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Cannabidiol in Inflammatory Bowel Diseases: A Brief Overview

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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-toxicityand 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. Copyright © 2012 John Wiley & Sons, Ltd.

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THE URGENT NEED OF NEW DRUGS FOR INFLAMMATORY BOWEL DISEASES

In the last 50 years, the incidence of inflammatory bowel diseases (IBD), namely ulcerative colitis and Crohn's disease, has dramatically increased in industrialized countries (Cosnes *et al*., 2011), and despite their increasing epidemiological impact, a pharmacological treatment for these diseases is still disappointingly inadequate. Prevailing therapies for IBD include chronic administration of glucocorticosteroids and sulfasalazine. Unfortunately, these drugs often possess only limited beneficial action (Fascì Spurio *et al*., 2012). Steroids are effective in the short-term treatment of acute flares of either form of IBD, but they are not suitable for maintenance therapies due to a variety of systemic adverse reactions (Hanauer and Stathopoulos, 1991; Engel and Neurath, 2010). Sulfasalazine and its derivative 5-aminosalicylic acid (5-ASA) are effective only in mild-to-moderate phases of the disease and in preventing relapse. Biological drugs such as monoclonal anti- tumor necrosis factor-alpha (TNFα) antibody (Infliximab) by one side had a revolutionary impact in the management of steroid-resistant forms of IBD, obtaining encouraging results in the maintenance of the remission of the relapsing form of ulcerative colitis and Crohn's disease (Wilhelm *et al*., 2008). However, the long-term safety of this drug, the possibility to induce severe risks for developing cancer, i.e. leukemia and lymphoma (Rosh *et al*., 2007), together with the high costs of the therapy for the patients, force gastroenterologists to accurately evaluate its introduction in the therapy and to consider the risks/benefits ratio regarding its use. It is also undeniable that there is an urgent need for the identification of drugs that may efficiently control IBD evolution, with manageable side toxicity and low costs for patients. To this aim, identification and characterization of molecular targets for novel anti-IBD drugs appear to be crucial.

CANNABIS PREPARATIONS: USE AND LIMITATIONS FOR IBD THERAPY

In the USA, *Cannabis* preparations were indicated for the treatment of diarrhea a century ago. Nowadays, there are numerous evidences indicating the successful use of *Cannabis*-based products against IBD (Lahat *et al*., 2012). Despite the fact that *Cannabis sativa* has traditionally been used for centuries as an analgesic and anti-inflammatory remedy, modern pharmacological therapy of inflammation with cannabinoids is still at the beginning. Cannabinoids extracted from the marijuana plant (*Cannabis sativa*) and synthetic cannabinoids have numerous effects on gastrointestinal (GI) functions. The natural cannabinoids comprise Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabichromene, cannabidiol (CBD) and cannabinol (Turner and Elsohly, 1981; Russo, 2011). The chemical and pharmacological characterization of cannabinoids and the discovery of 'endocannabinoid' compounds have been widely investigated in the last years. Pharmacological effects of natural/synthetic cannabinoids depend upon their interaction with specific

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G-protein coupled receptors (cannabinoid receptors), namely CB1 and CB2 (Grotenhermen, 2005). While CB1 receptors are mainly expressed in the central and in the peripheral nervous system (Pacher *et al*., 2006), CB2 receptors have been identified in the cells of immune system (Pertwee, 2006). Cannabinoid receptors, their endogenous ligands [anandamide (AEA) and 2-arachidonoyl-glycerol] together with specific enzymes [fatty acid amide hydrolase (FAAH) and monoacylglycerol-lipase] which are involved in endocannabinoid synthesis and metabolism are commonly called 'endocannabinoid system' (Pertwee, 2008).

Recent experimental data support an important role for natural cannabinoids in GI diseases (Schicho and Storr, 2012). In fact, *Cannabis* has been proposed to treat GI pathological conditions that range from enteric infections and inflammation to disorders of motility, emesis and abdominal pain (Izzo and Sharkey, 2010).

Converging data demonstrated that endocannabinoids may inhibit the release of a wide class of pro-inflammatory mediators, including interleukin-1 beta (IL-1β), TNF-α and nitric oxide (Burstein and Zurier, 2009), thus controlling the cellular pathways leading to inflammatory responses orchestrated by massive cytokines release occurring in IBD. A huge number of studies confirmed that *Cannabis* preparations significantly suppress the severity of colitis in experimental animal models of IBD (Massa *et al*., 2004; Izzo and Camilleri, 2009). Moreover, the beneficial effect of cannabinoids has been revealed as a powerful tool to regulate gut motility and paves the way to the future development of new class of drugs capable to regulate bowel dysfunction ranging from classical ulcerative colitis and Crohn's disease to ileitis and gastric ulcers, secretory diarrhea, paralytic ileus, irritable bowel syndrome, colon cancer and gastro-esophageal reflux conditions (Izzo and Coutts, 2005).

