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Early life adversity-induced vulnerability for opioid addiction: from circuit regulation to epigenetic modification.

Early life stress reconfigures the transcription processes to induce vulnerable brain circuits and lead to disease states. Our lab identified that early social isolation (ESI) stress during adolescence increases vulnerability to opioid addiction by disrupting the function of the prefrontal cortex (PFC) to ventral tegmental area (VTA) circuits. We found that ESI stress potentiates heroin seeking in mice and reduces the activity of PFC-VTA projecting neurons (i.e., reduced spontaneous firing frequencies). Further transcriptomic studies revealed that these altered functional changes are due to abnormal transcriptional profiles within the PFC-VTA projection. Among these transcriptional changes, the minichromosomal maintenance complex proteins MCM3 and MCM7 are the hub genes regulating the cell cycle, DNA damage and repair, and chromatin accessibility. CRISPR-Cas9-mediated conditional knockdown (cKD) of MCM3 and MCM7 in PFC-VTA projecting neurons attenuates ESI-potentiated heroin seeking. Using bulk ATAC-seq and RNA-seq, we found that MCM3 and MCM7 cKD alter chromatin accessibility and gene transcription, supporting the model that the MCM3 and MCM7-mediated dysregulation of gene expression may serve as a central epigenetic switch for ESI-induced opioid addiction vulnerability.

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