Cannabidiol and Inflammatory Bowel Disease

Cannabidiol can produce dramatic improvements on inflammatory bowel diseases of all kinds. Probably many of the gut ailments that health providers encounter are part of the spectrum of inflammatory bowel disease which ranges from leaky gut to intestinal cancer and diverticulosis but clearly involves ulcerative colitis and Crohn's disease. The specific causes have yet to be defined but there's probably a triggering event that initiates the process and changes in the bowel lining that perpetuated it. The major problem here is one of an inflammatory condition of the bowel.

Cannabidiol (CBD) has specific actions and mechanisms that control the inflammation process everywhere but particularly the gut. The lining of the intestines is replaced every few days which makes it quite sensitive to toxins and irritants as well as neurotransmitters from the brain. CBD works through several of these mechanisms including both common effects on the neurotransmitters as well as anti-inflammatory effects on the immune system. We're still discovering the exact mechanisms that appear to be involved with inflammatory gut conditions. Bottom line is that CBD has been effective in preventing and resolving inflammatory bowel disease in several animal models through a variety of mechanisms.

In clinical human experience providers have seen dramatic response to several types of inflammatory conditions using low doses of cannabidiol. These results have been seen very quickly and at low doses. Typically, the pain is reduced immediately and gut symptoms like cramping, diarrhea and bleeding resolve in less than a week.

One of the most popular categories of drugs used for inflammatory bowel disease are called tumor necrosis factor blockers or inhibitors. Examples are Enbrel, Remicade, and Simponi. These drugs are usually taken by injection on a weekly or monthly basis but they're only effective in about half the patients and associated with serious side effects. Standard cost is about $1000 per injection. CBD blocks TNF more effectively by calming the immune macrophages that are producing these inflammatory substances that incite intestinal damage and pain without side effects.

Cannabidiol can probably enhance or replace these very expensive TNF blockers and prevent recurrences in the whole spectrum of inflammatory gut conditions as well as improve overall health in many ways.

CBD quality counts, many available products do not contain the levels promised. Elixinol has consistently produced exemplary results across the full horizon of health concerns.


Philip W Blair, M.D., Medical Director, Pro Health Advisor
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Colitis/Crohn's

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Cannabidiol in inflammatory bowel diseases: a brief overview.

This minireview highlights the importance of cannabidiol (CBD) as a promising drug for the therapy of inflammatory bowel diseases (IBD). Actual pharmacological treatments for IBD should be enlarged toward the search for low-toxicity and low-cost drugs that may be given alone or in combination with the conventional anti-IBD drugs to increase their efficacy in the therapy of relapsing forms of colitis. In the past, Cannabis preparations have been considered new promising pharmacological tools in view of their anti-inflammatory role in IBD as well as other gut disturbances. However, their use in the clinical therapy has been strongly limited by their psychotropic effects. CBD is a very promising compound since it shares the typical cannabinoid beneficial effects on gut lacking any psychotropic effects. For years, its activity has been enigmatic for gastroenterologists and pharmacologists, but now it is evident that this compound may interact at extra-cannabinoid system receptor sites, such as peroxisome proliferator-activated receptor-gamma. This strategic interaction makes CBD as a potential candidate for the development of a new class of anti-IBD drugs.

Cannabidiol Reduces Intestinal Inflammation through the Control of Neuroimmune Axis

Daniele De Filippis¹,5*, Giuseppe Esposito²*, Carla Cirillo³, Mariateresa Cipriano¹,5, Benedicte Y. De Winter⁴, Caterina Scuderi², Giovanni Sarnelli⁸, Rosario Cuomo³, Luca Steardo², Joris G. De Man⁴, Teresa Iuvone¹,5*

¹ Department of Experimental Pharmacology, University of Naples FEDERICO II, Naples, Italy, ² Department of Human Physiology and Pharmacology V. Erspamer, University of Rome “La Sapienza”, Rome, Italy, ³ Department of Clinical and Experimental Medicine, University of Naples FEDERICO II, Naples, Italy, ⁴ Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology, University of Antwerp, Antwerp, Belgium, ⁵ Endocannabinoid Research Group, Pozzuoli, Italy

