Comment

Pharmacology

Pharmacology 2014;93:1–3
DOI: 10.1159/000356512

Received: October 18, 2013
Accepted: October 21, 2013
Published online: December 17, 2013

Cannabis Finds Its Way into Treatment of Crohn's Disease

Rudolf Schicho[a] Martin Storr[b]

[a]Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Graz, Austria;
[b]Department of Medicine II, Klinikum Grosshadern, Ludwig Maximilian University, Munich, Germany

Key Words
Inflammatory bowel disease · Cannabinoids · Prospective study

Abstract
In ancient medicine, cannabis has been widely used to cure disturbances and inflammation of the bowel. A recent clinical study now shows that the medicinal plant *Cannabis sativa* has lived up to expectations and proved to be highly efficient in cases of inflammatory bowel diseases. In a prospective placebo-controlled study, it has been shown what has been largely anticipated from anecdotal reports, i.e. that cannabis produces significant clinical benefits in patients with Crohn's disease. The mechanisms involved are not yet clear but most likely include peripheral actions on cannabinoid receptors 1 and 2, and may also include central actions.

In ancient medicine, cannabis has been widely used to cure disturbances and inflammation of the bowel. A recent clinical study now shows that the medicinal plant *Cannabis sativa* has lived up to expectations and proved to be highly efficient in cases of inflammatory bowel diseases (IBD). In a prospective placebo-controlled study, Naftali et al. [1] have shown what has been largely anticipated from anecdotal reports, i.e. that cannabis produces significant clinical benefits in patients with Crohn's disease. The mechanisms involved are not yet clear but most likely include peripheral actions on cannabinoid (CB) receptors 1 and 2 (CB_1 and CB_2), and may also include central actions.

The past 10 years have seen a constant rise in publications dealing with the anti-inflammatory effects of CBs and the potential underlying mechanisms. Preclinical data on the ameliorating effect of synthetic and natural CBs in animal models mimicking features of IBD have been rapidly evolving. The reasonable idea that CBs would also be beneficial in IBD patients was mainly based on results from experiments in CB receptor knockout mice and on data using CB receptor agonists and antagonists. Following a previous publication of a retrospective, observational study by Naftali et al. [2] and a questionnaire performed by a different group in patients with ulcerative colitis and Crohn's disease [3], both revealing symptom relief and improvement after use of cannabis, Naftali et al. [1] have now presented a placebo-controlled prospective study in 21 patients with Crohn's disease unresponsive to standard IBD treatment. Although the primary end point of induction of remission was statistically not achieved, they were able to demonstrate that an 8-week treatment with tetrahydrocannabinol (THC)-rich cannabis caused a decrease in the Crohn's disease activity index in 90% of patients without producing significant side effects. The authors rightfully concluded that a larger patient group is warranted for future studies.

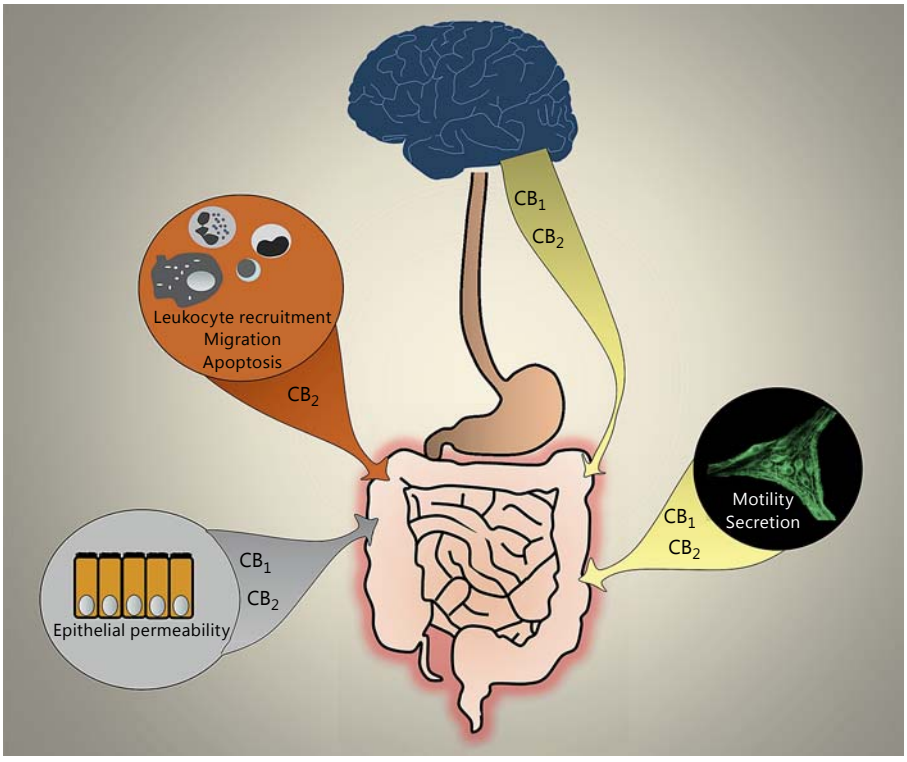
This is the first clinical trial on the effect of cannabis in IBD, and it confirms what has been suggested for a long time from experimental studies, namely that CBs may

