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Brain tissue oxygen regulation in awake and anesthetized neonates

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ABSTRACT

Inhaled general anesthetics are used commonly in adults and children, and a growing body of literature from animals and humans suggests that exposure to anesthesia at an early age can impact brain development. While the origin of these effects is not well understood, it is known that anesthesia can disrupt oxygen regulation in the brain, which is critically important for maintaining healthy brain function. Here we investigated how anesthesia affected brain tissue oxygen regulation in neonatal rabbits by comparing brain tissue oxygen and single unit activity in the awake and anesthetized states. We tested two common general anesthetics, isoflurane and sevoflurane, delivered in both air and 80% oxygen. Our findings show that general anesthetics can greatly increase brain tissue PO_2 in neonates, especially when combined with supplemental oxygen. Although isoflurane and sevoflurane belong to the same class of anesthetics, notable differences were observed in their effects upon neuronal activity and spontaneous respiration. Our findings point to the need to consider the potential effects of hyperoxia when supplemental oxygen is utilized, particularly in children and neonates.

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1. Introduction

Inhaled general anesthetics are used commonly in the course of surgery, imaging and other medical procedures in adults and children, yet their impact upon brain function is not entirely understood. It is known that these drugs suppress neuronal activity by acting primarily upon GABA receptors (Jia et al., 2008) and cause decreased firing frequency in a majority of neurons. As they also produce depression of vascular and respiratory centers (Bosch et al., 2017), it is important to consider how these anesthetics may affect oxygen regulation within the brain.

Normal brain function depends upon maintaining the oxygen partial pressure (PO_2) in brain tissue within a relatively narrow range that is sufficiently high to prevent hypoxia and low enough to minimize generation of toxic oxygen species. The brain achieves this balance by ensuring stable blood flow via cerebrovascular autoregulation (Dagal and Lam, 2009), which regulates the response of cerebral arteries to fluctuations in arterial pressure, ensuring sufficient oxygen for basal neuronal activity. In addition, brain PO_2 is regulated indirectly by carotid bodies and the respiratory center, which adjust breathing rate in response to arterial PO_2 (Prabhakar and Semenza, 2015). More focal changes in neuronal activity are supported by the hemodynamic response (Buxton et al., 2004), which dilates local blood vessels in order to increase blood flow to active brain regions.

This system potentially can be disrupted not only by pathologies such as cerebrovascular diseases (Goadsby, 2013), but also by drugs, including general anesthetics, which decrease neuronal firing and depress respiration, altering oxygen consumption and delivery in brain tissue. Moreover, it has been found that at higher concentrations general anesthetics can directly affect vessels, causing vasodilation (Matta et al., 1999) and thus the increased delivery of oxygen to brain tissue. These opposing effects create a complex picture of the influence of general anesthetics upon oxygen regulation in the brain. However, our previous findings (Aksenov et al., 2012, 2015) suggest that the decrease in neuronal activity during anesthesia is large enough to produce an overall increase in brain tissue oxygen.

Changes in tissue PO_2 induced by anesthesia are of particular concern for the developing brain. A number of studies have linked anesthesia exposure in young children with the development of a variety of pathologies later in life (Flick et al., 2011; Lee et al., 2015).

Abbreviations: PO_2, Oxygen Partial Pressure; ROS, Reactive Oxygen Species.

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Both human and animal studies have indicated (Crosby and Davis, 2013; Lee et al., 2015; Olsen and Brambrink, 2013; Sun, 2010; Taylor, 2009) that exposure to anesthesia, especially at an early age, can affect a variety of aspects of neuronal development, leading to deficits in learning and memory. Although the origin of these complications is not yet known, changes in PO_2 could play a role. General anesthesia often is delivered in hyperoxic mixtures (typically 60%, 80% or 100% O_2) (Edmark et al., 2003) in order to avoid hypoxia, yet hyperoxia resulting from brain tissue oxygen dysregulation can potentially lead to damage as well (Scheuer et al., 2017).

The goal of this work is to evaluate the effects of general anesthesia on the regulation of tissue PO_2 in neonatal rabbits. Based on our previous findings regarding the effects of anesthesia on neuronal activity and tissue PO_2 in adult rabbits, we hypothesized that brain tissue oxygen regulation would be significantly altered in neonates under general anesthesia during spontaneous respiration. In order to assess the impact of anesthesia on brain oxygen regulation, we used chronically implanted electrodes to measure PO_2 and single unit activity in the somatosensory cortex in neonatal rabbits. By using the same electrodes to record PO_2 and single unit firing rate, we were able to examine these changes at precisely the same location. Two anesthetics were chosen: sevoflurane, which is the most commonly used general anesthetic in children and adults, and isoflurane, which is often used in the developing world, as well as for research studies in animal models. Anesthesia delivery was tested in air as well as in combination with 80% O_2. Our results indicate that each drug affected to a different degree neuronal firing and intracortical tissue PO_2, as well as respiration, and that the tissue PO_2 changes during hyperoxia were significantly greater when anesthesia was delivered with a higher-than-air oxygen concentration.

