BETA-CARYOPHYLLENE MITIGATES COLLAGEN ANTIBODY INDUCED ARTHRITIS IN MICE THROUGH A CROSS-TALK BETWEEN THE CANNABINOID 2AND PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA RECEPTORS

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Introduction: b-caryophyllene (BCP) is a cannabinoid receptor 2(CB2) agonist that tempers the inflammatory cascade in arthritis. An interaction between the CB2receptor and peroxisome proliferator-activated receptor gamma (PPAR-γ) has been suggested and PPAR-γ activation exerts anti-arthritic effects. The aim of this study was to better characterize the therapeutic activity of BCP and to investigate PPAR-γ involvement using a collagen antibody induced arthritis (CAIA) experimental model.

Materials and methods: Collagen type II antibody–induced arthritis was induced in balb/c mice as follows: on day 0, animals were intraperitoneally (ip) injected with 1.5mg of 5-clone monoclonal antibody cocktail (Chondrex); on day 3, mice received LPS (50 μg/100 μl/ip). At day 3CAIA animals were daily treated with BCP (10 mg/kg/100μl/os, CAIA + BCP) or its vehicle (100 μl of corn oil) until the end of the experiment (day 14). Sham animals (n=20) received 100μl of corn oil (n=10, Sham) or BCP (n=10, Sham + BCP).

Results: BCP significantly hampered the severity of the disease, as demonstrated by both the clinical and histological scores. The natural cannabinoid reduced circulating pro-inflammatory cytokines such as TNF-α, IL-6, Il-1β and increased the anti-inflammatory cytokine IL-13. BCP also decreased joint expression of TNF-α, IL-6, Il-1b and of matrix metalloproteinases (MMPs) 3and 9. Joints excised by arthritic mice treated with vehicle had an increased mRNA expression of COX2and NF-κB, whereas showed a reduced expression of the PPARγ coactivator-1alpha, PGC-1α and PPAR-γ compared to sham animals. These changes induced by arthritis were reverted following BCP treatment. Finally, BCP reduced the enhanced NF-κB activation and increased the reduced expression of PGC-1a and PPAR-γ in human articular chondrocytes stimulated with LPS. These effects were abolished by AM630, an antagonist of the CB2receptor.

Discussion and conclusions: BCP tempers the inflammatory cascade in arthritis and an involvement of both CB2and PPAR-γ was demonstrated in the anti-arthritic effect of BCP. The effect induced by the phytocannabinoid on the PGC-1a is dependent by the CB2receptor. The present results suggest that BCP ameliorates arthritis through a cross talk between CB2and PPAR-γ. However, BCP deserves to be deeply investigated in randomized clinical trials.