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Cannabidiol (CBD): a killer for inflammatory rheumatoid arthritis synovial fibroblasts

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Abstract

Cannabidiol (CBD) is a non-intoxicating phytocannabinoid from cannabis sativa that has demonstrated anti-inflammatory effects in several inflammatory conditions including arthritis. However, CBD binds to several receptors and enzymes and, therefore, its mode of action remains elusive. In this study, we show that CBD increases intracellular calcium levels, reduces cell viability and IL-6/IL-8/MMP-3 production of rheumatoid arthritis synovial fibroblasts (RASF). These effects were pronounced under inflammatory conditions by activating transient receptor potential ankyrin (TRPA1), and by opening of the mitochondrial permeability transition pore. Changes in intracellular calcium and cell viability were determined by using the fluorescent dyes Cal-520/PoPo3 together with cell titer blue and the luminescent dye RealTime-glo. Cell-based impedance measurements were conducted with the XCELLigence system and TRPA1 protein was detected by flow cytometry. Cytokine production was evaluated by ELISA. CBD reduced cell viability, proliferation, and IL-6/IL-8 production of RASF. Moreover, CBD increased intracellular calcium and uptake of the cationic viability dye PoPo3 in RASF, which was enhanced by pre-treatment with TNF. Concomitant incubation of CBD with the TRPA1 antagonist A967079 but not the TRPV1 antagonist capsazepine reduced the effects of CBD on calcium and PoPo3 uptake. In addition, an inhibitor of the mitochondrial permeability transition pore, cyclosporin A, also blocked the effects of CBD on cell viability and IL-8 production. PoPo3 uptake was inhibited by the voltage-dependent anion-selective channel inhibitor DIDS and Decynium-22, an inhibitor for all organic cation transporter isoforms. CBD increases intracellular calcium levels, reduces cell viability, and IL-6/IL-8/MMP-3 production of RASF by activating TRPA1 and mitochondrial targets. This effect was enhanced by pre-treatment with TNF suggesting that CBD preferentially targets activated, pro-inflammatory RASF. Thus, CBD possesses anti-arthritic activity and might ameliorate arthritis via targeting synovial fibroblasts under inflammatory conditions.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Figures

Fig. 1. Assessment of cell viability, TRPA1...

Fig. 2. Mean intracellular calcium levels and...

Fig. 3. Modulation of intracellular calcium levels...

Fig. 4. Modulation of intracellular calcium levels...

Fig. 5. IL-6, IL-8, MMP-3 production, and...

Fig. 6. Proposed hypothetical mechanism of CBD-

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