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Linking Stress to Opioid Addiction: Exploring Genetic and Neuroepigenetic Mechanisms

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Opioid use disorder (OUD) presents a significant global health challenge, underscoring the urgent need for a comprehensive understanding of the biological basis of addiction. OUD is a multifaceted disorder that genetic, environmental, and societal factors collectively shape individual susceptibility. While environmental stressors account for approximately 40-50% of addiction vulnerability, the precise molecular mechanisms underlying the interplay between stress and OUD remain elusive. This study leverages large-scale, multi-omics data across stress and addiction phenotypes, post-mortem human tissue analyses, human induced pluripotent stem cell (hiPSC)-derived neurons, and in vitro models of stress and opioid exposure to investigate the complex relationship between physiological stress and opioid misuse. We observe that dexamethasone-exposed hiPSC-derived forebrain neurons exhibit a robust upregulation of FKBP5, which encodes a glucocorticoid receptor co-chaperone, of up to seven-fold. We will present transcriptomic and epigenomic profiles associated with amplified adaptive stress reactivity. We aim to functionally dissect their impacts on cellular response to opioid exposure to identify key genes, pathways, and networks at the intersection of maladaptive stress and addiction risk. These findings may inform novel preventative care strategies to identify individuals most vulnerable to developing addiction and guide the integration of stress response into personalized treatments for OUD.