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Psilocybin Reduces Opioid Seeking Behavior and Impacts mRNA Expression in the Prefrontal Cortex in a Pre-Clinical Model of Fentanyl Self-Administration

Opioid use disorder (OUD) leads to thousands of overdose deaths annually. FDA-approved treatments for OUD are methadone, buprenorphine and naltrexone. While these medications reduce mortality and provide symptomatic relief, they are associated with risk of overdose, precipitated withdrawal, and inadequate suppression of craving. Individuals living with OUD need alternative prospects to pharmacologically treat and support their recovery. Clinical studies have demonstrated psilocybin has therapeutic potential for treatment of substance use disorders, with a low abuse potential and safe therapeutic profile. Data published from our lab support these findings; we have demonstrated that an acute administration of psilocybin following opioid abstinence, but prior to relapse testing, reduces heroin craving behavior in a rodent opioid self-administration (SA) model. Due to the rise of human use of synthetic opioid agonists, we evolved our rodent opioid SA model from heroin to fentanyl SA. We hypothesized that an acutely administered dose of psilocybin that reduced heroin seeking behavior would be efficacious for reducing fentanyl craving behavior. We tested this by administering psilocybin following three weeks of forced abstinence, prior to a cue-induced relapse test. Rats in the psilocybin treatment group responded significantly less on the cue-paired lever during relapse testing compared to vehicle-treated rats. Additionally, we report psilocybin may accelerate extinction of opioid craving and reduce seeking behavior following a fentanyl re-exposure event during abstinence. Bulk RNA sequencing from the prefrontal cortex (PFC) of rats that underwent fentanyl SA with psilocybin treatment was performed to begin to identify mechanisms through which psilocybin may reduce fentanyl seeking behaviors. We report significant biological pathways of genes regulated in the PFC following psilocybin and fentanyl and highlight key gene expression signatures that may be evaluated in future studies to understand the molecular consequences of psilocybin use in the context of reduction of opioid seeking behaviors.

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