Abstract

Enteric glial cells (EGC) actively mediate acute and chronic inflammation in the gut; EGC proliferate and release neurotrophins, growth factors, and pro-inflammatory cytokines which, in turn, may amplify the immune response, representing a very important link between the nervous and immune systems in the intestine. Cannabidiol (CBD) is an interesting compound because of its ability to control reactive gliosis in the CNS, without any unwanted psychotropic effects. Therefore, the rationale of our study was to investigate the effect of CBD on intestinal biopsies from patients with ulcerative colitis (UC) and from intestinal segments of mice with LPS-induced intestinal inflammation. CBD markedly counteracted reactive enteric gliosis in LPS-mice through the massive reduction of astroglial signalling neurotrophin S100B. Histological, biochemical and immunohistochemical data demonstrated that S100B decrease was associated with a considerable decrease in mast cell and macrophages in the intestine of LPS-treated mice after CBD treatment. Moreover, the treatment of LPS-mice with CBD reduced TNF-α expression and the presence of cleaved caspase-3. Similar results were obtained in ex vivo cultured human derived colonic biopsies. In biopsies of UC patients, both during active inflammation and in remission stimulated with LPS+INF-γ, an increased glial cell activation and intestinal damage were evidenced. CBD reduced the expression of S100B and iNOS proteins in the human biopsies confirming its well documented effect in septic mice. The activity of CBD is, at least partly, mediated via the selective PPAR-gamma receptor pathway. CBD targets enteric reactive gliosis, counteracts the inflammatory environment induced by LPS in mice and in human colonic cultures derived from UC patients. These actions lead to a reduction of intestinal damage mediated by PPARgamma receptor pathway. Our results therefore indicate that CBD indeed unravels a new therapeutic strategy to treat inflammatory bowel diseases.

Introduction

Despite the ancient assumption that enteric glial cells (EGC) may serve as a mere mechanical support for enteric neurons, nowadays the knowledge on these cells is consistently expanded. EGC play a fundamental role in the maintenance of gut homeostasis since they assure the correct trophism of vicinal neurons in the myenteric plexus [1] and actively participate in the course of intestinal inflammation [2] where they appear as a first defensive line against pathogens [3].

Enteroglial cells share analogue features with glial cells in the brain. EGC play important functions in the maintenance of the enteric nervous system (ENS) homeostasis, but they may also proliferate and be activated in response to injury and inflammation undergoing reactive gliosis (entero-gliosis), a dynamic process [4]. Enteric astroglial and microglial cells release neurotrophins, growth factors and cytokines cross-talking with other infiltrating immune cells such as macrophages, neutrophils and mast cells [5,6,7].

Abnormalities in the enteroglia network were described in the intestinal mucosa of patients with inflammatory bowel diseases (IBD) [8], measures as the reactive enteric gliosis, i.e. the massive over-expression and secretion of S100B protein, a cell-specific astroglial derived signalling molecule [9]. The activation of EGC is therefore regarded as a general alteration of the whole enteric nervous system homeostasis. S100B protein, which is released by enteric glial cells, emerges as a pivotal signal molecule that extensively participates in the onset and in the progression of the inflammatory status as it orchestrates a wide range of signal activation pathways, directly correlated with the severity of gut degenerative processes [8].

Molecules which may counteract intestinal inflammation targeting EGC could represent putative novel approaches to amplify the current pharmacological tools to treat gut inflammatory diseases. In this sense, a huge amount of data produced in the recent years demonstrated that cannabidiol (CBD) the non-psychotropic cannabinoid deriving from Cannabis Sativa, appears as a very promising compound because of its antiinflammatory,
Cannabinoids Receptor-2 (CB2) agonist ameliorates colitis in IL-10−/− mice by attenuating the activation of T cells and promoting their apoptosis

Udai P. Singha, Narendra P. Singha, Balwan Singhb, Robert L. Pricec, Mitzi Nagarkattia, and Prakash S. Nagarkatti

aPathology, Microbiology and Immunology, School of Medicine, University of South Carolina, Columbia, SC 29208, USA
bNational Primate Research Center, Emory University, Atlanta GA 30329, USA
cDepartment of Cell and Developmental Biology, University of South Carolina, Columbia, SC 29208, USA

