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## **Withdrawal-induced anhedonia as a protective factor in opioid addiction**

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To determine genetic and epigenetic mechanisms underlying vulnerability to addiction it is helpful to identify the effects of initial drug exposure that predict subsequent levels of drug use. The goal of Study 1 was to evaluate whether anhedonia, an affective sign of opioid withdrawal, predicts addiction vulnerability. Rats were first tested for withdrawal sensitivity following acute injections of morphine (i.e., “acute dependence”), measured as elevations in intracranial self-stimulation (ICSS) thresholds (anhedonia-like behavior) during naloxone-precipitated and spontaneous withdrawal. They were then tested for addiction vulnerability using various measures of morphine self-administration (MSA) including acquisition, demand, extinction, and morphine- and stress-induced reinstatement. Greater naloxone-precipitated and spontaneous withdrawal severity was associated with lower addiction vulnerability on multiple MSA measures. These data suggest that high anhedonia during withdrawal from initial opioid exposure is protective against subsequent opioid addiction vulnerability in rodents. In Study 2, we conducted RNA-seq on tissue collected from the prefrontal cortex of male and female rats 23 hrs following a similar regimen of morphine injections as was used to produce anhedonia in Aim 1. Overall, mRNA expression of 683 genes was significantly affected, with an overlap between males and females of 31%. Of this subset, enrichment was greatest in genes associated with cell death/survival, cell signaling, cell morphology, cellular development, and cellular assembly/organization. Current and future efforts are directed towards identifying which of these transcriptomic changes are critically important in conferring resilience to opioid addiction.