Sex differences

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Sex hormones modulate sensitivity to anesthesia

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Although clinical data suggest that men and women respond differently to anesthesia, several important confounders limit the interpretability of these observations. A new study shows that female mice are more resistant to anesthetics than males.

To determine if sex influences response to anesthesia, Wasilczuk and colleagues compared induction and emergence time in male and female C57BL/6J mice exposed to isoflurane anesthesia, using the righting reflex to distinguish awake from anesthetized mice. The researchers observed that female mice took longer to become anesthetized and recovered faster than male mice, indicating that females were more resistant to isoflurane than males.

Next, to investigate the role of sex hormones in differences in anesthetic sensitivity, the investigators compared the responses of castrated males and ovariectomized females to those of gonadally intact controls after exposure to isoflurane. While ophorectomy had no effect on the response of females to isoflurane, castration increased anesthetic resistance in males and eliminated all sex differences in anesthetic sensitivity between males and females. Conversely, testosterone administration increased anesthetic sensitivity in male mice, further demonstrating the role of testosterone in anesthetic sensitivity.

The researchers hypothesized that testosterone exerted its effects on the brain via its conversion into estradiol by aromatase, an enzyme expressed in the preoptic hypothalamus, a region involved in the control of sleep and wakefulness. Administration of letrozole – an aromatase inhibitor – reduced anesthetic sensitivity in males, while estradiol administration had opposite effects, confirming the hypothesis.

Although electroencephalograms failed to reveal sex differences in neuronal activity in the brains of mice under anesthesia, whole-brain mapping of c-Fos expression – an indirect marker of neuronal activity – revealed differences in the number of c-Fos-positive neurons between males and females, notably an increase in c-Fos expression in the hypothalamus of male mice.

Altogether, these results demonstrate that the female brain is more resistant to volatile anesthetics and suggest that testosterone increases anesthetic sensitivity through its conversion into estradiol and modulation of hypothalamic circuits. These findings could explain the higher rates of unintended awareness reported by women under general anesthesia and suggest that women require different anesthetic protocols from men.

Alexandra Le Bras

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