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Gene-Wide Association Study of Opioid-Induced Allodynia During Withdrawal in Heterogeneous Stock Rats

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Genetic variability accounts for 20-60% of the vulnerability to opioid use disorder (OUD) in humans. Pain is a driving force for opioid misuse and relapse. Preclinical rat studies suggest opioid self-administration (SA) could be independent from pain. This phenomenon produced challenges researching the link between OUD and pain. We hypothesize this discrepancy resulted from a lack of genetic diversity within animal models. Using heterogenous stock rats (HS), a genetically diverse model relevant to OUD, we aimed to probe the relationship between opioid SA and hyperalgesia, perform gene-wide association studies of opioid-induced allodynia, and identify predictive gene variations. We hypothesize oxycodone SA and hyperalgesia are correlated, and this relationship strengthens or weakens based on the animal's addiction index (AI). A timecourse of mechanical sensitivity throughout withdrawal into protracted abstinence was completed using naïve HS and HS subjected to oxycodone SA. Von Frey behavior was performed at six timepoints following withdrawal: 4hrs, 12hrs, 24hrs, 1wk, 2wks, and 3wks. Results demonstrate oxycodone SA rats exhibit allodynia throughout protracted abstinence, and AI's correlated to the intensity and extent of mechanical hypersensitivity. Differentiation between naïve versus oxycodone animals, and high versus low AI animals was apparent at 12hrs and 24hrs, respectively. Low AI rats recovered to baseline by 1wk while high AI animals showed consistent hyperalgesia without baseline recovery. These data suggest oxycodone SA produces hyperalgesia following cessation, and mechanical sensitivity 12-24hrs into withdrawal may be predictive of the animals AI and oxycodone-seeking behavior. Assessment of gene variants predictive of oxycodone SA-induced allodynia is ongoing.