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Voluntary oxycodone self-administration reveals genetic variation in analgesic tolerance and hyperalgesia in rats

Chronic opioid exposure can lead to the development of analgesic tolerance, opioid-induced hyperalgesia, and allodynia reflecting opioid-induced behavioral plasticity. We used male and females from multiple inbred Hybrid Rat Divergence Panel (HRDP) strains to examine genetic differences in thermal analgesia (tail immersion) and mechanical sensitivity (von Frey) before and after extended oxycodone self-administration. Thermal analgesia was determined by tail withdrawal latencies across 5 timepoints post-oxycodone (1 mg/kg, ip) and summarized as the area under the withdrawal-latency curve. Tolerance was defined as the change in area under the curve between trials. Most strains exhibited classic tolerance to oxycodone, but several were tolerance resistant. Total oxycodone intake was only weakly related to tolerance at both individual- and strain-mean levels, suggesting that the mechanisms regulating oxycodone consumption and those governing analgesic tolerance are at least partly dissociable. Heritability was estimated from the mixed-effects models of various phenotypes. Baseline and post-exposure analgesia and thermal sensitivity were moderately heritable, whereas tolerance and change in thermal sensitivity showed lower heritability. Oxycodone self-administration produced robust mechanical allodynia that was strongly dependent on strain. Initial mechanical sensitivity demonstrated moderate-to-high heritability, while opioid-induced changes showed reduced heritability. Together, these findings demonstrate that genetic background strongly shapes baseline thermal and mechanical sensitivity and analgesic responsiveness, while opioid-induced adaptations such as tolerance, opioid-induced hyperalgesia, and allodynia are weakly heritable and partially dissociable from drug intake. These findings highlight that there are likely distinct genetic influences on opioid consumption versus opioid-induced tolerance, hyperalgesia, and allodynia.

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