

Psychostimulant-induced Alterations in Epigenetic DNA Methylation of Neural Genes: Toward a Pharmacological Separation of Euphoric and Neuroadaptive Mechanisms?

Undieh AS, Novikova S and Lakshmikuttyamma A. Department of Pharmacology, Physiology and Neuroscience, City University of New York School of Medicine, New York, NY 10031.

Epigenetic remodeling has gained prominence as a leading hypothesis to explain the underlying mechanism of addiction and drug-mediated neuroadaptive states. In hopes of detecting addiction-related epigenetic signatures, we have examined the effects of psychostimulants, notably cocaine, on epigenetic DNA methylation in brain regions of neonatal, adolescent and adult mice. Analyses of differentially methylated DNA regions indicate significant up or down alterations in promoter DNA methylation of hundreds of neural genes at each developmental age. Clustering of differentially methylated genes suggests functional implications across a broad range of cellular signaling pathways some of which relate to the substrates of neuroplasticity. Whereas the effects of cocaine on extracellular dopamine levels and euphoric/hedonic behavior occur within minutes of drug administration, no significant changes in DNA methylation occur within three hours of drug exposure. Our ongoing efforts seek to decipher whether the euphoric effects of psychostimulant drugs are mediated through classical transmembrane signaling cascades while another nonconventional mechanism may mediate the remodeling of the epigenome leading to neuroadaptations that are associated with addiction. If so, then it may ultimately be possible to pharmacologically isolate the euphoric effect from the “addictive” mechanism of the drugs.