KARGER

E-Mail karger@karger.com
www.karger.com/pha

0031–7012/13/0932–0001$38.00/0

Rudolf Schicho, PhD
Medical University of Graz
Institute of Experimental and Clinical Pharmacology
Universitätsplatz 4, AT–8010 Graz (Austria)
E-Mail rudolf.schicho@medunigraz.at



Color version available online

Fig. 1. Potential targets and mechanisms of CBs involved in the improvement of IBD. Natural and synthetic CBs act via intestinal CB_1 and CB_2 receptors to regulate epithelial permeability, motility, secretion (via the enteric nervous system), as well as leukocyte migration, recruitment and apoptosis. As the site with the highest CB_1 expression (but also some CB_2 expression), the brain may modulate motility, the sensation of pain and unpleasantness, thus positively influencing the inflammatory process.

provide anti-inflammatory effects and symptomatic benefit in patients with IBD. The physiological basis for the beneficial effects of cannabis has been established a while ago and unraveled since then. The discovery of CB receptors and endogenous molecules activating these receptors led to the description of a coordinated network that is inherent to the mammalian organism, the so-called endocannabinoid system. This system consists of the canonical CB receptors (CB_1, CB_2), their endogenous ligands anandamide and 2-arachidonoyl glycerol (2-AG), also called endocannabinoids, and their synthesizing and degrading enzymes. What capsaicin, the pungent ingredient of chili, is for vanilloid receptors and morphin for opioid receptors is THC, the psychedelic ingredient of cannabis, for CB receptors: the predominant herbal ligand. Thus, THC mimics the actions of anandamide and 2-AG.

The wall of the gastrointestinal tract houses all components of the endocannabinoid system. Recent data show that these components are differentially expressed in human IBD indicating a regulatory role in the disease progression [4]. While anandamide and its synthesizing enzyme display lower levels in ulcerative colitis, expression of CB_2 receptors and enzymes responsible for synthesis and degradation of 2-AG were increased [5]. The findings indicate that the CB_2 receptor plays a key role in the ameliorating effect of CBs in IBD. The precise mechanism as to how CBs contribute to the improvement of IBD, however, is not clear but by use of experimental models of intestinal inflammation we are able to define a picture on how and at which targets CBs cause improvement of inflammation.

CB_1 and CB_2 receptors are located at the colonic epithelium, and a protective effect of THC via epithelial permeability is conceivable (fig. 1). Therefore, CBs could enhance epithelial wound closure in the colon [6]. One of the prominent features of CBs in experimental intestinal inflammation is their effect on immunocytes which mainly express CB_2 receptors. Upon CB_2 activation, T cells undergo apoptosis and decreased proliferation in colitis [7]. Additionally, activation of CB_2 diminishes the recruitment of neutrophils, T cells and macrophages to the inflamed colon [7]. CB receptors are also found in the enteric nervous system (ENS), which controls gut motility and secretion [8]. CB_1 receptors present in the ENS represent a break that protects the ENS from hyperstimulation, a situation easily caused by overexpression of inflammatory mediators that activate the ENS during IBD. Therefore, activation of CB receptors by THC may reduce hypermotility associated with the inflammation of the gut

[9]. The reduction of hypermotility may consequently alleviate diarrhea producing beneficial effects for the patient.

