Adolescence Chronic Caffeine Exposure Promotes Diurnal, Biphasic Mood Cycling and Reduces Dendritic Pruning Through DNA Epigenetics in Mice

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Caffeine is the most commonly used psychoactive substance in the world. During adolescence, excessive caffeine consumption is associated with increased smoking, marijuana use and elevated cocaine sensitivity. Yet, little is known about the effect of chronic caffeine on behaviors that may be regulated by epigenetic processes. Adolescent mice exposed to chronic caffeine exhibited a circadian-dependent pattern of mood fluctuations with manic-like behavior during the dark phase and depressive-like behavior during the light phase. Specifically, during the dark cycle mice chronically exposed to caffeine were hyperactive, less sensitive to prepulse inhibition of the startle response. On the other hand, during the light cycle mice chronically exposed to caffeine were hypoactive in a novel open-field environment, more anxious and less motivated to escape the forced swim test. Because caffeine has been shown to alter the DNA methylation profile of peripheral tissues, we examined the effect of chronic caffeine on DNA methylation in the brain. We identified CpGs within the promoter region (-5Kb from the transcription start site) of 10,448 genes. We identified differential methylation in the promoter region of 21 genes in the mPFC and 18 genes in the NAc. Following Bonferroni correction (0.05/21 for the mPFC and 0.05/18 for the NAc), 4 genes in the mPFC and 6 genes in the NAc had significantly altered DNA methylation in the promoter region. Interestingly, we found that the mood fluctuations were associated with a reduction of promoter DNA methylation of the *Wasf1* gene, which encodes the WAVE1 protein. The reduction of WAVE1 protein expression is correlated with increased immature dendritic spine density in the mPFC. Overall, our finding provides a novel mechanism describing how chronic caffeine intake during adolescence promotes diurnal, biphasic mood behaviors, which may be correlated insufficient pruning of dendritic spines in the mPFC.