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DNA damage and repair processes are involved in opioid addiction

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Opioid use disorder (OUD) is a debilitating disease that exhibits a high relapse rate. Opioid-induced chronic changes in gene expression underlie neuroplastic alterations within the brain reward circuitry such as the prefrontal cortex (PFC), which lead to the life-long propensity for relapse. We know that epigenetic changes are underlying opioid abuse-induced transcriptional plasticity. However, the causes for the epigenome changes and consequently transcriptome alterations remain unclear.

DNA damage and repair processes maintain chromatin integrity for proper epigenetic signature and gene expression. Post-mitotic neurons are especially susceptible to DNA damage (e.g., DNA breaks). These DNA damages trigger DNA repair responses, which involve extensive chromatin remodeling to incorporate DNA repair machinery and consequently alter chromatin structure and gene expression to affect behaviors.

Here, we showed that DNA damage is increased in postmortem PFC tissues from OUD subjects and in PFC tissues from mice underwent heroin self-administration. Additionally, the increased DNA damage is accompanied by altered gene expression involved in DNA damage repair signaling. Moreover, introducing DNA damage into the PFC potentiates heroin-seeking behavior. Furthermore, we characterized the cell type-specific alterations in DNA repair sites and the associated changes in chromatin accessibility and gene expression. We found that heroin alters the DNA damage and repair profiles, which is accompanied by overall increased chromatin accessibility. These changes in chromatin are related to heroin-induced transcriptional alterations, which converge on signaling pathways involved in DNA damage/repair and addiction. This study provides a novel pathway by which drugs of abuse regulate gene expression.