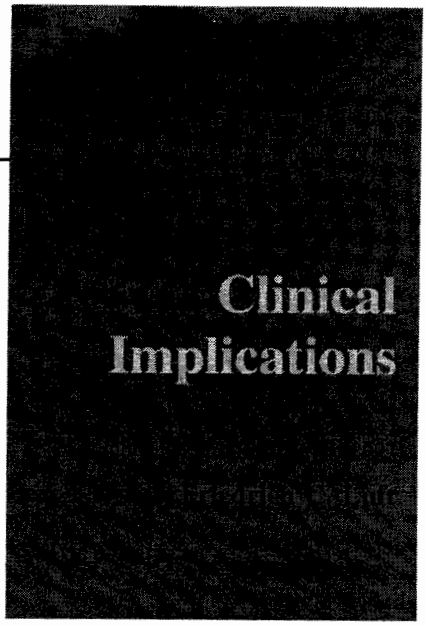
Endocannabinoids, just a gut feeling



Marijuana (Bill Clinton claimed, "I never inhaled"), hashish, cannabis, and their derivatives are well known to all teenagers and most adults. The compounds stimulate appetite, inhibit vomiting, improve gastro-intestinal mobility, and possibly ameliorate other gastro-intestinal conditions [1, 2]. Thus, the fate of marijuana seems to largely rest in the stomach. Δ^9-Tetrahydrocannabinol (THC) was identified to be the main constituent of cannabinol 50 years ago (Fig. 1). Two cannabinol receptors, CB_1 and CB_2, were subsequently identified, as well as their endogenous endocannabinoid ligands, anandamide and 2-arachidonylglycerol (2-AG). In the gastrointestinal tract, the endocannabinoid system interacts prominently within the enteric nervous system (ENS). The ENS consists of nerve fibers that innervate the tissues of the gut. The neurons are found in two major plexuses, namely the myenteric plexus between the external muscle layers and the submucosal plexus within the submucosa. The ENS is the final common pathway of the central nervous system (CNS)-mediated control of gastro-intestinal function. Cannabinoids act at many points between the brain gut axis interconnection [2].

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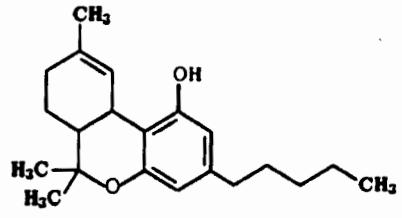
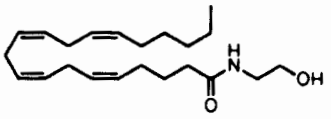
In this issue, D'Arbenio et al. [3] report on the state of the endocannabinoid system in patients with celiac disease and in rats with a drug-induced condition that exhibits similarities to celiac disease. The authors found that the endocannabinoid system is upregulated in celiac disease, and the regression of the upregulation occurs with remission. The rats exhibited a similar pattern after methotrexate administration. What do marijuana derivatives have to do with bowel function, and what purpose could this upregulation serve? The endocannabinoid system is upregulated in the gastrointestinal tract in several inflammatory bowel diseases (perhaps all) and in experimental models of colitis.

Celiac disease, also known as nontropical sprue and gluten-induced enteropathy, is an inflammatory condition of the small intestine precipitated by ingestion of wheat, rye, and barley in persons with certain genetic predispositions. Screening studies for antigliadin, anti-endomysial, and anti-tissue transglutaminase antibodies are associated with a much higher incidence. The best serological marker for celiac disease is the presence of anti-endomysial IgA antibodies detected by immunofluorescence. An enyzme-linked immunosorbent assay is available. The condition is by no means trivial; about 10% of patients labeled with "irritable bowel disease" actually have celiac disease. The diagnosis is made on the basis of malabsorption and small intestinal biopsy. The condition improves when a gluten-free diet is instituted.

The cannabinoid CB1 receptor was first found in rat brain, while the cannabinoid CB2 receptor was initially identified on the surface of macrophages. The two receptors may be just a beginning; at least five other putative cannabinoid receptors in the brain, cardiovascular system, and elsewhere have been postulated. The CB1 receptor is affiliated primarily with neurons. The receptor has a high density in the CNS, ENS, sympathetic and sensory nerves, liver, cardiovascular tissues, and fat. The CB2 receptor is generally found outside of nervous tissue, such as in immune tissues, spleen, thymus, and other immune cell populations. In the gastrointestinal tract, the CB2 receptor



Δ^9-tetrahydrocannabinol (THC)



Anandamide

Fig. 1 The structure of cannabinoids is shown. THC is explanatory (ask your kids). Anandamide is an arachidonic acid derivative that is present in the brain and believed to be an endogenous agonist for cananbinoid receptors

is also in abundance in the ileum, muscle layers containing the myenteric plexus, and stomach. Both receptors are coupled to G proteins, adenylyl cyclase, and mitogen-activated protein kinases. CB1 receptors are also directly coupled to A-type and inward rectifying potassium channels, as well as to L-/N-/P-/ and Q-type calcium channels.

