Clin Exp Rheumatol. 2019 Mar 18. [Epub ahead of print]

Role of cannabinoid receptor 2 in mediating interleukin-1β-induced inflammation in rheumatoid arthritis synovial fibroblasts.

Fechtner SC[1], Singh AK[1], Ahmed S[2].

Author information

Abstract

OBJECTIVES: Recent studies showed that the expression of cannabinoid receptor 2 (CB2), not CB1, is upregulated at both the mRNA and protein levels in rheumatoid arthritis synovial fibroblasts (RASFs), however, little is known about its endogenous role in pro-inflammatory cytokine signalling in RASFs. Our aim was to investigate the role of CB2 receptor in mediating IL-1β-induced inflammation in human RASFs.

METHODS: Human RASFs were pretreated with CB2 selective agonist (JWH-133), followed by stimulation with interleukin-1β (IL-1β, 10 ng/mL). The role of CB2 in IL-1β signalling was examined using small interfering RNA (siRNA) or an overexpression plasmid specific for CB2.

RESULTS: Pretreatment with JWH-133 did not reduce IL-1β-induced IL-6 and IL-8 production and amplified the cellular expression of cyclooxygenase-2 (COX-2) by >2-fold in human RASFs. Furthermore, the knockdown of CB2 using siRNA markedly inhibited IL-1β-induced IL-6, IL-8, ENA-78, and RANTES production by more than 50% and completely abrogated COX-2 expression in human RASFs. MMP-2 and MMP-9 activity was also reduced by 50% with CB2 knockdown. On the contrary, overexpression of CB2 in human RASFs further increased IL-1β-induced IL-6, IL-8, and RANTES by approximately 3-fold whereas ENA-78 expression increased by 1.5-fold. Immunoprecipitation analysis to study the protein-protein interactions revealed that JWH-133 coordinates CB2 association with TGFβ-activated kinase 1 (TAK1), a key signalling molecule, to increase IL-1β-induced nuclear translocation of transcription factors nuclear factor-κBp65 (NF-κBp65) and activation protein-1 (AP-1).

CONCLUSIONS: Overall, our results indicate for the first time that CB2 mediates IL-1β-induced signalling pathways in RASFs and may serve as a potential target to manage pain and inflammation in RA.

PMID: 30943136