Abstract

Inflammatory bowel disease (IBD) is a chronic intestinal inflammation caused by hyperactivated effector immune cells that produce pro-inflammatory cytokines. Recent studies have shown that the cannabinoid system may play a critical role in mediating protection against intestinal inflammation. However, the effect of cannabinoid receptors induction after chronic colitis progression has not been investigated. Here, we investigate the effect of cannabinoid receptor-2 (CB2) agonist, JWH-133, after chronic colitis in IL-10−/− mice. JWH-133 effectively attenuated the overall clinical score, reversed colitis-associated pathogenesis and decrease in body weight in IL-10−/− mice. After JWH-133 treatment, the percentage of CD4+ T cells, neutrophils, mast cells, natural killer (NK1.1) cells, and activated T cells in the LP of colitis mice declined after JWH-133 treatment in the intestinal lamina propria (LP) and mesenteric lymph nodes (MLN). JWH-133 was also effective in ameliorating dextran sodium sulphate (DSS)-induced colitis. In this model, JWH-133 reduced the number and percentage of macrophages and IFN-γ expressing cells that were induced during colitis progression. Treatment with aminoalkylindole 6-iodopravadoline (AM630), a CB2 receptor antagonist, reversed the colitis protection provided by JWH-133 treatment. Also, activated T cells were found to undergo apoptosis following JWH-133 treatment both in-vivo and in-vitro. These findings suggest that JWH-133 mediates its effect through CB2 receptors, and ameliorates chronic colitis by inducing apoptosis in activated T cells, reducing the numbers of activated T cells, suppressing induction of mast cells, NK cells, and neutrophils at
Effect of vanilloid drugs on gastrointestinal transit in mice

*1Angelo A. Izzo, 2Raffaele Capasso, 1Luisa Pinto, 1Giulia Di Carlo, 1Nicola Mascolo & 1Francesco Capasso

1Department of Experimental Pharmacology, University of Naples ‘Federico II’, via D. Montesano 49, 80131 Naples, Italy and 2Department of Pharmaceutical Sciences, University of Salerno, Via Ponte Don Melillo 84084 Fisciano (SA), Italy

1 We have studied the effect of capsaicin, piperine and anandamide, drugs which activate vanilloid receptors and capsazepine, a vanilloid receptor antagonist, on upper gastrointestinal motility in mice.
2 Piperine (0.5–20 mg kg\(^{-1}\) i.p.) and anandamide (0.5–20 mg kg\(^{-1}\) i.p.), dose-dependently delayed gastrointestinal motility, while capsaicin (up to 3 mg kg\(^{-1}\) i.p.) was without effect. Capsazepine (15 mg kg\(^{-1}\) i.p.) neither per se affected gastrointestinal motility nor did it counteract the inhibitory effect of both piperine (10 mg kg\(^{-1}\)) and anandamide (10 mg kg\(^{-1}\)).
3 A per se non effective dose of SR141716A (0.3 mg kg\(^{-1}\) i.p.), a cannabinoid CB\(_1\) receptor antagonist, counteracted the inhibitory effect of anandamide (10 mg kg\(^{-1}\)) but not of piperine (10 mg kg\(^{-1}\)). By contrast, the inhibitory effect of piperine (10 mg kg\(^{-1}\)) but not of anandamide (10 mg kg\(^{-1}\)) was strongly attenuated in capsaicin (75 mg kg\(^{-1}\) in total, s.c.)-treated mice.
4 Pretreatment of mice with N\(^{\text{3}}\)-nitro-l-arginine methyl ester (25 mg kg\(^{-1}\) i.p.), yohimbine (1 mg kg\(^{-1}\) i.p.), naloxone (2 mg kg\(^{-1}\) i.p.), or hexamethonium (1 mg kg\(^{-1}\) i.p.) did not modify the inhibitory effect of both piperine (10 mg kg\(^{-1}\)) and anandamide (10 mg kg\(^{-1}\)).
5 The present study indicates that the vanilloid ligands anandamide and piperine, but not capsaicin, can reduce upper gastrointestinal motility. The effect of piperine involves capsacin-sensitive neurones, but not vanilloid receptors, while the effect of anandamide involves cannabinoid CB\(_1\) but not vanilloid receptors.

Keywords: Anandamide; piperine; capsazepine; primary afferent neurones; vanilloid receptors; cannabinoid receptors; capsaicin; intestinal motility

Abbreviations: DMSO, dimethyl sulphoxide; l-N\(^{\text{3}}\)-NAME, N\(^{\text{3}}\)-nitro-l-arginine methyl ester; VR1, vanilloid receptor (subtype 1)

Introduction

A subpopulation of primary afferent neurones has been characterized by using the sensory neurotoxin capsaicin (Maggi & Meli, 1988), the active ingredient of chilli (from the Capsicum family). These neurones are small, ‘dark’ and type ‘B’, and give rise to unmyelinated afferent fibres (Torsoli et al., 1993). Capsaicin-sensitive sensory neurones can modulate intestinal motility as they convey signals coming from the gastrointestinal tract to the central nervous system and may simultaneously release transmitters (from the same terminal which is activated by an adequate stimulus) able to affect enteric neurotransmission (Holzer, 1991).

