Involvement of Suv39H1 in the development of the depressive/psychotic-like phenotype induced by adolescent THC exposure

P.Prini[1], E. Zamberletti[1], F. Penna[1], M. Gabaglio[1], D. Parolaro[1,2], T. Rubino[1]

[1]Dept. of Theoretical and Applied Science, University of Insubria, Busto Arsizio (Va), Italy
[2]Zardi-Gori Foundation, Milan

We have recently demonstrated that adolescent female rats treated with the psychoactive ingredient of cannabis delta-9-tetrahydrocannabinol (THC), develop a depressive/psychotic-like phenotype in adulthood. Moreover, we observed that adolescent, but not adult, THC exposure leads to this phenotype, suggesting that adolescence may represent a vulnerable period for the psychiatric consequences of THC exposure. However, the neurobiology of this vulnerability is not clear. In the last years, several papers support an involvement of epigenetic mechanisms in the pathogenesis of psychiatric illnesses, such as depression and drug abuse. In line with this data, in the PFC of THC-treated animals we observed increased tri-methylation of Lysin9 on the histone H3 (H3K9me3, associated with transcriptional repression) 2 hours after the end of the THC treatment. Moreover, 24 hours later, this increase was still present together with increased di-methylation of Lysin9 and acetylation of Lysin14 on histone H3 (H3K9me2 and H3K14Ac, associated with transcriptional repression and activation respectively). Forty-eight hours after the last THC, these alterations returned to control levels, whereas acetylation of Lysin9 (H3K9ac) significantly increased. In contrast, adult THC exposure induced only a significant increase of H3K9me3, 2 hours after the last THC injection. Therefore, these biochemical data confirm the major vulnerability of the adolescent brain to THC adverse effects.

Since the histone modification mainly disrupted by the adolescent THC exposure was the H3K9me3, the goal of the present work was to investigate the enzyme responsible of this modification, Suv39H1 after adolescent THC exposure, by Western Blot. To this aim, adolescent female rats were treated with increasing doses of THC twice a day from PND 35 to 45 and the analysis was performed in the PFC 2, 24 and 48 hours after the last THC injection. Moreover, to understand if Suv39h1 was already altered during the treatment, we performed the same analysis in the middle of THC treatment, at PND39.

Two and 24 hours after the end of the treatment, we observed a significant increase in SUV39H1 protein levels that return to control 24 hours later. These data fit well with the increase in H3K9me3 observed at the same time-point. The increase in Suv39H1 is was already present at PND39.

In order to understand the possible role of the H3K9me3 in the development of the depressive/psychotic-like phenotype induced by the adolescent THC exposure, we next administered Chaetocin (0.05 mg/kg, one a day, i.p.), a selective inhibitor of SUV39H1, during the adolescent THC treatment and we performed behavioral tests at PND 75.

Chaetocin administration significantly prevented the cognitive deficit induce by the adolescent THC exposure in the Novel Object Recognition test. On the contrary, Chaetocin administration did not prevent social deficit in the Social Interaction test and behavioral despair in the Forced Swim Test.

As a whole, these data suggest that pharmacological modulation of SUV39H1 prevents cognitive deficits, but not the alterations of emotional behaviors, suggesting that the increase of H3K9me3 might play a role in the development of cognitive deficits induced by adolescent THC exposure.