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Presentation preference: Talk

A tale of two opioids: The genetics of fentanyl and morphine lethality in mice

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Despite signs of progress in pre-pandemic opioid overdose rates, lethal overdoses rose to record levels during the COVID pandemic. The cause of overdose and opioid death is opioid-induced respiratory depression. We have observed substantial genetic and sex effects on respiratory sensitivity to morphine. We hypothesize that genetic variation in inbred strains of mice will also influence the inherent variability to respiratory depression to fentanyl. Using the founders of the Diversity Outbred (DO), we found substantial sex and genetic effects on respiratory response and opioid survival. A high-throughput system estimated respiratory depression with a cage-floor pressure sensor that tracked activity and thorax movement from breathing. We determined the survival time or recovery time in response to an opioid using this system. The fentanyl LD_{50} of both sexes of the eight inbred strains was calculated. It ranged from 1.2 mg/kg for male NZO/HILtJ to 200 mg/kg for male 129S1/SvImJ mice (>150X). The magnitude of the fentanyl LD_{50} range is in stark comparison to the LD_{50} for morphine which varies by four-fold across the same population. We observed very different patterns of strain specific recovery times for the two opioids. In comparison to morphine, in which mice often recovered from the sublethal dose within a few hours, the respiratory rhythm of mice treated with a fentanyl did not return to baseline for upwards of 24 hours. Our results suggest that despite their common mechanism of action through the opioid receptor, genetic variation alters the response to opioids in a drug-specific fashion. NIDA 5R01DA048890