Detecting genetic variation in morphine LD_{50} in founder strains of the Collaborative Cross and Diversity Outbred mouse populations

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As epidemic levels of opiate abuse have spread nationwide, overdose has become increasingly prevalent. Understanding mechanisms and predictors of overdose will be critical to alleviating this problem. Given the variability in exposure patterns and life history in people with opiate addiction, laboratory animals may more effectively be used to characterize mechanisms of overdose liability. The genetic capabilities of the laboratory mouse, can enable identification of variable mechanisms of respiratory depression and lethality associated with opioid overdose. Although there is some evidence for strain differences overdose sensitivity, the effects of genetic variation on morphine overdose susceptibility has been poorly characterized to date. Determining precise quantitative metrics associated with lethality will facilitate genetic dissection of the mechanisms underlying susceptibility and resistance. Using PiezoSleep monitors (Signal Solutions, LLC) to detect respiratory rhythms, we have defined an automated high-throughput technology to monitor respiratory depression associated with morphine administration. The LD_{50} for the eight founder strains of the Collaborative Cross/Diversity Outbred population ranged from 225 mg/kg - 882 mg/kg with some strain × sex interactions. Using PiezoSleep data we were able to determine the time to death or time to recovery for each mouse. These quantitative measurements were used to estimate heritability of these morphine sensitivity traits by intraclass correlation (time to death ICC= 0.338, time to recovery ICC= 0.345). We can now begin mechanistic dissection through genetic mapping and systems genetic analysis and application of pharmacological interventions such as naloxone administration. Having identified an efficient, automated and precise phenotyping system and demonstrating substantial genetic variation in respiratory suppression, a detailed genetic analysis of the biological mechanisms of overdose risk is feasible. Evidence of variability in lethality, and recovery of respiratory suppression indicates that it will be possible to identify protective mechanisms and intervention target pathways using advanced mouse genetic techniques.

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