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Deciphering the Molecular Effects of Acute and Chronic-Intermittent Opioid Exposure on iPSC-derived Medium Spiny Neurons

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Opioid Use Disorder (OUD) is characterized by multiple cyclic stages including drug exposure, intoxication, withdrawal and preoccupation/anticipation. The first stage of opioid use disorder, response to drug exposure is highly variable in humans with side effects ranging from drowsiness and constipation to euphoria. Following the initial exposure from prescription and nonmedical self-exposure, about ~6% and up to 20% individuals develop OUD respectively. Thus, the response to drug exposure, and the variation of this response across individuals, is critical to our understanding of the etiology of addiction. However, the molecular response to opioid exposure in human cells and how it varies between individuals has not been fully characterized. We aim to uncover the molecular mechanisms underlying drug exposure response by exposing human stem cell derived medium spiny neurons (hiMSNs), the most abundant neuron population in the nucleus accumbens, to opioids. hiMSNs display morphological and transcriptome features of bonafide MSNs and are positive for markers of mature MSNs, CTIP2 and DARPP32 In our study, hiMSNs were exposed to fentanyl for (i) single 4-hour exposure and (ii) two consecutive 4-hour exposures. Significantly differentially dysregulated genes in the exposed hiMSNs reveal significant enrichment for pathways associated with opioid abuse, medication and drug-induced dyskinesia. Genes implicated such as PENK, PDYN, PPP1R1B, DRD1 and PDYN, have been shown to play crucial roles in reward signaling. The identification of susceptibility genes that may confer risk will provide the basis to understand the pathogenesis of OUD for future development of therapeutic interventions to prevent disease progression.