

Time Window for DNA methylation in Incubation of Cocaine Craving

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One of the major challenges of cocaine addiction is the high rate of relapse to drug use after periods of withdrawal. During the first few weeks of withdrawal, cue-induced cocaine craving intensifies, or “incubates”, and persists over extended periods of time. Although several brain regions and molecular mechanisms were found to be involved in this process, the underlying epigenetic mechanisms are still unknown. To examine this question, we used a rat model of incubation of cocaine craving, in which rats are trained to self-administer cocaine (0.75mg/kg, 6hrs/day for 10 days, FR-1), and cue-induced cocaine-seeking is examined in an extinction test performed after 1 day or 30 days of withdrawal. We found that the withdrawal period, as well as cue-induced cocaine seeking, are associated with broad, time-dependent enhancement of DNA methylation alterations in the nucleus accumbens (NAc). These gene methylation alterations were partly negatively correlated to gene expression changes. Intra-NAc injections of a DNA methyltransferase inhibitor (RG108, 100 μM) abolished cue-induced cocaine seeking in the extinction test on day 30, and up to 1 month after treatment. We then attempted to zoom-in on the critical time window for treating the methylation changes caused by incubation of cocaine craving, and found it to be around three weeks (21-25 days) after late withdrawal. We further tested possible genes that respond to the significantly decreased cue-induced cocaine-seeking behavior. Our findings suggest that although incubation of cocaine craving is dynamic, the break-point for heightened craving occurs downstream, after three weeks of withdrawal, in correlation with DNA methylation.