Stimulation of CB2 receptor affects activation and polarization of CD4+ T lymphocytes

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Cannabinoids from Cannabis sativa possess anti-inflammatory and immunomodulatory properties, but the mechanisms responsible for these actions still haven't been unraveled. CB2 is the cannabinoid receptor expressed primarily on immune cells and mediates the immunoregulatory functions of cannabinoids. Here we used a classical in vitro assay for Th lineage specific differentiation of naïve CD4+ T lymphocytes from mouse spleens to study any potential ability of two CB2 selective compounds in the activation and differentiation of T lymphocytes. T lymphocytes were activated by anti-CD3 and anti-CD28 for 3 days in the presence of JTE907 and CB65 (10-6M and 10-7M), highly selective inverse agonist and selective agonist respectively. Our results indicate that only JTE907(10-6M) was able to reduce activation of T lymphocytes by a significant downregulation of IL-2R, and a decrease of CD44 and CD69 markers whereas CB65 was not. Under non-polarizing condition, CB65 and JTE907 were able to differentiate Th0 cells towards the Treg phenotype while, under polarizing condition, they were able to polarize towards Th2 phenotype. These effects were evaluated after 6 days of culture by analysis of specific transcription factor expression (mRNA and protein). Conversely, both cannabinoids counteracted in vitro-induced polarization of Th1 cells and didn't have any effect on Th9 and Th17 polarization. Intracellular signals induced by CB65 and JTE907 in Th2 and Treg-oriented polarization involved the activation of p38, which peaked at 48h from the start of cell activation, and the activation of STAT5A transcription factor, both involved in the activation of GATA3 (Th2 specific) and Foxp3 (Treg specific) transcription factors. They didn't induce any modulation of SMAD3, a transcription factor involved in FoxP3 expression. Collectively these results indicate that the selective triggering of CB2 receptor can drive the immune response towards a specific T cell phenotype thus allowing the development of specific ligands to use as pharmacological tools in Th-specific mediated pathologies.