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THE ENDOCANNABINOID SYSTEM AND THE CONTROL OF GASTROINTESTINAL FUNCTION

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Introduction

Cannabinoids (CBs) have long been used to attempt to improve gastrointestinal (GI) function in a variety of conditions associated with disordered intestinal motility, inflammation, and pain. After the discovery of delta-9-tetrahydrocannabinol, a substantial effort was made to discover the mechanism of action of cannabis in the GI tract. These studies were largely focused on GI motility and revealed that cannabinoids reduced the release of acetylcholine from nerve terminals in the enteric nervous system [1]. This effect leads to a slowing of motility and is seen throughout the length of the gut. With the discovery and cloning of the CB1 and CB2 receptors and the isolation of endogenous ligands for these receptors, notably 2-arachidonoylglycerol (2-AG) isolated from the canine GI tract [2], it has become apparent that the gut is a major site of action of the endocannabinoid system (ECS). The ECS is active under physiological and pathophysiological conditions and serves to regulate a variety of GI functions. In this paper, some of the recent findings on the localization and action of the ECS in the GI tract will be highlighted. The main findings are illustrated schematically in the Figure.

Key Points

- The ECS is a novel regulatory system involved in the control of gut function in health and disease.
- The ECS in the GI tract is involved in the regulation of gastrointestinal motility, secretion, sensation, and inflammation.
- CB1 and CB2 receptors are expressed on selective populations of neurons of the enteric nervous system. They modulate synaptic and junctional transmission in the GI tract under physiological (CB1 receptors) and pathophysiological conditions (CB1 and CB2 receptors). They are also expressed on the extrinsic innervation of the gut and regulate visceral sensitivity under pathophysiological conditions.

State of the Art

CB1 receptors were the first components of the ECS to be localized in the GI tract [3]. Consistent with the actions of CBs in the gut, they were found on cholinergic neurons, which are the excitatory motor neurons, major classes of interneurons, and primary afferent neurons of the enteric nervous system. Double-labelling studies also revealed that CB1 receptors were absent from the intrinsic neurons that regulate relaxation of the gut and express nitric oxide synthase. CB1 receptors are also

present on the epithelium of the human gut. Recently, CB2 receptors were localized on neurons of the enteric nervous system and on immune cells in the lamina propria of the mucosa [4]. Like CB1 receptors, these were also largely found on excitatory neurons and were mostly absent from inhibitory motor neurons. Under physiological conditions, these receptors do not appear to be functional in the control of motility. In intestinal inflammation, CB2 receptor expression is upregulated on epithelial cells and the neuronal receptors are able to regulate enhanced motor function [4]. CB1 and CB2 receptors are also found on extrinsic nerves innervating the gut. Vagal afferent neurons express CB1 receptors and spinal afferents express both CB1 and CB2 receptors, being involved in nociceptive transmission and pain sensation from the gut [5].

As noted above, both major endocannabinoids have been isolated from the gut. Anandamide levels are higher in the colon than the ileum [6] and are elevated in states of intestinal inflammation [7, 8]. 2-AG is found at higher levels than anandamide in the GI tract, is more abundant in the small intestine than in the colon, and unlike anandamide is not altered in intestinal inflammation [6, 7]. Degradation of anandamide is largely accomplished by fatty acid amide hydrolase (FAAH), which is distributed throughout the wall of the gut [9]. Monoacylglycerol lipase, which degrades 2-AG, is found in the intestinal epithelium and also in the enteric nervous system [10]. To date, the localization of the biosynthetic enzymes of the ECS has not been determined.

