Modulation of BDNF expression following repeated exposure to cocaine during adolescence

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Repeated exposure to cocaine causes long-lasting functional and structural changes in the rat brain that could contribute to the development of addiction. In the recent years, emerging data have implicated neurotrophic factors, including Brain Derived Neurotrophic Factor (BDNF), in the action of cocaine.
Evidence exixsts that adolescents are more sensitive abuse than adults to drug suggesting that adolescence might represent a factor of vulnerability for drug addiction.
To this end, we decided to investigate the effect of repeated exposure to cocaine during adolescence (20 mg/kg), i.e. from postnatal day (PND) 28 to PND 42, on the BDNF system and sacrifice the animals after 3 or 48 days of drug withdrawal, i.e at PND 45 or PND 90. We added a degree of complexity to our experimental plan by exposing the animals to an acute stress at PND 45 and PND 90, to evaluate the dynamic response of the BDNF system.
Molecular analyses were carried out using RT-PCR technique. Total RNA was isolated by single step guanidinium isothiocyanate/phenol extraction and the samples were run in 384 well formats in triplicate as multiplexed reactions. Data were analyzed with the comparative threshold cycle ($\Delta\Delta$Ct) method using 36B4, ß-actin and 18S as reference genes. RNA measures were taken in the same animals as the protein measures. Molecular analyses of protein extracts were carried out using Western Blot technique in total homogenate and crude synaptosomal fraction.
Real Time PCR revealed a significant increase of BDNF mRNA levels in the prefrontal cortex of PND 90 cocaine-treated rats, an effect that was primarily due to the modulation of BDNF isoform IV. Interestingly, stress reduced BDNF expression in cocaine-treated rats, at variance from saline-treated rats exposed to stress, revealing a dysregulation of the physiological modulation of the neurotrophin. The enhancement of BDNF mRNA levels was paralleled by an increase of BDNF precursor and mature forms of the protein and by the preferential activation of the PI3K pathway. Notably, such effects were confined to prefrontal cortex and were not dependent on the circulating levels of corticosterone that were increased in the stressed rats only and not influenced by cocaine.
To summarize, our data show a long-lasting effect of cocaine delivered during adolescence on the neurotrophin expression and a dysregulation of the dynamic modulation of BDNF following acute stress suggesting that abuse of cocaine during adolescence may compromise the neuroplastic and neuroprotective mechanisms mediated by the neurotrophin in the rat medial prefrontal cortex.