Cannabinoid Acids as Antiinflammatory Agents

Summary

Principal Investigator: ROBERT ZURIER

Affiliation: University of Massachusetts Medical School

Country: USA

Abstract: The overall object of this proposal is to determine biochemical and molecular mechanisms whereby cannabinoid acids without psychoactive activities modulate the function of cells (macrophages, synovial cells) which participate in initiation and propagation of joint tissue injury in patients with rheumatoid arthritis. The cannabinoid acids to be studied include ajulemic acid (AjA), and tetrahydrocannabinol-11 oic acid. These compounds do not alter behavior, are given by mouth, and do not injure gastric mucosa. Oral administration of AjA, a synthetic nonpsychoactive analog of the tetrahydrocannabinol (THC) carboxylic acid metabolite THC-11-oic acid, prevents joint cartilage and bone damage in an animal model of arthritis. Preliminary studies indicate that addition of cannabinoid acids to cells in vitro suppress gene expression of several inflammatory cytokines, and enhances apoptosis. Oral administration of AjA to humans attenuates IL-11beta production by activated monocytes. The main hypothesis of the proposal is that cannabinoid acids antagonize activation of the transcription factor NFkB due to and/or independent of activation of peroxisome proliferator activated receptor gamma (PPARy), leading to enhancement of apoptosis and downregulation of NFkB target genes (Il-1, IL-6, IL-8, COX-2). The role of eicosanoids in the actions of cannabinoid acids will be investigated also. Cells will be obtained from healthy volunteers, and patients with osteoarthritis and rheumatoid arthritis. Cannabinoid acids will be added to cells in vitro. Cells obtained from healthy volunteers before and after oral administration of AjA will be studied ex vivo. Experiments are designed to determine whether cannabinoid acids are bona fide ligands for PPARy and to investigate mechanisms by which cannabinoid acids alter NFkB signaling. Investigations will include use of gene transfection, western blotting, and immunomicroscopy. Completion of this proposal will provide a greater understanding of antiinflammatory and immunomodulatory effects of cannabinoid acids, and may lead to more rational design of these compounds for treatment of patients with diseases characterized by disordered immune responses, inflammation, and tissue injury.

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more information: NIH RePORT

http://projectreporter.nih.gov/project_info_description.cfm?projectnumber=5R01DA013691-03