Discovering Long-Lasting Novel Epigenetic Mechanisms Associated with Cocaine Addiction: The Role of the SWI/SNF Remodeling Complex in the Nucleus Accumbens

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Over one million individuals in the United States are addicted to cocaine, yet limited knowledge of underlying molecular mechanisms prevents effective treatment development. Chronic cocaine use is believed to cause long-lasting chromatin modifications which may explain the persistence of drug addiction. Despite being implicated in chromatin modifications, the overall functions of the SWI/SNF chromatin remodeling complex in cocaine addiction remain unknown. Therefore, this study investigated the role of SWI/SNF subunits in cocaine addiction and long-term withdrawal. A cocaine addiction murine model with a 30-day withdrawal period was used to assess long-lasting epigenetic changes in the nucleus accumbens (NAc), a major brain reward region. Subcellular fractionation and mass spectrometry were conducted on NAc tissue to measure protein abundance changes in the chromatin. Multiple subunits of the SWI/SNF remodeling complex decreased in abundance following cocaine re-exposure, including SMARCB1 ($p=0.019$), BRD7 ($p=0.026$), and SMARCC2 ($p=0.044$), and did not increase during withdrawal. These results indicate that the SWI/SNF remodeling complex does not remain bound to chromatin during long-term withdrawal and may be downregulated following relapse to cocaine. However, not all SWI/SNF subunits demonstrated significant changes across groups, suggesting some are not implicated in addiction. The findings of this study uncover novel long-lasting epigenetic changes associated with cocaine addiction, revealing downregulations of specific SWI/SNF subunits, thus identifying a potential composition of the SWI/SNF remodeling complex involved in chromatin dynamics following relapse. Novel regulations identified in this study may provide targets for cocaine addiction treatments.