The action of capsaicin on afferent neurones is traditionally regarded as involving two phases: an acute excitatory effect which lead to transmitter release, followed by desensitization and damage after prolonged or repeated exposure (Holzer, 1991). In recent years it has been shown that the action of capsaicin on afferent neurones can be mediated through activation of specific receptors, namely vanilloid receptors (Caterina et al., 1997; Tominaga et al., 1998). Vanilloid receptors can be also activated by other irritant principles present in ‘hot’ spices, such as piperine, the active ingredient of black pepper (Piper nigrum) and zingerone, isolated from ginger (Zingiber officinallis) (Liu & Simon, 1997; Sterner & Szallasi, 1999). Capsaicin, piperine and gingerone are structurally similar, as they share a vanillyl moiety essential for bioactivity (Sterner & Szallasi, 1999). A functional vanilloid receptor (VR1) has been cloned (Caterina et al., 1997) and a vanilloid receptor antagonist, namely capsazepine, is available for pharmacological characterization (Sterner & Szallasi, 1999). VR1 is a cation channel that is expressed in a major sub-group of small ‘dark’ neurones of the dorsal root, trigeminal and vagal sensory ganglia (Caterina et al., 1997; Hellwell et al., 1998; Sterner & Szallasi, 1999; Szolcsanyi, 2000) and in several brain areas (Sasamura et al., 1998). The discovery of vanilloid receptors suggests the existence of endogenous vanilloid receptor ligands; in fact, the first of such vanilloids has been identified as anandamide (arachidonylethanolamide) (Zygmunt et al., 1999; Smart et al., 2000), originally isolated as an endogenous cannabinoid receptor ligand (Devane et al., 1992). These findings suggest the existence of endogenous vanilloid receptor modulators lacking a vanillyl motif (Sterner & Szallasi, 1999).

Given the importance of primary afferent neurones in the control of intestinal motility in vivo and since vanilloid receptors are highly expressed on these neurones (Szallasi & Blumberg, 1999), we have evaluated the effect vanilloid drugs on upper gastrointestinal transit in mice. We have used anandamide, capsaicin and piperine, which activate vanilloid
Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis.

Inflammatory bowel disease affects millions of individuals; nevertheless, pharmacological treatment is disappointingly unsatisfactory. Cannabidiol, a safe and non-psychotropic ingredient of marijuana, exerts pharmacological effects (e.g., antioxidant) and mechanisms (e.g., inhibition of endocannabinoids enzymatic degradation) potentially beneficial for the inflamed gut. Thus, we investigated the effect of cannabidiol in a murine model of colitis. Colitis was induced in mice by intracolonic administration of dinitrobenzene sulfonic acid. Inflammation was assessed both macroscopically and histologically. In the inflamed colon, cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) were evaluated by Western blot, interleukin-1beta and interleukin-10 by ELISA, and endocannabinoids by isotope dilution liquid chromatography-mass spectrometry. Human colon adenocarcinoma (Caco-2) cells were used to evaluate the effect of cannabidiol on oxidative stress. Cannabidiol reduced colon injury, inducible iNOS (but not cyclooxygenase-2) expression, and interleukin-1beta, interleukin-10, and endocannabinoid changes associated with 2,4,6-dinitrobenzene sulfonic acid administration. In Caco-2 cells, cannabidiol reduced reactive oxygen species production and lipid peroxidation. In conclusion, cannabidiol, a likely safe compound, prevents experimental colitis in mice.


Potential targets and mechanisms of cannabinoids involved in the improvement of inflammatory bowel diseases (IBD)

Natural and synthetic cannabinoids act via intestinal cannabinoid receptors 1 and 2 to regulate epithelial permeability, motility, secretion (via enteric nervous system), as well as leukocyte migration, recruitment and apoptosis. As the site with the highest CB1 expression (but also some CB2 expression), the brain may modulate motility, the sensation of pain and unpleasantness thus positively influencing the inflammatory process.