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Cannabinoids cool the intestine

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Abstract

Cannabinoids inhibit motility and secretion in the intestine. They are now assigned the additional task of curbing excessive inflammation, suggesting that drugs targeting the endogenous cannabinoid system could be exploited for inflammatory bowel disease.

Inflammatory bowel diseases (IBDs) such as ulcerative colitis and Crohn's disease affects over a million people in the United States[1], with an estimated indirect cost from work loss of $3.6 billion annually[2]. Many of these individuals suffer from pain, diarrhea and poor ability to digest their food, and in up to half of those with IBD, the disease is so severe that it ultimately requires surgery to remove the affected bowel segment.

Despite recent therapeutic advances and improved understanding of the underlying pathologies, patients with IBD are often resistant to treatment, justifying the continued search for new therapeutic approaches. Although the mechanisms underlying ulcerative colitis and Crohn's disease are different, they share one pathological feature: chronic inflammation. In a recent issue of the *Journal of Clinical Investigation*, Massa *et al.* provide evidence that stimulation of cannabinoid receptors protects against colonic inflammation[3].

As their model, the authors induced bowel inflammation in mice by treatment with different chemical agents, an approach commonly used to explore endogenous protective mechanisms and to screen potential therapeutic agents. The authors began with an experiment testing chemical agents in mice lacking the CB1 subtype of cannabinoid receptor; such agents induced more severe colitis in the CB1 knockout mice than in wild-type mice. Moreover, pretreatment of wild-type mice with a CB1 antagonist caused a similar increase in the inflammatory response.

The authors then performed the converse experiments. They found that either treatment of wild-type mice with a CB1 receptor agonist or genetic ablation of fatty acid amidohydrolase (FAAH), the enzyme that degrades the endogenous cannabinoid agonist anandamide[4], reduced inflammation in response to chemicals. The authors also observed an increase in the expression of CB1 receptors in intrinsic neurons of the inflamed mouse colon. Together, these findings suggest that anandamide counteracts inflammation. Another endocannabinoid, 2-arachidonoylglycerol, is unlikely to be involved because its abundance in tissue is unaffected by genetic ablation of FAAH[5].

These findings may offer a new therapeutic approach to IBD. CB1 receptors in the brain mediate the addictive psychological effects of marijuana, so treating a chronic disease with a drug that directly stimulates CB1 receptors would be socially objectionable. Recent evidence indicates, however, that drugs which target endogenous cannabinoids may not have the same

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potential for abuse. A potent FAAH inhibitor, for example, elicits cannabinoid-like antianxiety effects in mice without producing many of the other behavioral effects of psychoactive cannabinoids[6].

The results of Massa *et al.* would therefore warrant testing FAAH inhibitors as anti-inflammatory agents in the mouse model, as a prelude to clinical trials in IBD. It should be noted, however, that the effect of FAAH inhibitors may not be entirely due to elevated levels of anandamide, as they also elevate the level of noncannabinoid substrates such as oleoylethanolamide[6] or prostamides generated via COX-2 (ref. 7).

Historically, marijuana has been used to treat diarrhea and has been advocated for the treatment of a variety of other gastrointestinal problems, including Crohn's disease[3]. More recent pharmacological studies have clearly established that cannabinoids inhibit gastrointestinal motility and secretion by acting on CB1 receptors located on the terminals of both intrinsic and extrinsic submucosal neurons[8]. When administered to mice with chemically induced enteritis, cannabinoids also reduce inflammation[9] and fluid accumulation[10] in the gut. In these latter studies, high levels of anandamide and 2-arachidonoylglycerol as well as increased expression of CB1 receptors have been detected in the inflamed intestines.

The novelty in the findings of Massa *et al.*[3] is the active protective role of the endocannabinoid system, as indicated by the altered inflammatory response of mice lacking CB1 receptors or FAAH. Furthermore, CB1 activation reversed the electrophysiological signs of smooth muscle irritability and, at the same time, blunted the increase in tissue myeloperoxidase activity, a measure of leukocyte infiltration. These observations suggest that endocannabinoids protect the gut not only by decreasing bowel motility but also by inhibiting the inflammatory process itself.

The nature of the anti-inflammatory effect of endocannabinoids, however, remains to be elucidated. The exaggerated increase in myeloperoxidase activity in the inflamed bowel of CB1 knockout mice[3] indicates that in wild-type mice endocannabinoids actively inhibit leukocyte infiltration caused by the chemical treatment. This may be due to inhibition of the release of chemokines and proinflammatory cytokines, such as TNFα. TNFα has been implicated in the pathogenesis of IBD[11], its likely source being activated macrophages and mast cells[12]. Cannabinoids suppress TNFα release from both cell types[13,14] (although the CB1 antagonist SR141716 was also reported to suppress TNFα release in a different model of bowel injury[15]). In a mouse model of myocardial ischemia-reperfusion injury, cannabinoids attenuated the increase in myeloperoxidase activity via CB2 receptors[16]. The anti-inflammatory potential of CB2 receptors in the gut should therefore be explored.

