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Review

Cannabinoids in intestinal inflammation and cancer

Angelo A. Izzo[a,*], Michael Camilleri[b,*]

[a] Department of Experimental Pharmacology, University of Naples Federico II and Endocannabinoid Research Group, Naples, Italy
[b] C.E.N.T.E.R. Program, Mayo Clinic, Rochester, MN 55905, USA

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ABSTRACT

Emerging evidence suggests that cannabinoids may exert beneficial effects in intestinal inflammation and cancer. Adaptive changes of the endocannabinoid system have been observed in intestinal biopsies from patients with inflammatory bowel disease and colon cancer. Studies on epithelial cells have shown that cannabinoids exert antiproliferative, antimetastatic and apoptotic effects as well as reducing cytokine release and promoting wound healing. *In vivo*, cannabinoids – via direct or indirect activation of CB_1 and/or CB_2 receptors – exert protective effects in well-established models of intestinal inflammation and colon cancer. Pharmacological elevation of endocannabinoid levels may be a promising strategy to counteract intestinal inflammation and colon cancer.

Contents

1. Introduction 118
2. Intestinal inflammation 118
 2.1. Studies on intestinal epithelial cells 118
 2.2. Endocannabinoid and cannabinoid receptor changes in human intestinal biopsies 118
 2.3. Effect of cannabinoid drugs in experimental models of IBD 119
 2.4. Visceral sensation in the inflamed gut 120
 2.5. Intestinal motility in the inflamed gut 120
 2.6. Anandamide as an endovanilloid in the inflamed gut 120
 2.7. Distribution of FAAH polymorphism in patients with Crohn's disease 120
3. Intestinal cancer 121
 3.1. Studies on colorectal cancer cell lines 121
  3.1.1. Antiproliferative/apoptotic effects CB_1 or CB_2 receptor activation 121
  3.1.2. Antiproliferative/apoptotic effects via prostamides production 121
  3.1.3. Antimetastatic actions of cannabinoids 122
  3.1.4. Oestrogens and CB_1 receptors 122
 3.2. Endocannabinoid and cannabinoid receptor changes in human intestinal cancer biopsies 122
 3.3. Effect of cannabinoid drugs in experimental models of colon cancer 122

* Corresponding authors.
E-mail addresses: aaizzo@unina.it (A.A. Izzo), Camilleri.michael@mayo.edu (M. Camilleri).

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4. Non-psychotropic plant cannabinoids in intestinal inflammation and cancer 122
4.1. Intestinal inflammation 123
4.2. Intestinal cancer 123
5. Anandamide-related acylethanolamides and their role in intestinal inflammation and cancer 123
6. Paradoxical beneficial effects of rimonabant in intestinal inflammation and cancer 123
7. Conclusions 123
Conflict of interest 123
Acknowledgements 124
References 124

1. Introduction

The marijuana plant *Cannabis sativa* is possibly one of the oldest plants cultivated by humans, but it has also been a source of controversy throughout history [1,2]. The plant has provided insights to medicine and has pointed the way in the last two decades toward a host of medical challenges from analgesia to weight loss through [1,2]. The main active ingredient in *Cannabis* is Δ^9-tetrahydrocannabinol (Δ^9-THC), which activates two Gi/o-coupled membrane receptors, named CB_1 and CB_2 receptors [3]. CB_1 receptors are located throughout the gastrointestinal tract, mainly in myenteric and submucosal neurons, but they are also expressed by in non-neuronal cells such as epithelial cells (reviewed in Izzo and Camilleri [4]). CB_2 receptors are mainly located on inflammatory and epithelial cells, although recent evidence suggests the presence of CB_2 receptors in myenteric and submucosal neurons [5,6].