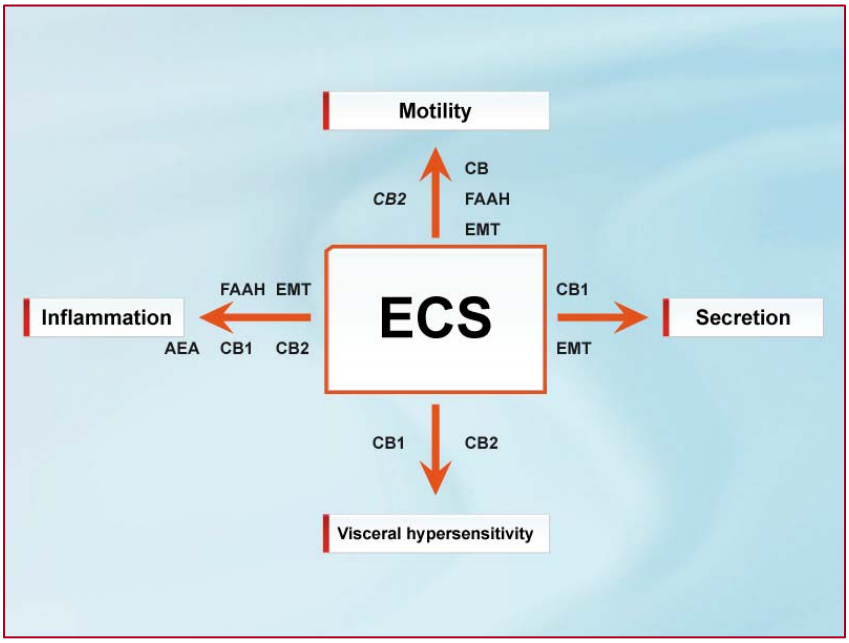

Figure: Schematic illustration of the functional roles of the endocannabinoid system (ECS) in the gastrointestinal tract. The ECS regulates four major functional elements in the gut: motility, secretion, inflammation, and sensation in health and disease. Major components of the ECS that have been defined in each of these functional roles are shown: CB1 and CB2 receptors, anandamide (AEA), fatty acid amide hydrolase (FAAH), and the endocannabinoid membrane transporter (EMT). For motility, the CB2 receptors only appear to be active under pathophysiological conditions and are shown italicized.

The functions of the ECS in the GI tract have yet to be fully elucidated, but there is good evidence that there is endocannabinoid "tone" in the GI tract [1, 3]. This is defined as a baseline activity of the ECS in the gut that is reduced by blocking CB receptors. Consistent with this concept, when CB1 antagonists are given to animals and humans, there is enhanced gut motility [11, 12], possibly due to some degree of enhanced secretion in the gut, and intestinal inflammation is exacerbated [11, 13]. In states of inflammation, visceral hyperalgesia is observed after treatment with a CB1 receptor antagonist, suggesting

that the ECS is able to attenuate visceral sensitivity in inflammation [14]. Under baseline conditions, the ECS is not apparently active in regulating sensitivity of the gut, since neither CB1 nor CB2 antagonists alter baseline visceral sensitivity to graded colorectal distension [14]. Some of the observations noted above with regard to CB1 receptors have been confirmed by the use of genetically modified mice lacking these receptors.

In order to raise local levels of endocannabinoids, animals have been treated with compounds that inhibit FAAH or block the activity of the putative endocannabinoid membrane transporter (EMT). Under these conditions, GI motility is reduced, consistent with an action of the ECS in limiting the extent of propulsion in the gut [6]. These effects are completely reversed by a CB1 receptor antagonist, being presumably mediated by anandamide. It is likely that they occur at the level of the enteric nervous system, but this has yet to be shown conclusively. The role of 2-AG in motor function is not yet as well established. FAAH inhibitors are capable of attenuating the degree of colitis induced by chemical agents administered intraluminally [7, 8]. Recently, it was shown that this effect was mediated by CB1 and CB2 receptors, both of which completely abolish the protective effects of specific FAAH inhibitors and EMT blockers in colitis [8]. In a similar vein, the EMT inhibitor VDM11 was shown to block the secretory effects of cholera toxin in the mouse ileum, an action effect shown to be mediated by CB1, but not CB2 receptors [15]. Of note also is a role for CB2 receptors in regulation of intestinal hypersensitivity in states of colonic irritation. Here a CB2 receptor antagonist was found to reverse the degree of analgesia induced by a strain of probiotic bacteria given to rats that had been treated with a butyrate enema as a model of irritable bowel syndrome (IBS) [16]. Further evidence for the involvement of ECS in the pathophysiology of IBS was provided when it was shown in a clinical study that single nucleotide polymorphisms of the FAAH gene were more strongly associated with some forms of IBS [17].

Priorities for Future Studies

There is considerably more work required to fully establish the roles of the specific elements of the ECS in the various organs of the gut, as well as the many functions that have been only studied to a limited extent. The role of the ECS in the regulation of secretion is not well established and whether the ECS regulates intestinal blood flow has yet to be determined. The biosynthetic enzymes of the ECS are not as well characterized as the other components of this system and are not yet described in the gut. Similarly, there are novel endocannabinoid ligands that have been discovered and which may be expressed in the gut, as may some new putative receptors of the ECS, such as GPR55. In pathophysiological states, the ECS has already been shown to play important roles as noted above, however, there are many conditions where this has yet to be examined and where it is important to do so in the near future.

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