The cannabinoid TRPA1 agonist cannabichromene inhibits nitric oxide production in macrophages and ameliorates murine colitis

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BACKGROUND AND PURPOSE

The non-psychotropic cannabinoid cannabichromene is known to activate the transient receptor potential ankyrin-type1 (TRPA1) and to inhibit endocannabinoid inactivation, both of which are involved in inflammatory processes. We examined here the effects of this phytocannabinoid on peritoneal macrophages and its efficacy in an experimental model of colitis.

EXPERIMENTAL APPROACH

Murine peritoneal macrophages were activated *in vitro* by LPS. Nitrite levels were measured using a fluorescent assay; inducible nitric oxide (iNOS), cyclooxygenase-2 (COX-2) and cannabinoid (CB_1 and CB_2) receptors were analysed by *RT*-PCR (and/or Western blot analysis); colitis was induced by dinitrobenzene sulphonic acid (DNBS). Endocannabinoid (anandamide and 2-arachidonoylglycerol), palmitoylethanolamide and oleoylethanolamide levels were measured by liquid chromatography-mass spectrometry. Colonic inflammation was assessed by evaluating the myeloperoxidase activity as well as by histology and immunohistochemistry.

KEY RESULTS

LPS caused a significant production of nitrites, associated to up-regulation of anandamide, iNOS, COX-2, CB_1 receptors and down-regulation of CB_2 receptors mRNA expression. Cannabichromene significantly reduced LPS-stimulated nitrite levels, and its effect was mimicked by cannabinoid receptor and TRPA1 agonists (carvacrol and cinnamaldehyde) and enhanced by CB_1 receptor antagonists. LPS-induced anandamide, iNOS, COX-2 and cannabinoid receptor changes were not significantly modified by cannabichromene, which, however, increased oleoylethanolamide levels. *In vivo*, cannabichromene ameliorated DNBS-induced colonic inflammation, as revealed by histology, immunohistochemistry and myeloperoxidase activity.

CONCLUSION AND IMPLICATIONS

Cannabichromene exerts anti-inflammatory actions in activated macrophages – with tonic CB_1 cannabinoid signalling being negatively coupled to this effect – and ameliorates experimental murine colitis.