Clinical studies report learning disabilities and attention-deficit/hyperactivity disorders (ADHD) in those who had anesthesia early in life. We have found that rats, primarily males, neonatally exposed to GABAergic anesthetics exhibit behavioral abnormalities, exacerbated responses to stress and reduction in expression of hypothalamic K⁺-2Cl⁻ (Kcc2) Cl⁻ exporter. The latter is implicated in development of psychiatric disorders, including male predominant comorbid with ADHD autism spectrum disorders. We tested whether parental early life exposure to sevoflurane, the most frequently used anesthetic in pediatrics, affects early life exposure to sevoflurane, the most frequently used anesthetic in pediatrics, affects early life expression in specific F1 groups. A number of studies have shown that exposure of F0 parents to anesthetics, particularly sevoflurane, affects the next generation of unexposed rats. In this study, we used anesthetics to induce stress (Fig. 1A,B). Bisulfite sequencing revealed increased CpG site methylation in the hypothalamus (D). This work was supported by the National Institutes of Health (R01NS091542 and R01NS091543S to A.E.M.), HAF (to L.S.), the Jerome H. Modell Endowed Professorship to N.G. and the National Natural Science Foundation of China (U1404007 and 81771149 to J.Z.).

**Background** Clinical studies report learning disabilities and attention-deficit/hyperactivity disorders (ADHD) in those who had anesthesia early in life. We have found that rats, primarily males, neonatally exposed to GABAergic anesthetics exhibit behavioral abnormalities, exacerbated responses to stress and reduction in expression of hypothalamic K⁺-2Cl⁻ (Kcc2) Cl⁻ exporter. The latter is implicated in development of psychiatric disorders, including male predominant comorbid with ADHD autism spectrum disorders. We tested whether parental early life exposure to sevoflurane, the most frequently used anesthetic in pediatrics, affects early life expression in specific F1 groups. A number of studies have shown that exposure of F0 parents to anesthetics, particularly sevoflurane, affects the next generation of unexposed rats. In this study, we used anesthetics to induce stress (Fig. 1A,B). Bisulfite sequencing revealed increased CpG site methylation in the hypothalamus (D). This work was supported by the National Institutes of Health (R01NS091542 and R01NS091543S to A.E.M.), HAF (to L.S.), the Jerome H. Modell Endowed Professorship to N.G. and the National Natural Science Foundation of China (U1404007 and 81771149 to J.Z.).

**Methods** Sprague-Dawley rats (F0), unexposed or exposed to 2.1% sevoflurane for 6 h on postnatal day (P) 5, were used to produce 4 groups of offspring (F1) control father/control mother (con-M*con-F), exposed father/control mother (sevo-M*con-F), exposed father/exposed mother (sevo-M*sevo-F) and exposed father/exposed mother (sevo-M*sevo-F). Results Male, but not female, progeny of sevoflurane-exposed parents were affected. F1 males of both exposed parents exhibited impaired spatial memory (Fig. 1K-M) and decreased expression of the hippocampal and hypothalamic Kcc2 (Fig. 2H). Offspring of only exposed sires had abnormalities in elevated plus maze and prepulse inhibition of startle (Fig. 1E-I), but normal spatial memory, and decreased expression of the hippocampal and hypothalamic Kcc2 exporter. The latter is implicated in development of psychiatric disorders, including male predominant comorbid with ADHD autism spectrum disorders. We tested whether parental early life exposure to sevoflurane, the most frequently used anesthetic in pediatrics, affects early life expression in specific F1 groups. A number of studies have shown that exposure of F0 parents to anesthetics, particularly sevoflurane, affects the next generation of unexposed rats. In this study, we used anesthetics to induce stress (Fig. 1A,B). Bisulfite sequencing revealed increased CpG site methylation in the hypothalamus (D). This work was supported by the National Institutes of Health (R01NS091542 and R01NS091543S to A.E.M.), HAF (to L.S.), the Jerome H. Modell Endowed Professorship to N.G. and the National Natural Science Foundation of China (U1404007 and 81771149 to J.Z.).

**Results** Male, but not female, progeny of sevoflurane-exposed parents were affected. F1 males of both exposed parents exhibited impaired spatial memory (Fig. 1K-M) and decreased expression of the hippocampal and hypothalamic Kcc2 (Fig. 2H). Offspring of only exposed sires had abnormalities in elevated plus maze and prepulse inhibition of startle (Fig. 1E-I), but normal spatial memory, and decreased expression of the hippocampal and hypothalamic Kcc2 exporter. The latter is implicated in development of psychiatric disorders, including male predominant comorbid with ADHD autism spectrum disorders. We tested whether parental early life exposure to sevoflurane, the most frequently used anesthetic in pediatrics, affects early life expression in specific F1 groups. A number of studies have shown that exposure of F0 parents to anesthetics, particularly sevoflurane, affects the next generation of unexposed rats. In this study, we used anesthetics to induce stress (Fig. 1A,B). Bisulfite sequencing revealed increased CpG site methylation in the hypothalamus (D). This work was supported by the National Institutes of Health (R01NS091542 and R01NS091543S to A.E.M.), HAF (to L.S.), the Jerome H. Modell Endowed Professorship to N.G. and the National Natural Science Foundation of China (U1404007 and 81771149 to J.Z.).

**Conclusions** Our findings provide the first experimental evidence that neonatal exposure to sevoflurane may also affect the next generation of males through epigenetic modification of Kcc2 expression, while F1 females may be at a diminished risk.

**References:**

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