Adolescent THC exposure and vulnerability to drug abuse: sex differences

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Several evidence suggests that the use of cannabis, during adolescence might lead to neurobiological changes that can affect adult brain functions and behavior (Realini et al., 2009). Biochemical and behavioral data from our research group showed that exposure to cannabinoid during adolescence in male rats produces an increased vulnerability to cannabinoids and heroin but not to nicotine intake in adulthood (unpublished data). In keeping with epidemiological data in humans, differences between the two sexes in drug seeking and intake have been well-documented in animal studies (Becker and Hu, 2008), with most recent findings related to abuse of cannabinoids (Fattore et al., 2010). Clinical and preclinical findings indicate that sex and gonadal hormones may account for individual differences in susceptibility to the reinforcing effects of addictive substances, and that differences in vulnerability to drug abuse may be mediated by the same biological mechanisms (Fattore et al., 2009). The aim of this study was to evaluate if cannabis exposure during adolescence was able to induce neurobiological changes not only in male but also in female rats, by investigating whether exposure to THC may increase the reinforcing effects of drugs of abuse, such as nicotine, heroin and cannabinoids in adulthood, in order to identify possible sex-specific differences. To this end, behavioral studies have been conducted on female rats using the chronic intravenous self-administration (IVSA) procedure in rats. Results were then compared to those obtained previously in our laboratory on male rats. Female adolescent Sprague-Dawley (for nicotine and heroin studies) and Lister Hooded rats (for WIN55,212-2 studies) (Deiana et al., 2007) at 35 postnatal day (PND) were treated intraperitoneally with increasing doses of THC (2.5, 5 and 10 mg/kg) or with cannabinoid vehicle twice/day for 11 consecutive days. Once animals reached the adulthood (PND 75), we studied the effects of THC exposure on acquisition of nicotine (30 μg/kg/infusion), heroin (30 μg/kg/infusion) and the cannabinoid agonist WIN55,212-2 (12.5 μg/kg/infusion) intravenous self-administration behavior using a continuous-reinforcement (fixed-ratio, FR-1) schedule of reinforcement. Faster acquisition and higher rate of drug intake was considered as index of vulnerability to drug abuse. Data from nicotine self-administration in female rats showed no significant difference between rats exposed and not-exposed (control) to THC during adolescence. On the other hand, THC adolescence exposure increased both heroin and WIN55,212-2 intake as compared to corresponding control groups. Altogether, these results seem to support the hypothesis that adolescence exposure to THC increases the vulnerability to heroin and cannabinoid, but not to nicotine, abuse in adult females. Comparison of results obtained in females with those observed in male rats shows that the average intake of drugs during the last ten days of self-administration training is significantly higher in females than in males. This increased vulnerability of female rats to drug taking as compared to males is in line with previous studies on sex-dependent differences showing that females are more sensitive than males to cannabinoid-induced behavioral effects.

References:
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