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RESEARCH ARTICLE

Long Withdrawal of Methylphenidate Induces a Differential Response of the Dopaminergic System and Increases Sensitivity to Cocaine in the Prefrontal Cortex of Spontaneously Hypertensive Rats

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Abstract

Methylphenidate (MPD) is one of the most prescribed drugs for alleviating the symptoms of Attention Deficit/Hyperactivity Disorder (ADHD). However, changes in the molecular mechanisms related to MPD withdrawal and susceptibility to consumption of other psychostimulants in normal individuals or individuals with ADHD phenotype are not completely understood. The aims of the present study were: (i) to characterize the molecular differences in the prefrontal dopaminergic system of SHR and Wistar strains, (ii) to establish the neurochemical consequences of short- (24 hours) and long-term (10 days) MPD withdrawal after a subchronic treatment (30 days) with Ritalin® (Methylphenidate Hydrochloride; 2.5 mg/kg orally), (iii) to investigate the dopaminergic synaptic functionality after a cocaine challenge in adult MPD-withdrawn SHR and Wistar rats. Our results indicate that SHR rats present reduced [^{3}H]-Dopamine uptake and cAMP accumulation in the prefrontal cortex (PFC) and are not responsive to dopaminergic stimuli in when compared to Wistar rats. After a 24-hour withdrawal of MPD, SHR did not present any alterations in [^{3}H]-Dopamine Uptake, [^{3}H]-SCH 23390 binding and cAMP production; nonetheless, after a 10-day MPD withdrawal, the results showed a significant increase of [^{3}H]-Dopamine uptake, of the quantity of [^{3}H]-SCH 23390 binding sites and of cAMP levels in these animals. Finally, SHR that underwent a 10-day MPD withdrawal and were challenged with cocaine (10 mg/kg i.p.) presented reduced [^{3}H]-Dopamine uptake and increased cAMP production. Wistar rats were affected by the 10-day withdrawal of MPD in [^{3}H]-dopamine uptake but not in cAMP accumulation; in addition, cocaine was unable to induce significant modifications in [^{3}H]-dopamine uptake and in cAMP levels after the 10-day withdrawal of MPD. These results indicate