Background: Sevoflurane administered to neonatal rats induces neurobehavioral abnormalities and epigenetic reprogramming of their germ cells; the latter can pass adverse effects of sevoflurane to future offspring. As germ cells are susceptible to reprogramming by environmental factors across the lifespan, we hypothesized that sevoflurane administered to adult rats could induce neurobehavioral abnormalities in future offspring, but not in the exposed rats themselves.

Methods: Sprague-Dawley rats were anesthetized with 2.1% sevoflurane for 3 h every other day between postnatal days 56 and 60. Twenty-five days later, exposed rats and non-exposed controls were mated to produce offspring (see Diagram above for Study design).

Results: Surprisingly, exposed G1 males, but not G1 females, exhibited persistent neurobehavioral deficiencies, exaggerated hypothalamic-pituitary-adrenal (HPA) axis responses to restraint, elevated levels of testosterone and reduced testis weight (Fig. 2). Changes in hypothalamic-pituitary-testicular (HPT) axis functioning and expression of hypothalamic aromatase and estrogen receptors were consistent with a role for systemic testosterone/brain estradiol in G1 sex-specific effects of sevoflurane (Fig. 3).

Only the male offspring (G2) of exposed parents exhibited neurobehavioral deficiencies, but had unaltered HPA and HPT axis functioning (Fig. 4). Finally, down-regulated K’-2Cl (Kcc2) Cl exporter expression in G1 and G2 male hypothalamus and hippocampus, and hyper-methylated Kcc2 promoter in G1 sperm and ovary and G2 male hypothalamus and hippocampus support the involvement of epigenetic mechanisms in sevoflurane’s intergenerational effects.

Conclusions: Adult sevoflurane exposure affects brain development in male offspring by epigenetically reprogramming both parental germ cells, while induces neuroendocrine and behavioral abnormalities only in exposed males. Sex steroids may be required for mediation of the adverse effects of adult sevoflurane in exposed males.