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High-Throughput Screening of Circadian Rhythms and Strain-Dependent Relationships with Cocaine Addiction in Genetically Diverse Mouse Populations

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Circadian disruption is commonly observed in addiction and increases vulnerability to drug abuse. However, the genetic mechanisms underlying the link between circadian rhythms and addiction are still unknown. To examine this link, we used Collaborative Cross (CC) and Diversity Outbred (DO) mice, which have expansive genetic and phenotypic variation that allows for high-precision genetic analyses. We first measured molecular rhythms in skin fibroblasts from CC and DO founder strains composed of 5 inbred (A/J, C57BL/6J, 129S1/SvlmJ, NOD/ShiLtJ and NZO/HiLtJ) and 3 wild-derived strains (CAST/EiJ, PWK/PhJ and WSB/EiJ), and found that the period of molecular rhythms was significantly shorter in CAST/EiJ, but longer in A/J and PWK/PhJ than C57BL/6J. Consistent with their molecular rhythms, A/J displayed significant longer period of behavioral rhythms in wheel-running activities than CAST/EiJ. We also observed that the amplitude of molecular rhythms was significantly higher in 129S1/SvlmJ and WSB/EiJ relative to C57BL/6J, but lower in NOD/ShiLtJ. Heritability estimates were 50% for the period and 37% for the amplitude, indicating that circadian parameters were attributed to strains. Interestingly, these circadian parameters were correlated with addiction-related behaviors in cocaine self-administration. Furthermore, we characterized circadian phenotypes in CC004/TauUnc and CC041/TauUnc, which exhibited extreme high and low behavioral responses to cocaine respectively. CC041/TauUnc displayed longer circadian period in molecular and behavioral rhythms than CC004/TauUnc. Additionally, we observed a significant reduction in amplitude from CC041/TauUnc relative to CC004/TauUnc in male. Together, our data suggests strain-dependent relationships between circadian phenotypes and cocaine addiction.