth weight or litter size between the two groups. Stereological examination, however, revealed 9% fewer cells in the granular layer of the dentate gyrus of isoflurane-exposed adult rats compared to controls (545,914 ± 32,895 vs. 501,061 ± 42,434, respectively; Mean ± S.D., *P = 0.01). In contrast, there were no changes in the CA1 region.

Conclusions: Our results show that maternal isoflurane anesthesia in rodents causes region-specific cell loss in the hippocampus of adult male offspring. These changes may account for the behavioral deficits reported in animals exposed to isoflurane in utero and suggest that the developing brain may be vulnerable to isoflurane neurotoxicity during the 2nd trimester.

References:
