 Isoflurane Exposure During Brain Development Alters Seizure Responses Later in Life

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Background

An intricate balance of glutamate and gamma-aminobutyric acid (GABA) activity guides brain development. Isoflurane anesthesia, a GABA agonist and glutamate receptor antagonist, has detrimental histological effects on the developing rat brain. We hypothesize that isoflurane exposure during postnatal brain development will lower seizure thresholds later in life. This study evaluates the effects of isoflurane treatment during brain development on seizure thresholds during adolescence and adulthood in male rats.

Methods

Male Sprague-Dawley (SD) or Fischer (F) rats were treated with 2.5% isoflurane (SD n=20, F n=17), 1% isoflurane (SD n=18, F n=16), or no isoflurane (SD n=18, F n=16) for 45 minutes on post-natal day (PND) 16-18. Conulsive current (CC) curves were generated for tonic (hindbrain), tonic (forebrain), and limbic seizures during adolescence (PND 30-40) and adulthood (PND 60-63) using standard electrical stimulation protocols and staircase estimation techniques. CC curves were compared between groups using Probit analysis. A p-value < 0.05 was considered significant.

Results

During adolescence: SD rats treated with 2.5% isoflurane had higher tonic seizure thresholds vs. 1% isoflurane or naive (p<0.05). SD rats treated with 2.3% isoflurane also showed a trend toward higher clonic seizure thresholds vs. naive (p=0.076) but similar thresholds vs. 1% isoflurane. Limbic seizure thresholds were not altered by isoflurane treatment in SD rats. Conversely, F rats treated with 2.5% isoflurane had lower tonic seizure thresholds vs. 1% isoflurane or naive (p<0.05). Isoflurane treatment did not affect clonic seizure thresholds in F rats. F rats treated with 2.5% isoflurane had higher limbic seizure thresholds vs. naive (p<0.05) and a trend toward higher limbic thresholds vs. 1% isoflurane (p=0.06).

During adulthood: In SD rats, isoflurane treatment did not alter tonic seizure thresholds; however, 2.5% isoflurane increased clonic seizure thresholds vs. 1% isoflurane (p<0.05) and showed a trend toward higher clonic thresholds vs. naive (p=0.054). In F rats, treatment with either 2.5% or 1% isoflurane increased tonic seizure thresholds vs. naïve (p<0.05), but thresholds were similar between F rats treated with 2.5% or 1% isoflurane. Isoflurane treatment did not alter clonic seizure thresholds in F rats.

Discussion

Isoflurane exposure during brain development altered seizure thresholds later in life. The effects were rat strain and age dependent. Isoflurane tended to increase SD seizure thresholds during adolescence and adulthood. Interestingly, in F rats isoflurane lowered tonic seizure thresholds during adolescence yet increased them during adulthood. Isoflurane increased limbic seizure thresholds during adolescence in F but not SD rats. Our results are unexpected and suggest complex and multi-factorial responses to isoflurane exposure during brain development. Further study is needed.