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Genomic Assessment of the Prefrontal Cortex in Differential Responsivity of Sucrose Preference and Fentanyl Escalation in Sprague-Dawley Rats

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Background: The “loss of control” phenomenon seen in opioid use disorder (OUD), known as escalation of intake, is well-established in preclinical rodent models. Antecedent behavioral characteristics, such as valuation of hedonic reinforcers prior to drug use, may impact the trajectory of fentanyl intake over time. Moreover, phenotyping escalation of fentanyl intake may reveal the underlying genetic markers associated with OUD.

Methods: Male and female Sprague-Dawley rats (n=58) were trained in a sucrose reinforcement task using a progressive ratio schedule. Individual differences in responsivity to sucrose were hypothesized to predict escalation of fentanyl intake. Rats underwent daily 1h acquisition sessions for i.v. fentanyl self-administration (2.5 µg/kg; FR1) for 7 days, then 21 6h escalation sessions. Approximately 18h after the last self-administration session, tissue from prefrontal cortex was collected for RNA sequencing and qPCR. Permutation testing was used to assess gene expression using original and post-hoc statistical models involving behavior during escalation.

Results: Sucrose breakpoints did not predict fentanyl infusions across 1h sessions but did predict fentanyl infusions across 6h sessions; however, the association with sucrose breakpoints was with the initial daily levels rather than the temporal changes over the three weeks. Our permutation analysis did not identify associations between behavior and gene expression.

Discussion: Valuation of the hedonic reinforcer sucrose predicted initial daily levels of fentanyl infusions in 6h sessions but not temporal changes. Bulk-sequencing did not identify differentially expressed genes in connection to behavior. Future investigations with greater statistical power will continue to seek clues into genomic markers of OUD.

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