Isoflurane Anesthesia Causes Significant Alterations in Structure and Neurochemistry in the Neonatal Piglet Brain

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Abstract

Introduction: The effect of anesthetic exposure on the brain during the first 2 years of life is a current focus of contemporary pediatric anesthesia research. A clinically relevant, standardizable animal model is required to study anesthesia-induced developmental neurotoxicity (AIDN). Animal data suggest that the neonatal brain is susceptible to general anesthesia, but research has failed to elucidate its mechanisms. This pilot study was designed as a preclinical animal model to evaluate structural and functional changes in the entorhinal cortex and hippocampus of neonatal piglets after isoflurane exposure. We selected these areas due to their role in learning and memory.

Methods: 20 neonatal piglets (10-14 days old, 2-3 kg) were randomized to 1) control (n=10); or 2) isoflurane, 2% (n=10). For the anesthesia exposure group, sevoflurane 8% in 100% O2 via face cone is used to induce anesthesia, followed by isoflurane 2% in 50% O2/50% air for 3h. Standard perioperative monitoring is maintained throughout the study period. Following exposure, piglets are allowed to recover for 48h.Brains are harvested after transcardiac perfusion/fixation (PBS-4% PFA). Tissue is analyzed using histopathology, immunohistochemistry, transcriptome analysis, and microRNA (miRNA) expression analysis.

Results: Brain sections were stained for doublecortin (immature neuronal marker) and Iba1 (marker for activated microglia). A significant increase in staining for both proteins was seen in isoflurane animals when compared to controls. (Figures 1 and 2) Expression of inflammatory genes, channel proteins, and cell cycle proteins were found to be altered after isoflurane exposure. (Figure 3) Several miRNAs (miR-338, miR-214, miR-7138-5p, miR-199a-3p, and miR-20a) were found to be significantly downregulated. (Figure 4)

Discussion: Isoflurane causes significant cell activation in the brain of neonatal piglets, including progenitor glial cells, microglia, and immature neurons, and mature neurons. Effects of isoflurane are linked to inflammation, channels, cell cycle proteins, and miRNAs. These changes persist, even after 48h. Taken together, our findings suggest novel mechanisms for isoflurane-induced neurotoxicity.

Background

- Millions of children receive general anesthesia each year in the U.S., with more than 7 million of them being under the age of 4 years.
- Juvenile animal studies have suggested an increase in apoptosis and neurocognitive deficits after anesthesia exposure.
- The research community has called for a clinically relevant, standardizable, translatable animal model to study AIDN.
- Apoptosis, a normal finding in the developing mammalian CNS, may not be the only benchmark to explain neural injury after anesthesia exposure.
- Neuroinflammation, which has been linked to other anesthesia-related neurocognitive dysfunction such as postoperative cognitive dysfunction, may be a superior experimental target.

References


Acknowledgements

- Study supported by start-up funds and an Intramural Grant from Nationwide Children’s Hospital.