The Effect of Chronic Cocaine on Behavioral Sensitization and Allopregnanolone Levels in Rat Serum and Brain Samples

Medications that target dopamine are of potential interest in treating cocaine use disorder and addiction because of dopamine's role in reward and motivation. GABAergic neurosteroids, steroids produced de novo in the brain that affect GABA transmission, have prospective efficacy in treating substance use disorders. Allopregnanolone is a progesterone-derived neurosteroid and a positive allosteric modulator of GABAA receptors. Previous studies have demonstrated allopregnanolone administration can reverse many of the reinforcing effects of cocaine dependence, although the mechanism by which this occurs is unknown. In this study, we tested whether chronic cocaine decreases allopregnanolone levels in male and female rats, thus explaining why restoration of hypothesized decreased levels of allopregnanolone confers positive effects in cocaine-dependent individuals. We administered cocaine or saline daily for 14 days and measured locomotor activity and stereotyped behavior, then assessed allopregnanolone levels in serum and brain 24 hours later. Locomotor activity and stereotyped behavior were potentiated in cocaine-treated animals in both sexes, but sensitization was not confirmed. We found no differences in allopregnanolone levels between cocaine- and saline-treated animals of either sex in any of the five identified brain regions nor in serum. However, there was significant sex differences in serum and in all brain regions not involved in dopaminergic systems. These data suggest the role of sex-dependent differences in allopregnanolone levels that may elucidate sex differences in cocaine use disorder and addiction. These results demonstrate a need for further research into the pharmacology of allopregnanolone's actions in cocaine dependent animals and within the mesolimbic dopaminergic system.