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Selectively bred rats with low motivation to exercise may also be vulnerable to abuse drugs

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Background & Significance: Substance use disorder (SUD) often begins during teenage years. The inherently high activity levels of childhood begin to wane during those same teen years with a decrease in voluntary exercise. Yet, exercise, especially during youth, may protect against drug use and the transition to SUD. Pre-clinical data from our and other labs have suggested differences in exercise motivation has a genetic basis, and that such differences may underlie the development of SUD-like behaviors. **Hypothesis:** Rats selectively bred for the phenotype of either high or low voluntary running (HVR or LVR) would display different vulnerabilities for cocaine self-administration and the development of SUD-like behaviors. **Results and Discussion:** Findings from an initial experiment with adolescent females demonstrated that LVR rats self-administered more cocaine initially during acquisition, acquired cocaine self-administration after fewer sessions and required longer to extinguish cocaine-seeking than HVR rats. These data suggest that selection of the LVR phenotype may confer a genetically-mediated vulnerability to develop cocaine abuse. In a subsequent study, adenoviral-associated viral nucleus accumbens overexpression of the protein kinase inhibitor alpha gene induced a 3-fold increase voluntary running distance of LVR rats. Beyond wheel-running behavior as a natural reward, the above approach has significant potential for application in experiments to identify molecular mechanisms that lower the risk of drug abuse. Future studies will be aimed at identifying mechanisms to increase exercise that could produce novel therapies to counter SUD.