Infiltrating macrophages in the inflamed bowel may be not only the target but also the source of endocannabinoids. Bacterial components, such as lipopolysaccharide (LPS), are known to powerfully induce anandamide synthesis in macrophages through a pathway dependent on CD14 and NF-κB[5]. Anandamide may thus act as an autocrine-paracrine mediator to limit the release of cytokines by macrophages and mast cells and the neuronal release of the tachykinins and acetylcholine that control bowel motility (Fig. 1).

An important feature of IBD is the altered tissue response to enteric bacteria. Mutations in the gene *CARD15* (also called *NOD2*), which result in deficient activation of NF-κB in response to LPS, are associated with susceptibility to Crohn's disease[17]. A defect in NF-κB signaling is also expected to result in deficient activation of anandamide production given that NF-κB is required for LPS-induced anandamide synthesis [5]. Bowel inflammation can also increase FAAH activity[8], resulting in further reductions in anandamide levels.

It is not known whether anandamide levels are reduced and the activity of FAAH increased in the intestines of patients with IBD, but this could be verified using biopsy specimens. If confirmed, such changes may be interpreted as the weakening of an endogenous protective mechanism, which could be restored by preventing the breakdown of anandamide with a FAAH inhibitor. Biopsy results from humans could further support the case made by Massa *et al.* for targeting the endocannabinoid system to treat IBD, offering renewed hope to a much-suffering patient population.

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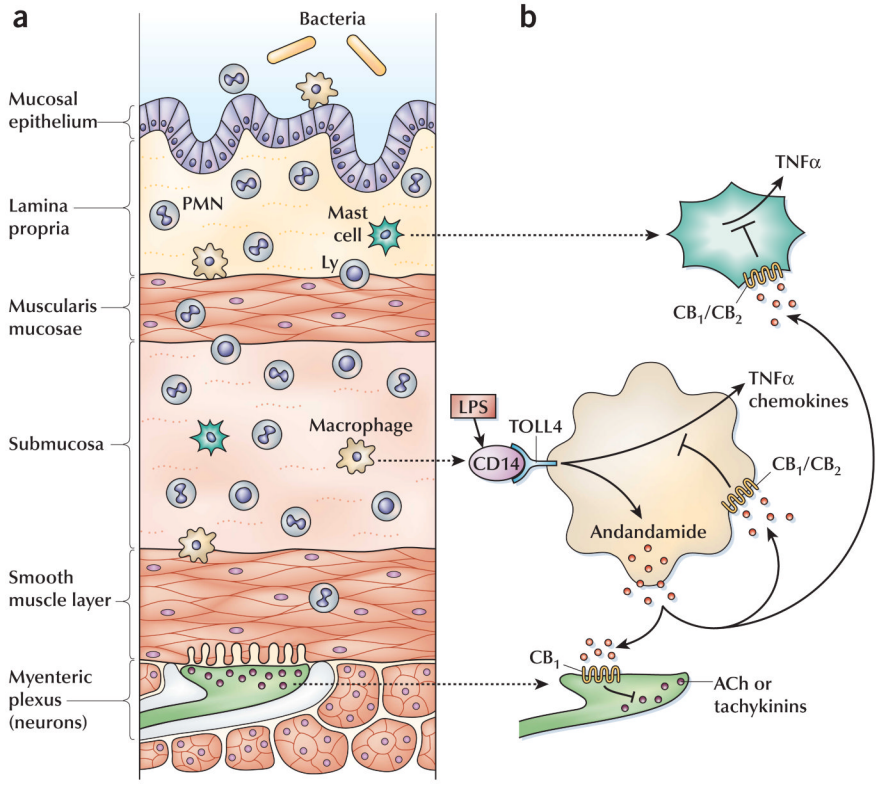

Figure 1.

Cellular source and proposed targets of anti-inflammatory endocannabinoids in IBD. (**a**) Cross-section of inflamed bowel with leukocyte infiltration (polymorphonuclear, lymphocytes, macrophages, mast cells). (**b**) In macrophages, LPS induces the production of TNFα and chemokines (such as MIP-2 and CXCL-8) as well as anandamide. Anandamide is released to act as an autocrine mediator to inhibit TNFα and chemokine production via CB1 or CB2 receptors or both. Activation of CB1 and CB2 receptors may similarly inhibit TNFα production in mast cells, with these effects resulting in decreased leukocyte infiltration and inflammation. Paracrine activation of CB1 receptors on extrinsic and intrinsic enteric neurons inhibits acetylcholine and tachykinin release, respectively, resulting in inhibition of gut motility. These effects are amplified by treatment with a FAAH inhibitor, which prevents the breakdown of anandamide.