Combination of cocaine and stress during adolescence alters glutamate homeostasis in the rat prefrontal cortex

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Adolescence is a developmental period characterized by impulsive choices that may lead to the beginning and escalation of illicit drug use. In this stage of life, the brain is in a unique state of transition as it undergoes profound structural and synaptic changes and, therefore, interfering with brain development during this delicate period may cause adverse consequences. Such effects may be the result of long-term neuroadaptations that involve, among the others, the glutamate system, as previously demonstrated. The main aim of our study was, therefore, to evaluate the response of the glutamate system to the long-term exposure to cocaine during adolescence [from postnatal day (PND) 28 to PND 42]. In addition, in our experimental design, we decided to incorporate an acute stress to evaluate whether the response of the glutamate system might be altered by the previous exposure to cocaine. Stress is one of the factors (together with drug priming and cue exposure) that may induce relapse even after long periods of abstinence. Thus, these analyses might help us to elucidate the role of glutamatergic processes in stress-induced reinstatement of cocaine seeking.

We thus exposed adolescent male rats to cocaine (20mg/kg/day); on PND 45, rats were subjected to swim stress (5 min) and sacrificed 15 min later. Critical determinants of glutamatergic homeostasis were measured in the medial prefrontal cortex (mPFC), which is still developing during adolescence and might be more vulnerable to stress, by means of Real Time PCR and Western blots. Circulating corticosterone levels and the time of immobility during the stress session were also measured.

We observed a general alteration of the three components of the glutamatergic synapse as a result of cocaine and stress interaction, whereas cocaine per sè did not produce any effect. In detail, we found activation of the presynaptic terminal measured as increased expression of the vesicular glutamate transporter together with reduced expression of glial glutamate transporters and increased activation of the post-synaptic terminal as measured by enhanced NMDA receptor phosphorylation. We also measured the time that the animals were immobile during the 5 min of forced swimming, an index of pro-depressive symptoms. Interestingly, adolescent cocaine-treated rats showed higher immobility when compared to saline-treated rats indicating a depressive-like state. The analysis of corticosterone plasma levels showed no changes in cocaine-treated rats and a significant increase in stressed animals, presumably independent from previous cocaine history.

These results indicate a coordinated series of changes which may result in a hyper-reactive glutamatergic synapse in the mPFC of rats with a prior cocaine history, once exposed to an acute stress, and may represent a contributing mechanism to the hypersensitivity to stress observed in abstinent cocaine addicts. In addition, the increased immobility observed in cocaine-treated rats coupled with cortical hypersensitive synapses may, at least in part, contribute to explain the negative emotional state observed during the initial phase of cocaine withdrawal.