Cannabinoids and gene expression: Adolescent THC exposure impacts genes involved in brain remodeling in the rat prefrontal cortex

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Recent papers support an involvement of epigenetic mechanisms in the development of psychiatric illnesses. In this line, we demonstrated that THC exposure during adolescence induced an increase of acetylation of Lysin14 on histone H3 (H3K14Ac, associated with transcriptional activation) in the Prefrontal Cortex (PFC) 24 hours after the last THC injection (PND 46). Interestingly, this increase was not present when THC was administered in adult rats. These data suggest that THC treatment triggers different epigenetic modifications in the PFC of adolescent and adult animals. Since histone modifications impact gene expression and adolescence is characterized by an intense neural remodeling and synaptic plasticity, the aim of this work was to investigate the effect of THC exposure on expression of genes related to plasticity.
To this aim, adolescent female rats were treated with increasing doses of THC twice a day from 35 to 45 PND and Real-Time PCR array analysis was performed 24 hours after the last THC injection. To clarify whether adolescence really represents a more vulnerable time window for the adverse effect of THC, the same protocol of THC administration and analyses were carried out in adult female rats (PND 75-85). We focused our studies on genes encoding for the endocannabinoid system or involved in plasticity processes. Our results indicate that THC exposure induced a decrease in mRNA levels of the considered genes, 24 hours after discontinuing THC treatment. This effect was intense and wide spread when THC exposure was performed in adolescent animals whereas was restricted to few genes when performed in adult rats.
However the wide spread reduction in gene expression observed after adolescent THC exposure did not correlate with the increased histone acetylation. To investigate whether the effect of histone acetylation occurred with a different time course, the same Real-Time PCR array analyses were performed 2 and 48 hours after the adolescent THC exposure.
Our results indicate that adolescent THC exposure induced a global decrease of mRNA analyzed 2 hours after the last THC injection, but this effect was less intense than 24h after. Intriguingly, all the mRNA analyzed returned to control levels or even increased 48h after the end of the treatment. This effect might rely on the enhanced gene transcription induced by H3K14 acetylation observed at 24h.
As a whole, these data suggest that chronic THC treatment induces a transcriptional repression of a set of genes involved in brain plasticity and these alterations are only evident when treatment is performed in adolescent rats. It can be hypothesized that the increase of H3K14 acetylation might represent a mechanism to counterbalance the strong transcriptional repression induced by adolescent THC exposure. These alterations in the steady state expression levels could negatively impact brain maturation, ultimately resulting in abnormal adult brain function and behavior.