Both immature stress response and GABAergic systems are involved in mediating the long-term developmental neuroendocrine abnormalities in rats exposed to sevoflurane as neonates

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Background

More than 1 in 4 children are exposed to general anesthesia in their first year of life. Numerous studies in species as divergent as rats and rhesus monkeys provide strong support for developmental neurocognitive deficiencies induced by neonatal exposure to general anesthetics. To what extent these data can be applied to human preemies and neonates requiring anesthesia for operative procedures is currently the subject of vigorous debate. An important factor contributing to this uncertainty is poor understanding of the full range of body systems affected by anesthetics and the underlying mechanisms of the developmental effects of general anesthetics even in rodent models. We investigated whether immature stress response and γ-aminobutyric acid (GABA) type A receptor systems are involved in mediating developmental effects of sevoflurane in rats.

Methods

Sprague-Dawley rats at postnatal days (P) 4, 5, or 6 were anesthetized with 2.1% sevoflurane for 6 h, maternally separated, and house-reared rats served as controls. Subgroup of P4, P5, or P6 male rats received a single injection of bumetanide (1.82 mg/kg, i.p.) or RU28318 (10 mg/kg, i.p.) 15 min prior to initiation of anesthesia with sevoflurane. All rats were sequentially evaluated in the elevated plus maze at ~P60, and for prepulse inhibition (PPI) of the acoustic startle response at ~P90. To assess immature stress response and corticosterone levels were measured at P120. Subsequently, the rats from each treatment group were used for cell electrophysiology.

Results

Figure 1: Sevoflurane increased serum corticosterone levels in P4–P6 pups. Adult rats exposed to neonatal sevoflurane responded to stress with increased corticosterone secretion, with a greater increase in male rats. Bumetanide or RU28318 administered prior to anesthetic exposure normalized the endocrine responses to stress in adulthood.

Figure 2: In adulthood, rats that were exposed to neonatal sevoflurane had altered hippocampal synaptic activity. Neither bumetanide nor RU28318 significantly affected the long-term synaptic effects of neonatal sevoflurane.

Summary

The results of this study together with our previously published 1–3 show that:

• Exposure of neonatal rats to sevoflurane anesthesia leads to acute and long-term endocrine and neurobehavioral abnormalities.

• Male rat pups appear to be more susceptible to the neurobehavioral and endocrine effects of neonatal sevoflurane exposure.

• Sevoflurane-induced increases in GABA, R-mediated depolarization and corticosteroid levels at the time of anesthesia may be involved in the mediation of the endocrine and neurobehavioral developmental effects of the anesthetic.

• Sevoflurane-induced developmental neuroendocrine abnormalities resemble those induced by neonatal stress, such as prolonged and repeated maternal separations.

References


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