Estradiol Is Involved in Mediating Electroencephalographic Hyperexcitatory and Anesthetic Effects of Sevoflurane in Neonatal Rats

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Introduction
Neonatal anesthesia induces profound developmental abnormalities in animal models via incompletely understood mechanisms. Recent studies demonstrated that long-term developmental effects of neonatal anesthesia were more prominent in males.1,3 We tested whether steroids in general and sex steroids in particular, are involved in mediation of sevoflurane-caused paradoxical cortical seizures during the early postnatal period.

The loss of the righting reflex (LORR) was employed to assess the role of steroids in the anesthetic effects of sevoflurane. LORR in animal models is used to assay ability of anesthetics to induce loss of consciousness in humans.

Methods
The study was approved by the local IACUC. Cortical electroencephalograms (EEGs), hippocampal synaptic activity, and serum levels of steroids were measured in postnatal day 4-6 male and female Sprague Dawley rats as described previously.1,3,4

Materials and methods

Rats were pretreated with vehicle or steroid hormone modifiers (see Results) 30 minutes prior to sevoflurane anesthesia (6% for 3-min induction and 2.1% for 57-min maintenance). LORR was assessed at 3.5% sevoflurane (~1MAC in P4-P6 rats).

Results
Sevoflurane caused similar isolated episodes of seizures and persistent regular spike activity in the EEGs during anesthesia with sevoflurane.

Exogenous estradiol increased sevoflurane-caused seizures, spikes, and serum levels of corticosterone. The estradiol synthesis inhibitor, formestane, depressed sevoflurane-caused seizures.

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Conclusions
These findings provide evidence for gender-independent acute electroencephalographic effects of sevoflurane at this age. Corticosterone and estradiol are involved in mediation of sevoflurane-caused seizures. Estradiol, but not corticosterone, also contributes to sevoflurane-caused spikes, by enhancing GABA-A receptor mediated excitation in the cortex. By enhancing GABA-A-mediated inhibition in more mature caudal regions of the brain, estradiol, contributes to sevoflurane-induced LORR.

References