More in detail, the ability of Δ^9-THC to protect from inflammation, damage and motility changes in a pre-clinical model of IBD (Jamontt *et al*., 2012), as well as the ability of cannabichromene to normalize intestinal motility in the inflamed gut (Izzo *et al*., 2012), have been recently described. Some studies also evaluated the effect of cannabinoid compounds alone or in combination. For instance, Jamontt and colleagues not only confirmed that Δ^9-THC and CBD exert an anti-inflammatory role in a rat model of colitis, but they also demonstrated that the combination of the two cannabinoids may be therapeutically beneficial because of a potentiated pharmacological effect (Jamontt *et al*., 2012).

Such evidences lead to postulate that the modulation of the activity of the cannabinoid system during gut inflammation might be a promising therapeutic tool for the treatment of those diseases characterized by inflammation. By consequence, it is not surprising that about 33–50% of people suffering from IBD have been using *Cannabis* to relieve IBD-related symptoms (Lal *et al*., 2011). This beneficial effect has been described also by Naftali *et al*. (2011) which reported that *Cannabis* may have a positive effect on Crohn's disease features, as showed by reduction in the disease activity index. In these cases, *Cannabis* preparations are taken as self-medication by patients with IBD in order to relieve symptoms such as abdominal pain, diarrhea and reduced appetite (Garcia-Planella *et al*., 2007; Lal *et al*., 2011).

As mentioned above, most of the anti-inflammatory pharmacological activities of cannabinoids depend upon their interaction at both CB1 and CB2 receptors in the gut (Izzo *et al*., 2001; Kimball *et al*., 2006; Storr *et al*., 2008; Wright *et al*. 2008). However, the indiscriminate binding with the receptors also in the central nervous system is accompanied to side effects such as euphoria, anxiety, psychomotor retardation and impairment of cognition and memory (Hall and Solowij, 1998). Such interaction is a self-limiting feature inherent to most of cannabinoids and explains why these compounds, despite their huge potentiality in pre-clinical studies, have had a partial and cautious clinical use (Pertwee, 2005).

CANNABIDIOL IN IBD: EVIDENCE FOR ITS FAST MOVING FROM PRE-CLINICAL DATA TO CLINICAL PRACTICE

As mentioned before, *Cannabis sativa* is the source of a unique set of compounds known collectively as plant cannabinoids or phytocannabinoids. Not all *Cannabis* compounds share at same time psychotropic and immunomodulatory functions. Among the wide range of cannabinoids extracted by this plant, one interesting exception is represented by CBD. CBD has been isolated across the 1930s and 1940s from marijuana, but its structure and configuration were fully elucidated only in the 1960s (Mechoulam *et al*., 1970). (−)CBD isomer is the major non-psychotropic constituent present in *Cannabis sativa*. For this reason, CBD may represent the most promising candidate for clinical utilization due to its remarkable lack of any cognitive and psychoactive actions, in addition to its excellent tolerability profile in humans (Mechoulam and Hanus, 2002).

A huge amount of data produced in recent years demonstrated that CBD appears as a very promising molecule because of its anti-inflammatory, antioxidant and anti-apoptotic effects in the central nervous system (Iuvone *et al*., 2009). Importantly, CBD has been demonstrated to display potent anti-inflammatory and immune-modulatory properties which, together with a lack of psychotropic activity and low toxicity (Mechoulam and Hanus, 2002), make it a very promising therapeutic candidate for a variety of inflammatory and pain-associated disorders, including IBD.

CBD has demonstrated the capability to mediate a strong inhibition of neutrophil chemotaxis and proliferation (Sacerdote *et al*., 2005), and this has been considered at the basis of its great efficacy as an anti-inflammatory drug, described both in acute and chronic animal models of inflammation (Costa *et al*., 2004). Along this line, in the last years, a growing number of studies highlighted the beneficial effect of CBD in gut disorders and, at the same time, they focused scientific interest toward a better comprehension of its molecular target(s) that may explain the beneficial actions in gut disturbances. Many protective functions of CBD have been related to the impressive antioxidant function displayed during inflammation; such antioxidant activity has been reported to markedly inhibit colon injury, inducible nitric oxide synthase expression (but not cyclooxygenase-2), and IL-1β, IL-10 (Borrelli *et al*., 2009); further effects of CBD on immune cells include the inhibition of release of interferon-gamma by mononuclear cells (Formukong *et al*., 1988; Watzl *et al*., 1991) and the suppression of chemokine production by

human B cells (Srivastava *et al*., 1998). All together, these observations explain why CBD has a so potent efficacy in decreasing the severity of experimental colitis in rodents (Borrelli *et al*., 2009; Schicho and Storr, 2012).