Anandamide was the first endogenous cannabinoid discovered in the brain. The compound also acts at the capsaicin receptor site, a transient receptor–potential vanilloid receptor (TRPV1). The fatty acid amide hydrolase enzyme (FAAH) degrades amandamide. 2-AG was first isolated from gut and interacts with both CB1 and CB2 receptors. 2-AG is catabolized both by FAAH and the monoacylglycerol lipase (MAGL).

Cannabinoids have been extensively studied in the gastrointestinal tract. Cannabinoid agonists are potent inhibitors of gastrointestinal contractility. CB1 receptor agonists that produce inhibition of motility have been synthesized. The effects involve enteric CB1 receptors rather than centrally mediated actions. When experimental animals in these studies were given croton oil, diarrhea, inflammation of the small intestine, and mucosal disruption subsequently occurred. Lymphocytes infiltrate the submucosal layer, and the CB1 receptor is upregulated. Cannabinoid agonists produce a dose-dependent suppression of the enhanced transit, and the mortality was reduced.

Wright et al. [4] studied the location of CB1 and CB2 receptors in human colonic tissue by immunohistochemistry. They treated primary colonic epithelial cells with both synthetic and endogenous cannabinoids in vitro. Receptor signaling events were determined by immunoblotting. They found that CB1-receptor immunoreactivity was evident in normal colonic epithelium, smooth muscle, and the submucosal myenteric plexus. CB1 and CB2 receptor expression was present on plasma cells in the lamina propria, whereas only CB2 was present on macrophages. CB2 immunoreactivity was seen in the epithelium of colonic tissue characteristic of inflammatory bowel disease. Cannabinoids enhanced epithelial wound closure either alone or in combination with lysophosphatidic acid through a CB1–lysophosphatidic acid 1 heteromeric receptor complex. Wright et al. [4] showed that CB1 receptors are expressed in normal human colon and that colonic epithelium is responsive biochemically and functionally to cannabinoids. Furthermore, the increased epithelial CB2 receptor expression in human inflammatory bowel disease tissue implies an immunomodulatory role that could have any impact on mucosal immunity.

Massa et al. [5] showed that the endogenous cannabinoid system protects against colonic inflammation. They infused 2,4-dinitrobenzene into the rectum or orally administered dextrane sulfate sodium of CB1-deficient (−/−) mice and control (+/+) mice. The CB1 −/− mice did much worse than the controls. In wild-type mice, a CB1 antagonist mimicked the phenotype of CB1 −/− mice. A CB1 agonist or genetic ablation of FAAH protected against the inflammatory agents. Their results suggested that the endogenous cannabinoid system represents a promising therapeutic target for inflammatory intestinal disease [6].

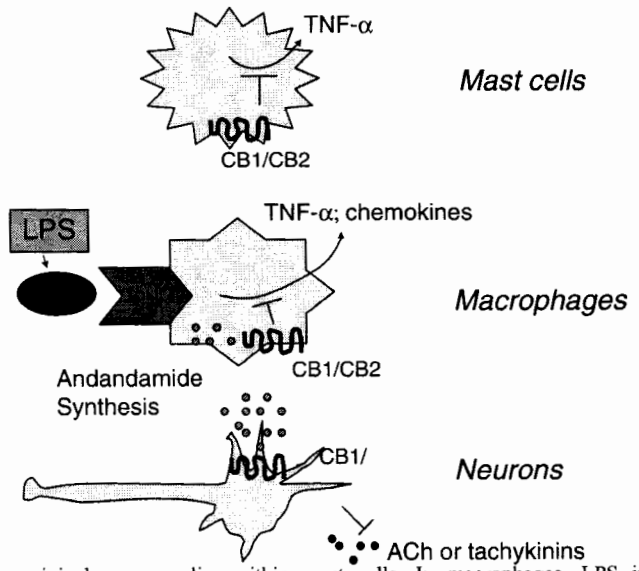


Fig. 2 The original program lies within mast cells. In macrophages, LPS induces the production of TNFα and chemokines, as well as anandamide. Anandamide is released to act as an autocrine mediator to inhibit tumor necrosis factor alpha (TNF-α) and chemokine production via CB1 or CB2 receptors. Paracrine activation of CB1 receptors on neurons inhibits acetylcholine release, resulting in inhibition of gut motility

Cannabinoids "cool the intestine" (Fig. 2). Kunos and Pacher [7] discuss the possibility that cannabinoids could have therapeutic potential. Bacterial components such as lipopolysaccharide (LPS) induce anandamide snythesis in macrophages through an NF-κB-dependent mechanism [7]. Mutations in caspase recruitment domain family member 14 (CARD14 alias NOD2, nucleotide-binding oligomerization domain containing 2) that result in impaired NF-κB activation in response to LPS are associated with susceptibility to inflammatory bowel disease. Inflammatory bowel disease can upregulate FAAH expression that could lead to reduced anandamide levels. However, D'Argenio et al. [3] showed that intestinal endocannabinoid levels peak with atrophy and regress with remission in patients with celiac disease. The interpretation would be that endocannabinoid over-activity represents an adaptive reaction to intestinal inflammation, namely a protective event. These findings are exciting and may open novel therapeutic avenues.

Respectfully,
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