

Linking chronic physiological stress to opioid exposure responses

OD is a multifaceted disorder in which genetic, environmental, and societal factors collectively shape individual susceptibility. While environmental stressors account for approximately 40% of addiction vulnerability, the precise molecular mechanisms linking chronic stress to OD remain poorly defined. Here, we integrate multi-omics analysis of post-mortem human brain tissue with studies in human induced pluripotent stem cell-derived cortical neurons (iNs) to investigate how chronic physiological stress modulates neuronal responses to opioid exposure. We exposed NGN2+ iNs to fentanyl (100 μ M) for four hours and measured global transcriptome response. Acute fentanyl exposure induced widespread transcriptional alterations associated with impaired synaptic plasticity. Notably, VGF, an activity-dependent neuropeptide precursor implicated in opioid-evoked plasticity, was significantly downregulated. Similarly, RGS4, a key modulator of μ -opioid receptors (MOR) was reduced, consistent with prior in vitro and in vivo observations following acute morphine and cocaine exposure. In contrast, fentanyl-induced upregulation of multiple ion channel genes, including KCNT2, KCNH1, KCNQ1, and ANO5, suggested reduced neuronal excitability. To model prolonged environmental stress preceding opioid misuse, iNs were chronically exposed to dexamethasone (1.5 μ M), a synthetic cortisol, prior to acute fentanyl treatment. Cortisol-primed neurons exhibited exacerbated transcriptional responses to fentanyl, with a greater number of downregulated genes involved in synaptic plasticity and neuronal function, including NRN1, KIRREL3, and CUX2, in addition to VGF and RGS4. Notably, CEBPD, the most upregulated gene following combined cortisol and fentanyl exposure, corresponds to a top transcription factor motif enriched in OD-sensitive enhancers identified in post-mortem human cortex. We aim to further detail transcriptomic and epigenomic signatures associated with amplified stress reactivity and acute opioid exposure. By functionally dissecting neuronal opioid exposure responses at the intersection of maladaptive stress and addiction risk, this work identifies candidate genes, pathways, and regulatory networks that may inform preventative care strategies and stress-informed, personalized interventions for OD.

Authors:

Submitter: Yike Huang, Postdoctoral associate, Whitehead Institute for Biomedical Research, Cambridge

Sofia Agudelo, BSc, Whitehead Institute for Biomedical Research

Zia Barnard, MSc, Whitehead Institute for Biomedical Research

Olivia Corradin, PhD, Whitehead Institute for Biomedical Research, Department of Biology, MIT

Yasmine Sami, BSc, Department of Brain and Cognitive Sciences, MIT