The great efficacy showed by CBD during colitis is partly linked to its ability to control also intestinal motility alteration. In fact, although CBD *per se* did not affect intestinal motility, it normalized croton oil-induced hypermotility *in vivo*. Similar results were obtained also *in vitro*, where CBD was able to inhibit ACh-induced contractions in the isolated ileum from both control and croton oil-treated mice (Capasso *et al*., 2008). Along this line, it has been demonstrated that CBD selectively controls intestinal motor alteration in another model of hypermotility (lypopolisaccharides-induced) both in rats and in mice (Lin *et al*., 2011).

While it is clear *why* CBD is a potent anti-inflammatory drug, it appears so puzzling to understand *how* this molecule exerts its activity. Although it has been proposed that CBD may modulate endocannabinoid function through its ability to inhibit FAAH (i.e. the enzyme which hydrolyses the endocannabinoid AEA), this compound, unlike Δ^9-THC, has very low affinity for both CB1 and CB2 receptors (Iuvone *et al*., 2009). As hypothesized by Capasso and colleagues, FAAH inhibition results in marked anti-inflammatory effects within the gut (Capasso *et al*., 2005). This is confirmed also in other gut disturbances not resembling typical IBD, such for instance intestinal sepsis (De Filippis *et al*., 2008). Schicho and Storr confirmed the anti-inflammatory and protective role of CBD in experimental IBD by demonstrating that the topical and systemic CBD administration improves trinitrobenzene sulfonic acid-induced colitis in mice (Schicho and Storr, 2012). Very importantly, these authors indicate that, in addition to intraperitoneal application, intrarectal delivery of CBD may represent a useful therapeutic administration route for the treatment of colonic inflammation. However, it is a common feeling that antioxidant effect cannot extensively explain *per se* the pharmacological capability exerted by CBD as potent inhibitor of gut inflammation.

The in-depth analysis of CBD-related pharmacology during gut disorders done by De Filippis and colleagues demonstrated that CBD may reduce intestinal inflammation severity through the control of neuro-immune axis (De Filippis *et al*., 2011). This study demonstrated that CBD appears as a key modulator of enteric glia-mediated neuroinflammation in the gut because of its capability to activate peroxisome proliferator-activated receptor-gamma (PPARγ). At confirmation that CBD may exert its beneficial effects by binding PPARγ, there are two recent studies in which the authors evaluated how CBD restores increased intestinal permeability consequent to pro-secretory agents (i.e. cytokines) application on epithelial cells (Alhamoruni *et al*. 2010, 2012).

CBD-mediated activation of PPARγ may represent a key mechanism that better explains the potent anti-inflammatory action of this compound during intestinal inflammation. PPARγ has an inestimable value as target for novel therapeutics against IBD (Lewis *et al*., 2011). Activation of PPARγ is in fact accompanied to massive inhibition of the activity of pro-inflammatory transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells, signal transducer and activator of transcription (STAT) and activator protein-1 (Ricote *et al*., 1998; Esposito *et al*., 2011). For these reasons, CBD-mediated modulation of PPARγ activation may result not only a beneficial approach in the management of ulcerative colitis or Crohn's disease but also a chemopreventive pharmacological tool capable to reduce the risk of and other pathologies related to persistent inflammation of the colon, such as colon cancer. In line with these observations, a significant chemopreventive effect of CBD on experimental colon cancer in mice has been proved (Aviello *et al*., in press).

CONCLUSION

The beneficial and immunomodulatory effects of CBD have been widely evidenced in experimental animal models of IBD. This compound possesses an extraordinary range of beneficial effects that may slow the course of the disease, ameliorate symptoms and potentially increase the efficacy of the drugs actually available for the therapy of invalidating gut disorders such as ulcerative colitis or Crohn's disease. Because of its well-known low toxicity even in humans and its complete lack of any psychotropic unwanted effects, CBD may represent a novel molecule or a lead compound to develop new pharmacological approach to ameliorate the current therapy of IBD with fast translation from pre-clinical studies to clinical practice.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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