CANNABINOID SELF-ADMINISTRATION IN THE RAT: GENDER DIFFERENCES AND EFFECT OF OVARIECTOMY

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Cannabinoids have been reported to sustain both drug-taking and drug-seeking behaviour, supporting the notion that *Cannabis* derivatives may serve as positive reinforcers in rodents. We recently demonstrated that intravenous self-administration (SA) of the cannabinoid CB1 receptor agonist WIN 55,212-2 (WIN) is differentially acquired, maintained and extinguished by Long Evans (LE), Lister Hooded (LH) and Sprague-Dawley (SD) male rats (Deiana et al. 2007), revealing the existence of strain-dependent differences in cannabinoid SA. In this study we verified whether sex-related factors might also be critical in the initiation, retention and extinction of such a behaviour. To this purpose, LE, LH and SD female rats, intact or bilaterally ovariectomized (OVX), along with respective intact male groups, were trained to self-administer WIN as previously described (Fattore et al. 2001), i.e. at the unit dose of 12.5mg/kg/inf, under a continuous (FR1) reinforcement schedule and lever-pressing as *operandum*. Results showed significant differences between LE males and intact females in the number of the acquisition sessions but not in the amount of the daily drug intake during maintenance or timing of extinction. Conversely, OVX females of the same strain showed lower rate of acquisition but higher level of WIN intake, with active responding persisting longer under extinction. With regards to LH strain, intact and OVX females acquired SA behaviour respectively at higher and lower percentage than LH males: however, once SA behaviour was acquired, OVX group showed the highest responding rate and the longest extinction. Finally, only one out of ten intact SD females, but not OVX females and males, does self-administer WIN as defined by significant differences between responding on the active versus inactive lever. Altogether, these findings revealed the existence of 1) strain-differences in cannabinoid SA also among the female population, as LE and LH but not SD rats developed and maintained stable WIN intake, and of 2) sex-differences in the development of cannabinoid SA, as female intact rats developed WIN SA faster than males (i.e. LE strain) or at higher percentage (i.e. LH strain). Moreover, OVX female LE and LH rats displayed lower ability to develop cannabinoid SA although following acquisition responded more for WIN, suggesting that ovarian hormones might play a critical role in modulating the reinforcing effect of cannabinoids and could be one major factor underlying the observed sex-differences.

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Deiana S, Fattore L, Sabrina Spano M, Cossu G, Porcu E, Fadda P, Fratta W (2006) Neuropharmacology 52:646-54.