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Epigenetics of incubation of Stress And Addiction: Overlaps and therapeutic Implications

Abstract:

Post-traumatic stress disorder (PTSD) and substance use disorder (SUD) are among the most prevalent and debilitating diseases worldwide that, in recent reports, exhibit high rates of comorbidity. A main intersection brain region that involves in both reward and fear behaviors is the nucleus accumbens (NAc), and therefore considered as a regulatory region in these disorders. We hypothesized that accumbal epigenetic dynamics, and specifically DNA methylation (DM), may be relevant to these pathologies. Therefore, we examined the accumbal DM generated by the "incubation of fear" model compared to accumbal DM generated by the "incubation of cocaine craving" model. Our data demonstrate broad changes in DM of PTSD-like and cocaine-addicted-like animals 30 days after the actual trauma/drug initial experience. More specifically, accumbal hypomethylation state was indicated and resulted in heightened fear expression or cocaine withdrawal response. Comparing the DM data sets revealed a significant overlap of 514 methylated regions between the two models, while ~50% of these regions presented the same methylation pattern while the rest regions showed opposite methylation pattern. Further analysis was focused only on the regions that had the same methylation direction. These results showed an enrichment in neuro-biological and functional pathways that are highly associated with both pathologies. Hence, we suggest that the incubation processes of each pathology may result in a homogenous epigenetic imprinting, which can explain the high comorbidity prevalence of these two disorders. As an applicative translation of our findings, we designed and tested a potential systemic epigenetic-directed pharmacological treatment in our PTSD-like model that successfully attenuated PTSD-like behaviors in animals. This aproach of treatment may offer a future remedy for PTSD or other epigenetic-regulated disorders, such as substance use disorder.