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Modeling Prenatal Opioid Exposure in human iPSC-derived medium spiny neurons to study the structural and functional effects of fentanyl-induced neurodevelopmental disruption

The underlying molecular and cellular effects of opioid exposure on the development of the brain are largely unknown, even with an escalating incidence of Neonatal Opioid Withdrawal Syndrome (NOWS). NOWS is associated with increased risk for neurodevelopmental and neuropsychiatric symptoms later in life, suggesting lasting effects of opioid exposure on brain development. Previously, our groups reported that perinatal exposure to the synthetic opioid fentanyl in mice resulted in structural and functional changes in medium spiny neurons (MSNs), the principal neurons of the striatum. Here, we developed a cell model to test the hypothesis that developmental exposure to opioids alters the structural and functional activity of human MSNs. Human induced pluripotent stem cells were differentiated into MSN-like neurons (hiPSC-MSNs) in vitro. We cultured hiPSC-MSNs in the presence of low (0.01 μ M), medium (0.3 μ M), or high (10 μ M) concentrations of fentanyl for 7 days (chronic exposure). To observe structural and morphological changes, we quantified neurite outgrowth of MSNs after the exposure paradigm using an immunocytochemistry assay with an open-source ImageJ macro. Furthermore, to observe the functional changes, we evaluated network connectivity in chronic fentanyl-exposed MSNs using a microelectrode-based assay (MEA). Fentanyl exposure resulted in a dose-dependent decrease in neurite length and network activity. The highest dose led to significant rates of cell death after seven days of exposure, whereas no overt cellular toxicity was observed at lower doses. These results establish hiPSC-MSNs as a tractable model to investigate the developmental consequences of fentanyl and other opioids, providing insights into fentanyl's effects in human striatal neurons.

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