It should be emphasized that the brain is the major site of CB_1 expression and that the presence of CB_2 has also been detected in the brainstem [8]. The use of cannabis in improving inflammation could therefore well include central effects, such as a reduction in pain sensation and relief of nausea and feeling of unpleasantness. One report suggests that a full anti-inflammatory response of CBs in gut inflammation includes the central nervous system since a peripherally restricted CB_1/CB_2 receptor agonist was either not effective or too weak to improve colitis, depending on the experimental model used [10].

In their prospective study, Naftali et al. [1] used THC-free cannabis as placebo with no other CBs present. However, we should consider that also other ingredients of cannabis, such as cannabidiol, cannabigerol and tetrahydrocannabivarine, all of them nonpsychotropic components of cannabis, have proven anti-inflammatory effects in experimental intestinal inflammation [9]. Their actions partly involve non-CB receptor mechanisms via, for instance, peroxisome proliferator-activated receptors (PPARs) and transient receptor potential cation channels subfamily V receptors (TRPVs) and should be regarded as additive beneficial effects of cannabis in the improvement of colitis in addition to THC-mediated effects.

In summary, in agreement with the ancient use of cannabis in intestinal disturbances and one decade of animal research, cannabis was shown in a clinical trial to reduce symptoms in patients with Crohn's disease. This elegant translation should be followed by larger trials confirming these results and by trials establishing the involved mechanisms to open a promising direction for future treatment of IBD.

Acknowledgements

R.S. is supported by grants from the Austrian Science Fund (FWF P 22771 and P 25633). M.S. is supported by the Deutsche Forschungsgemeinschaft.

Disclosure Statement

The authors have no conflict of interest to declare.

References

1 Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM: Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol 2013;11:1276–1280.

2 Naftali T, Lev LB, Yablecovitch D, Half E, Konikoff FM: Treatment of Crohn's disease with cannabis: an observational study. Isr Med Assoc J 2011;13:455–458.

3 Lal S, Prasad N, Ryan M, Tangri S, Silverberg MS, Gordon A, Steinhart H: Cannabis use amongst patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 2011;23:891–896.

4 Di Sabatino A, Battista N, Biancheri P, Rapino C, Rovedatti L, Astarita G, Vanoli A, Dainese E, Guerci M, Piomelli D, Pender SL, MacDonald TT, Maccarrone M, Corazza GR: The endogenous cannabinoid system in the gut of patients with inflammatory bowel disease. Mucosal Immunol 2011;4:574–583.

5 Marquéz L, Suárez J, Iglesias M, Bermudez-Silva FJ, Rodríguez de Fonseca F, Andreu M: Ulcerative colitis induces changes on the expression of the endocannabinoid system in the human colonic tissue. PLoS One 2009;4:e6893.

6 Wright K, Rooney N, Feeney M, Tate J, Robertson D, Welham M, Ward S: Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing. Gastroenterology 2005;129:437–453.

7 Singh UP, Singh NP, Singh B, Price RL, Nagarkatti M, Nagarkatti PS: Cannabinoid receptor-2 (CB_2) agonist ameliorates colitis in IL-10$^{(-/-)}$ mice by attenuating the activation of T cells and promoting their apoptosis. Toxicol Appl Pharmacol 2012;258:256–267.

8 Izzo AA, Sharkey KA: Cannabinoids and the gut: new developments and emerging concepts. Pharmacol Ther 2010;126:21–38.

9 Alhouayek M, Muccioli GG: The endocannabinoid system in inflammatory bowel diseases: from pathophysiology to therapeutic opportunity. Trends Mol Med 2012;18:615–625.

10 Cluny NL, Keenan CM, Duncan M, Fox A, Lutz B, Sharkey KA: Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone (SAB378), a peripherally restricted cannabinoid CB_1/CB_2 receptor agonist, inhibits gastrointestinal motility but has no effect on experimental colitis in mice. J Pharmacol Exp Ther 2010;334:973–980.