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How histone post-translational modifications impact nucleosome structure and accessibility: A molecular dynamics study

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Substance use disorders are chronic and relapsing conditions characterized by compulsive drug use and intense drug craving despite negative consequences. Recent studies have emphasized the crucial role of epigenetic changes in chromatin structure, which are associated with altered gene expression in response to drug abuse. The primary epigenetic mechanisms involved in these changes include DNA methylation, histone modifications, and non-coding RNAs. Although there is mounting evidence that biophysical factors play critical roles in epigenetic processes, the precise mechanisms by which physical forces regulate epigenetic modifications of chromosome structure in drug addiction and whether these changes can be inherited by subsequent generations remain unknown. This study focuses on histone post-translational modifications (PTMs), which can affect nucleosome structure and accessibility and play important roles in gene expression, DNA repair, and fundamental cellular processes such as mitosis and differentiation. Using all-atom molecular dynamics (MD) simulations, we demonstrate that histone PTMs within the nucleosome DNA entry/exit region can induce a relatively more open conformation of DNA on-site compared to the canonical nucleosome. Our simulation study provides an atomic-level understanding of the regulation mechanism by which a subtle modification induces dynamical changes in the nucleosome that promote DNA exposure for gene expression.