Addictive drugs and epigenetic regulation at opioid gene promoters in the rat brain reward circuitry

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The interaction between genes and environment is responsible for altering developmental trajectories thus lending vulnerability or resilience to mental disease conditions, including addictive behavior. At molecular level, epigenetic studies provide invaluable insights to elucidate the interaction between an individual's genome, environment and addictive drugs (Jaenisch and Bird, 2003). The presence of enduring effects, even after long periods of abstinence, have suggested the possibility that illicit drugs may cause persistent molecular events that are engendered by long-lasting epigenetic, transcriptional, and translational effects on brain systems (Cadet et al. 2016). Epigenetics is defined as heritable chemical modifications to DNA capable of influencing transcriptional activity independent of DNA-coding sequence (Weaver et al. 2004). Mainly, epigenetic mechanisms include DNA methylation and various chemical histone modifications which remain the most recognized and established epigenetic changes. These mechanisms work in tandem to cause chromatin remodeling and thus regulate gene expression.
Several studies provided strong evidence for a role of epigenetic changes in response to acute and repeated exposure to various drugs of abuse including alcohol, cocaine and amphetamine (Robison and Nestler, 2011). On these bases, we recently devoted much of our research effort to investigate whether the exposure to different illicit drugs is able to induce gene expression changes of opioid systems through chromatin modification. In this frame, we investigated epigenetic alterations promoted by ethanol (EtOH), cocaine or 3,4-methylendioxymetamphetamine (MDMA) exposure respectively, at opioid peptide precursor promoters in selected rat brain areas, adopting the Chromatin Immuno Precipitation (ChIP) technique. The following histone modifications were examined: H3K4 trimethylation and H3K9 acetylation, as permissive marks and the H3K27 trimethylation and H3K9 dimethylation, as repressive marks.
First, in the rat amygdala an increase of acH3K9 and a decrease of me3H3K27 were respectively assessed at pronociceptin (pN/OFQ) and prodynorphin (pDYN) gene promoters after acute EtOH exposure, consistent with our previous data on gene expression. Likewise after chronic EtOH treatment acH3K9 levels increased at pN/OFQ gene promoter in agreement with the reported pN/OFQ gene expression up-regulation (D'Addario et al. 2013). Furthermore, results obtained following chronic subcutaneous cocaine infusion demonstrated that cocaine induces histone changes in the nucleus accumbens (NAc) and in the lateral and medial caudate putamen, respectively (Caputi et al. 2014). In particular, the me3H3K4 and me3H3K27 changes at pDYN and pN/OFQ promoters were consistent with the observed gene expression alterations. Lastly, ChIP assay revealed that acute MDMA increased me3H3K4 at the pN/OFQ and pDYN promoters (Caputi et al. 2016). After either acute or repeated MDMA treatment a significant decrease of acH3K9 at the pN/OFQ promoter was observed, which correlated with gene expression results. Acute treatment also caused an acH3K9 increase and a me2H3K9 decrease at the pDYN promoter which matched its mRNA up-regulation. Present findings demonstrate that EtOH, cocaine and MDMA induce selective histone changes at DYN and N/OFQ promoter regions, and provide new insights for the development of therapeutic strategies targeting the epigenetic mechanisms underlying drug addiction.

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