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Module 3, Video 18: Sex Differences in the Use of Anesthetics and Analgesics for Survival Surgery

Many injury paradigms and other types of experimental manipulations require rodent surgery and potentially the use of pain medication following surgery. But males and females show physiologically distinct responses to various anesthetic and analgesic agents commonly used before, during and after surgery [1]. In this video, we will discuss evidence for sex-based differences in the interaction between the brain and various anesthetic agents.

There are a number of anesthesia choices for rodent surgeries and procedures. The ultimate choice should be based on the type of surgical procedure, the length of the procedure, the available equipment, as well as characteristics specific to the animal, including the animal's sex. Anesthetics used in rodent surgery include inhaled anesthetics and injectable anesthetics, both of which show evidence of sex differences.

For many anesthetics, a complete evaluation of sex differences in pharmacology profiles does not exist, with many anesthesia protocols advising for the use of different doses in males and females based on anecdotal evidence of "sensitivity" differences between males and females or preliminary evidence in humans. But as females are increasingly used in preclinical studies, mounting evidence points to the need for sexually dimorphic dosing regimens for many commonly employed anesthetics. The exact reasoning is unclear, but may be due to differences in plasma corticosteroids, sex hormones or hepatic enzymes.

For example, sex differences in the response to the same dose of ketamine have been observed in a variety of species and for different combinations with other anesthetics, with females usually showing greater clearance and lower drug or metabolite concentrations; thus, females usually require a higher dose of ketamine [2]. Differences in the expression and activity of cytochrome P450 enzymes, which are responsible for metabolizing 70 to 80% of all drugs [3], including ketamine, have been proposed as a possible mechanism [4]. These enzymes are also subject to hormonal regulation by estrogen, progesterone and testosterone [5]. Ketamine can also reduce serum concentrations of estradiol in adult cycling female rats [6]. Similar sexually dimorphic effects of ketamine have been observed with low-dose ketamine, which has been studied for its potential antidepressant effects in rodent models [7], suggesting that sex differences in the effects of ketamine cover a range of doses.

The example of ketamine illustrates a need to consider differential dosing between males and females. Similarly, differences in anesthesia responses can vary by rodent strain [9, 11-13] and the age of the animal used [14-16].

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Analgesics used before, during and after surgery, including opioids and non-steroidal anti-inflammatories, also show sex differences in their effectiveness. One hypothesis for the difference in analgesic effectiveness may be due to qualitative and quantitative sex differences in pain sensitivity [17]. Based on a 2020 analysis of over 500 studies investigating pain in rodents, the vast majority of quantitative sex differences in acute and chronic pain behavior reflect greater sensitivity in female rodents. Differences in pain may translate to analgesic efficacy. Somewhat in contrast to the consensus in humans, male rodents were overwhelmingly reported to be more sensitive to analgesics, mostly opioids, compared with female rodents [18-22]. Differences in the sensitivity to pain and analgesics also differ across the estrous cycle in rodents [23-25], suggesting that analgesic dosing should be optimized according to both sex and estrous cycle stage.

Although rarely addressed, the impact of sex-differentiated responses to anesthesia on experimental outcomes is possible [12, 26] [27]. There may also be sex differences in mortality following anesthetic use, particularly with inhalants [26].

In this video, we introduced some of the known sex differences in two medication types commonly used in rodent survival surgery: anesthetics and analgesics. Similar to other topics covered in this series, the limited inclusion of female animals in pharmacology studies means that many of the underlying mechanisms of these sex differences are unknown. However, the available evidence suggests that potential sex differences should be further investigated, laying the groundwork for personalized medicine approaches in surgical management.

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