A SINGLE EXPOSURE TO COCAINE DURING ADOLESCENCE SEGREGATES ANHEDONIC AND RESILIENT RATS: THE ROLE OF THE NEUROTROPHIN BDNF

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Introduction: Adolescence is a critical window of vulnerability since the brain is still maturing through profound neurochemical, structural and synaptic changes. In fact, the brain is extremely sensitive to external stimuli and it is clear that interfering with its proper maturation through early drug use might set the stage to develop drug addiction later on in life. We have previously demonstrated that a single exposure to cocaine during adolescence causes molecular and structural changes in the rat brain, highlighting the unique vulnerability of this period to drugs of abuse. Thus, the major aim of our work was to investigate the effect of a single injection of cocaine during brain development from both behavioural and molecular points of view, focusing our attention on the emotional response, accompanying the behavioural measurement with in-depth analysis of hippocampal BDNF-intracellular signalling, deeply involved in the regulation of emotion and of cocaine-induced neuroplasticity.

Materials and methods: Adolescent and adult male rats were treated intraperitoneally with 20 mg/kg/day of cocaine or saline at post-natal day (PND) 35or PND 66and sucrose intake, which represents a measure of anhedonia, was measured 7days later, i.e. at PND 42or PND 73, then animals were sacrificed. Hippocampi, a brain region involved in depressive-like state and addictive processes, were dissected and plasma was collected. Total RNA and proteins were extracted and analyzed via Real-Time PCR and western blots, respectively, whereas BDNF and corticosterone plasma levels were measured by using commercially available ELISA kits.

Results: At the behavioral level, we found that, in accordance with rates from the literature, while all the animals drank approximately the same amount of liquids, 60% of the adolescent cocaine-exposed rats showed a significant reduction of sucrose intake (-88%, $p<0.001$), a typical feature of depressive-like behaviours. The analysis of hippocampal BDNF signaling in adolescent rats revealed an overall reduction of the neurotrophin mRNA and protein levels, of its high affinity receptor trkB and of the Akt pathway in anhedonic rats whereas resilient rats were characterized by activation of BDNF signaling. Notably, anhedonia in cocaine-treated rats was associated with the overall decrease of BDNF and BDNF signalling pathway, an effect that could contribute to explain, at least in part, the pro-depressive phenotype in these rats. Moreover, corticosterone levels were increased in anhedonic rats while unaltered in resilient rats. Last, BDNF plasma levels were reduced in anhedonic rats but not in resilient rats. Interestingly, these findings were not observed in the hippocampus of adult rats, which indeed showed sucrose preference similar to saline-exposed rats.

Discussion: Our findings indicate, indeed, that a single injection of cocaine during adolescence, and not in adulthood, is sufficient to trigger a depressive-like state that persists for, at least, 7days, further pointing to BDNF as a marker of vulnerability for the adolescent brain. Moreover, these cocaine-induced neuroplastic alterations may contribute to promote drug-induced maladaptive mechanisms in the developing brain that might represent the first step toward the development of drug addiction later in life.