Gender and region-dependent consequences of THC adolescent exposure on behavior and synaptic plasticity

M. Gabaglio[1]*, E. Zamberletti[1,2], T. Rubino[1], D. Parolaro[1,2]

* Ph.D. School of Experimental and translational medicine,Neuroscience Division, University of Insubria
[1]Dept. of Theoretical and Applied Sciences, University of Insubria, Busto Arsizio (VA)
[2]Zardi Gori Foundation, Milan

In humans as in animals, gender differences have been frequently observed in the biological and behavioral effects of substances of abuse, including cannabis.
Accordingly, our previous works showed that exposure to delta-9-tetrahydrocannabinol (THC), the major psychotropic ingredient of Cannabis sativa, during adolescence results in long-term disturbances of cognitive performances and emotional reactivity in adult female rats, whereas preliminary findings suggested that this complex phenotype was not entirely present when the same treatment protocol was performed in adolescent male rats.
In this study, we fully investigated the long-term behavioral consequences of adolescent THC treatment in male rats, as compared to females.
To this aim, adolescent male Sprague-Dawley rats were treated with increasing doses of THC twice a day from PND 35 to 45 and, in adulthood, a series of behavioral tests were performed in order to check for the presence of (1) cognitive deficits (through the novel object recognition test, either classic and spatial), (2) social withdrawal (through the social interaction test) and (3) depressive-like behaviors (through the forced swim test).
Adolescent THC treatment induced a significant reduction of the discrimination index in the spatial but not in the classic version of the novel object recognition test, whereas it did not affect the other behaviors under investigation, suggesting that THC in male rats is associated with lasting cognitive impairment without alterations in the emotional sphere.
Based on these data, we investigated the possible molecular underpinnings of the cognitive impairment observed in adult THC-treated rats, by focusing our analyses in synaptosomal fractions from the hippocampus of adult THC- and vehicle-treated rats, a brain area particularly involved in the modulation of cognitive functions.
Interestingly, altered rearrangement of NMDA and AMPA receptor subunits were observed in THC-exposed rats. Indeed, in the post-synaptic fraction, the levels of the NMDA receptor subunit, GluN2B, were significantly increased in THC-treated animals, as well as the levels of the AMPA subunits, GluA1 and GluA2. Furthermore, changes in the levels of the pre-synaptic marker, synaptophysin, and the post-synaptic marker, PSD95, were also present.
In the same brain region, we also found significant alterations in both astrocyte and microglia markers, suggesting that adolescent THC might have promoted an aberrant glial reactivity within the hippocampus.
Intriguingly, these changes appear to be specific for the hippocampus, as they were not detected in the prefrontal cortex.
In conclusion, these data demonstrate for the first time that the gender-dependent detrimental effects induced by adolescent THC exposure on behavior may rely on its ability to trigger different region-dependent changes in synaptic plasticity in male and female rats. Specifically, the prevalence of alterations in the emotional sphere observed in females is associated with profound changes in the prefrontal cortex, whereas here we demonstrated that the cognitive impairment induced in male rats is strongly associated with a marked dysregulation in the hippocampus.