Endogenous ligands that activate cannabinoid receptors [i.e. the endocannabinoids, anandamide and 2-arachydonylglycerol (2-AG)] [7,8] have been identified in mammalian tissues, and their levels may increase in pathophysiological states affecting the intestine, such as inflammation and cancer [9]. Endocannabinoids are biosynthesized 'on demand' from membrane phospholipids and released from cells immediately after their production. Following receptor activation and induction of a biological response, endocannabinoids are inactivated through a reuptake process facilitated by a putative endocannabinoid membrane transporter (EMT) followed by enzymatic degradation catalysed by the fatty acid amide hydrolase (FAAH, in the case of anandamide) or by monoacylglycerol lipase (MGL, and possibly FAAH, in the case of 2-AG) [4,10,11]. These catalytic enzymes have also been identified in the digestive tract [12,13]. Apart from effects on cannabinoid receptors, the endocannabinoid anandamide may also activate the transient receptor potential (TRP) vanilloid type 1 (TRPV1), which is mainly expressed by primary afferent neurons and the orphan G-protein-coupled receptor GPR55 [3,14].

Although cannabinoids exert important physiological and pathophysiological actions in the digestive tract, including appetite regulation, emesis, protection of the gastric mucosa, intestinal ion transport, gastric emptying and intestinal motility [4,15–21], this review will focus on the role and the effects of cannabinoids in inflammation and cancer within the gut.

2. Intestinal inflammation

Some patients with inflammatory bowel disease (IBD) anecdotally report that they experience relief by smoking marijuana; in one series from Spain, about 10% of IBD patients consumed cannabis, typically before the diagnosis was made; one third of the patients informed their physician about use of Cannabis [22]. Enhancement of cannabinoid signalling, as revealed by the increased intestinal expression of CB_1/CB_2 receptors and/or endocannabinoid levels has been observed following inflammatory stimuli, both in animals and humans. Experiments on isolated epithelial cells and *in vivo* studies using well-established models of IBD indicates that the endogenous cannabinoid system, via CB_1 or CB_2 receptor activation, mediates protective mechanisms counteracting intestinal inflammatory responses that are considered pathophysiological in IBD. Moreover, cannabinoids may reduce hypermotility and visceral hypersensitivity associated with intestinal inflammation [9,23], and thus impact on some of the clinical manifestations of IBD.

2.1. Studies on intestinal epithelial cells

Cannabinoids have been shown to exert pharmacological actions on epithelial cells; these effects may explain the benefits observed in experimental models of IBD.

Epithelial cells play a pivotal role in host defence against microorganisms in the intestinal lumen, and in inflammatory responses. In addition to their function as barriers preventing absorption of potentially deleterious luminal substances, epithelial cells also express a variety of pro-inflammatory cytokines, which are up-regulated in IBD [24]. A number of cannabinoid receptor agonists, including the plant-derived Δ^9-THC, have been shown to exert an inhibitory effect on the expression of TNF-α-induced interleukin-release from the human colonic epithelial cell line HT-29 [25]; this inhibition on inflammatory process is sensitive to CB_2 antagonist. Furthermore, delayed wound healing, a typical feature of IBD patients [26] may be modulated by cannabinoid drugs [27]. Thus, the endogenous cannabinoid ligands anandamide (non-selective cannabinoid agonist), noladin ether (CB_1 selective receptor agonist) as well as the synthetic selective CB_1 agonist arachidonylcyclopropylamide, ACPA (but not the synthetic CB_2 agonist JWH133) induced wound closure in HT29 and DLD1 epithelial cells [27].

Overall, studies on intestinal epithelial cells have shown that cannabinoids can exert protective effect by promoting wound healing via CB_1 receptors activation and by suppressing the release of pro-inflammatory cytokines via CB_2 receptors activation (Fig. 1).

2.2. Endocannabinoid and cannabinoid receptor changes in human intestinal biopsies

Increased expression of cannabinoid receptors and/or enhanced endocannabinoid levels have been generally observed in intestinal biopsies of patients with gut inflammatory diseases, including ulcerative colitis, Crohn's disease, diverticulitis and celiac disease (CD).

A more than 2-fold elevation of anandamide, but not 2-AG, levels was found in mucosal biopsies from patients with untreated ulcerative colitis relative to control biopsies. Anandamide levels significantly correlated with clinical activity of the disease, while no correlation was found between endocannabinoid levels and endoscopic and histologic activities [28]. In a different study. Wright et al. determined the location of both CB_1 and CB_2 receptors in normal and IBD human colonic tissue. Epithelial CB_1 immunoreactivity was evident in acute-phase IBD (not specified by author,