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Characterizing the effects of fentanyl exposure on induced pluripotent stem cell-derived medium spiny neurons

Opioid use disorder (OUD) is a chronic condition characterized by a three-stage cycle: intoxication, withdrawal, and preoccupation. First drug exposure and subsequent individualized response are critical components of this cycle. This response varies between individuals, ranging from nausea to euphoria. Notably, a positive response to initial use is a major predictor of OUD susceptibility, indicating the need to understand the effects of opioid exposure on the etiology of addictive disorders. The nucleus accumbens plays a key role in opioid response and reward processing, and is primarily composed of medium spiny neurons (MSNs). We sought to characterize the effects of opioid exposure on the epigenomes of MSNs by leveraging induced pluripotent stem cell (iPSC)-derived MSNs (iMSNs). iMSNs recapitulate canonical MSN features, including morphology, expression of key proteins and canonical marker genes (e.g., DARPP32, BCL11B), and D1- and D2-MSN subtypes, confirmed by immunohistochemistry and single-cell RNA-sequencing. iMSNs underwent a dosage series of acute and chronic-intermittent exposures to fentanyl and 6-monoacetylmorphine, the primary active metabolite of heroin, and we observed no impact on cell viability. Acute conditions were defined as a one-time 4h exposure, while the chronic-intermittent condition was defined as 4h of exposure per day for 5 days. Next, we selected 3 drug exposure paradigms for bulk- and single-cell transcriptome-wide analysis: acute moderate dose (5 μ M), acute large dose (50 μ M), and chronic-intermittent. Bulk-sequencing revealed 5 and 112 DEGs at the acute moderate and large doses respectively, including PDYN and SYT1. Here, we will describe the impact of fentanyl exposure on iMSNs from all three conditions. Human tissue studies have revealed transcriptome differences associated with OUD, but whether these alterations are a direct consequence of opioid exposure remains an open question in the field. In vitro models hold the promise of answering these questions by complementing model organism studies of this condition.

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