Δ^9-Tetrahydrocannabinol treatment of adolescent mice induces a long lasting modulation of macrophage and lymphocyte cytokine production.

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Cannabis use has characteristics of very early onset, and it is known that more than 25% of teens have used it during their life. It has been recently shown that Δ^9-THC affects immune system function. We investigated whether the use of cannabis in adolescence would cause effects on the immune system that can persist in adulthood.
We measured T-cells and macrophage cytokine production. We used Balb C /J young and adult male mice, divided into 3 experimental groups: young and adult mice treated for 10 days with Δ^9-THC or vehicle, and whose immune parameters were evaluated at the end of treatment ;adolescent mice treated with Δ^9-THC or vehicle and housed for 47 days until adulthood, when the immunological assessments were performed. The Δ^9-THC effects on the immune system were investigated using the following protocol: 5 mg/kg for 3 days, 10 mg/kg for 3 days and 15 mg/kg for 4 days. These doses were chosen in agreement with the data present in the literature, as the plasma Δ^9-THC concentration reached in mice is comparable to that measured in plasma of human heavy smokers.In order to study acquired immunity, young and adult mice were immunized with KLH to induce an antigen-specific reaction. The Th1/Th2 balance was assessed by measuring the production of IFNγ, IL10 and IL4.In order to assess macrophage function we used peritoneal macrophages stimulated in vitro with LPS; IL1β and TNFα were assessed as proinflammatory cytokines, while IL10 as antinflammatory cytokine. All cytokines were measured by specific ELISA. At the end of treatment in both young and adult mice, a significant reduction in the production of IFNγ was observed, while IL4 and IL10 cytokines were significantly increased.When we measured immune response after immunization of adult mice that had been treated in adolescence, we observed that the production of IFNγ was still lower and that also the IL4 and IL10 levels were decreased compared with vehicle mice.Furthermore, we observed that in adolescent and adult animals the anti-KLH IgM titers measured in the serum after 10 days of chronic treatment with Δ^9-THC, are significantly reduced. The decrease in the production of antibodies persists also in the third group of study, 47 days after the last administration of the drug.Regarding the macrophage function, Δ^9-THC induced in both young and adult mice a significant increase of IL10 while TNFα and IL1β are decreased. Particularly interesting were the results obtained in mice treated in adolescent age with Δ^9-THC respect to vehicle ; in fact, we observed an opposite effect since IL1β and TNFα levels were significantly increased while IL10 production was lower, indicating a switch towards a proinflammatory phenotype of the macrophage. We observed similar results also at transcriptional level by measuring the mRNA of cytokines with Real Time-PCR.In order to rule out the possibility that in adult animals treated with Δ^9-THC as adolescent some residual Δ^9-THC could still be present we measured the Δ^9-THC concentration in the blood of mice by HPLC-Mass Spectrometry method: Δ^9-THC is present at the end of treatment, 1 month after the end of treatment Δ^9-THC is not present and there are some traces of the THC-COOH non- psychoactive metabolite, while neither Δ^9-THC nor metabolite are present at the time of immune evaluation. These results indicate that the immune system is profoundly altered by treatments with Δ^9-THC, with a dysregulated response. The effect of drug administration persists for a long time after the end of treatment, when neither Δ^9-THC nor its main metabolite is present in the blood. The altered immune system may condition the susceptibility of the host to immune related pathologies in adulthood and our observations draw the attention on the fact the history of drug abuse of each individual should be evaluated before proposing medicinal cannabis use.