2. Material and methods

2.1. Animal preparation

Five Dutch-belted rabbits (9-12 days-old) were used in accordance with the National Institutes of Health guidelines and protocols approved by the NorthShore University HealthSystem Research Institute Institutional Animal Care and Use Committee. The rabbit kits were born in a nest box containing shredded aspen bedding which was prepared in advance. The newborn rabbit kits were housed and nursed with the dam and began to open their eyes at 9–11 days.

At the age of 6 days animals were implanted with electrodes. For this procedure, animals were anesthetized with a mixture of ketamine (60 mg/kg) and xylazine (10 mg/kg). The recording assembly consisted of a silica tube (Polymicro Technologies, Phoenix, AZ) containing a bundle of four 25 μm diameter gold-silver alloy microwires with formvar insulation (California Fine Wire, Grover Beach, CA) that were gold-plated at the tip. These electrodes terminated at different levels within a distance of 100 μm. The microwires were connected to a small 6-pin connector that was embedded in dental acrylic. A 100 μm silver chloride wire was placed between the skull and dura mater to serve as the reference electrode. During implantation surgery, lambda was positioned at the level of bregma and the stereotaxic coordinates were as follows: anterior-posterior was 2 mm ventral to bregma, medial-lateral was 2.5 mm from midline, and dorsal-ventral was under visual control. After implantation, the electrode assembly was cemented to the skull using dental acrylic and 3 nylon support screws. The average surgery duration was 1 h. After completion of experiments, kits were euthanized on day 12th.

2.2. Experimental design

All experiments were performed beginning 3 days after surgery. The kits were restrained by means of a cloth sleeve. A recirculating warm water heating pad (T-Pump, Gaymar Industries Inc, Orchard Park, NY, USA) was used to maintain temperature. Respiration was measured using a pressure pad/respiration transducer (TSD110) (Biopac Systems, Inc, Goleta, CA, USA). PO_2 and single unit activity were recorded in separate experiments first in the awake state for 5–6 min. Kits then were anesthetized with either isoflurane (Piramal Enterprises Limited, Kohir Mandal, Andhra Pradesh, India) or sevoflurane (AbbVie Inc., North Chicago, IL, USA) at 1 MAC via a custom mask using calibrated vaporizers (Drager Vapor 19.1). The level of 1 MAC was determined by toe and tail pinch test and was on average 2% isoflurane and 4% sevoflurane for this group of animals. Anesthesia was delivered for 6 min in air, then for 6 min in 80% oxygen, and finally in air again for 6 min. Anesthesia was then stopped and recordings continued during the period of recovery for 8–9 min, after which the signals typically were lost due to excessive movements of the kits. Each kit was exposed to isoflurane and sevoflurane on different days using this paradigm.

Additional experiments were performed in each kit to measure the PO_2 response to 80% oxygen in the awake state. PO_2 was recorded for 1 min during air breathing. Oxygen concentration was then increased to 80% and PO_2 was recorded for 2 min. The inspired gas was then changed back to air, and PO_2 was recorded for an additional 2 min.

After each session rabbits were returned to the dam. Best efforts were made to prevent rejection of the rabbits by the dam (e.g., kits were wrapped in the nesting materials to maintain normal smell). None of the kits were rejected by the dam.

2.3. PO_2 and electrophysiological recording

The same electrodes were used in separate experiments for electrophysiology and PO_2 recording. The PO_2 electrodes were polarized at −0.7 V, and connected to an ammeter (Keithley 614) to record a current that was typically 3–10 nA during air breathing. The current was converted to voltage, notch and low-pass filtered (30 or 50 Hz), and amplified. As the electrodes were chronically implanted, PO_2 was calculated from current based on the initial calibration. In addition to quantitative analysis the direct fast Fourier transform was used to analyze the power spectrum of PO_2 data. After completion of experiments the same rabbits were used for single unit recording before and during isoflurane or sevoflurane delivery on different days. The multiple signals from the microwires were fed through a miniature preamplifier to a multichannel differential amplifier system (Neuralynx Inc, Bozeman, Montana, USA). The signals were amplified, band-pass–filtered (300 Hz–3 kHz), and digitized (32 kHz/channel) using a Neuralynx data acquisition system. Unit discrimination was performed offline using threshold detection followed by a cluster analysis of individual action potential wave shapes using Neuralynx analysis software. For each phase of exposure, the data were analyzed using the last minute of recording prior to the change in anesthesia or inspired oxygen concentration.

Electrode locations were confirmed by MRI using a 9.4T imaging spectrometer (BioSpec 94/30USR, Bruker Biospin MRI GmbH) operating at 1H frequency of 400 MHz. The spectrometer was equipped with an actively-shielded gradient coil (BFG-240-150-S-7, Research Resonance, Inc., Billerica, MA, USA). A single-turn, 20 mm-diameter circular RF surface coil was used for both transmission and reception. Anatomical images were acquired from subjects following euthanasia using a multi-slice gradient echo pulse sequence with a TR of 1.5 s, a TE of 11 ms, a 21.7 mm × 21.7 mm

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