EPIGENETIC MECHANISMS IN THE DEVELOPMENT OF PSYCHIATRIC DISORDERS TRIGGERED BY ADOLESCENT THC EXPOSURE IN MALE RATS.

1)Penna F.. 2)Prini P.. 3)Sciuccati E.. 4)Parolaro D.. 5)Rubino T..

UNIVERSITY OF INSUBRIA

Epidemiological studies suggest that heavy Cannabis use during adolescence confers an increased risk for developing psychiatric disorders later in life. Consistently, we have demonstrated that adolescent male rats exposed to THC (the psychoactive compound of Cannabis) developed a psychotic-like phenotype in adulthood. So far, the molecular underpinnings that make the adolescent brain so vulnerable to Cannabis adverse effects are still unknown. However, in the last years, the emerging role of epigenetic mechanisms in psychiatric diseases led us to hypothesize that alterations in epigenetic modifications could play a role in etiopathogenesis of the psychotic-like phenotype induced by adolescent THC exposure. To verify this hypothesis, we investigated the impact of adolescent THC exposure on epigenetic processes in the prefrontal cortex (PFC) and hippocampus (Hippo). To this aim, adolescent male rats were treated with increasing doses of THC from PND 35 to 45. Five different histone modifications (di-, and tri-methylation of lysine 9 (H3K9me2 and H3K9me3), tri-methylation of lysine 27 (H3K27me3), acetylation of lysine 9 (H3K9ac), and lysine 14 (H3K14ac)) were investigated 2, 24 and 48 hours after the last THC injection. In the PFC, H3K9me3 levels were significantly reduced 2 and 24 hours after the last injection. In order to assess whether this reduction was due to decreased methylation or increased demethylation, at the same interval of times we investigated changes in the levels of enzymes involved in these activities at H3K9 sites. We observed a significant increase of JMJD2A (the histone demethylase that specifically demethylates trimethylated Lys-9 of histone H3), 2 hours after the last THC injection. It is therefore possible that this increase in JMJD2A levels could account for the H3K9me3 reduction observed after the end of the treatment. In the hippocampus, adolescent THC treatment induced different modifications when compared to PFC. Indeed, H3K9me3 levels were significantly increased 2 hours after the last injection, whereas, 24 and 48 hours later H3K9me3 levels were significantly decreased. Moreover, at 24 hours we also observed a significant reduction in H3K9ac levels. In the search of the enzymes responsible of these modifications, we observed an increase of G9a (the histone methyltransferase that specifically mono- and demethylates Lys-9 of histone H3) 2 hours after the end of the treatment, and a significant increase of JMJD2A at 24 and 48 hours after the last injection. We can hypothesize that the increase of G9a led to the H3K9me3 enhancement, whereas the later increase of JMJD2A may cause the H3K9me3 reduction. These results suggest that, in the PFC and Hippo of male adolescent rats, THC may act on epigenetic features through the modulation of histone modifications occurring on lysine 9 of histone H3. Moreover, this modulation could be due to specific alterations of those enzymes acting on H3K9. Whether these epigenetic modifications play a relevant role in the onset of psychotic-like phenotype induced by adolescent THC exposure in male rats will be investigated in future studies.