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Sex Differences in Locomotor Activity and Behavioral Sensitization in Rats Administered Fentanyl

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Opioid overdoses have continued to increase, and women have experienced a greater rate of increase than males. Preclinical studies demonstrate marked sex differences in addiction-related behaviors, with females being more vulnerable due to a potential role of estradiol. We sought to understand how the estrous cycle, as a proxy measure of estradiol, influences sex differences in the sensitizing effects of fentanyl. In this ongoing study, we used male and female rats to investigate potential sex effects of fentanyl (20 μ g/kg subcutaneously) administration for 14 days and a forced abstinence period of 13 days on behavioral sensitization via locomotor activity (LMA) following a fentanyl challenge on day 28. Vaginal lavage samples were collected, and cytological characterization was used to determine the estrous stage. Consistent with previous research, fentanyl induced significantly higher levels of LMA compared to the control groups in both sexes. This effect was greater among females and after repeated administration or abstinence. Within the estrus group, a change in LMA from day 1 to 14 and across the abstinence period from day 1 to 28 was observed. The non-estrus group showed significantly greater LMA on day 14 but not 28, and the estrus group did not demonstrate significant differences from control on either timepoint. Our data validate previous investigations showing a greater impact of fentanyl on LMA and behavioral sensitization in females; however, our current data does not support the estrous stage impacting the change in LMA acutely or following an abstinence period.