

Cannabinoids and the Gastrointestinal Tract

Although the use of cannabinoids as antiemetics (anti-nausea) is well-established, with Dronabinol available to stimulate appetite and counter effects of cancer chemotherapy, the effect of cannabinoids on disorders of the gut has only recently been extensively studied.

The current state of knowledge of the biochemistry of cannabinoids is increasing at an exponential rate and, with discoveries of cannabinoid receptors in unexpected areas of the body, new potential research/treatment avenues are appearing at an increasing rate.

Grinspoon[i] reports anecdotal use of cannabis to control bowel movements in multiple sclerosis, and relief from the symptoms of Crohn's disease. Mikuriya[ii] records irritable bowel syndrome, as well as other inflammatory gastrointestinal conditions (principally among AIDS patients), as one of a wide variety of conditions for which cannabis has been prescribed or recommended for therapeutic use in California. Consroe et al[iii], in an anonymous survey of 112 MS patients, found a large proportion reported improvements in bowel and bladder dysfunction from smoked cannabis. There are no clinical trials currently published, although I understand GW trials of cannabis extracts on patients with bowel disorders are either under way or at an advanced stage of planning.

However, there does appear to be some scientific support for claimed therapeutic benefits, from the research literature concerning the actions and metabolism of cannabinoids and cannabinoid receptors. The wall of the intestine is composed of a type of muscle known as "smooth muscle", also found lining the walls of arteries and in other involuntary functions.

Intestinal Motility and Irritable Bowel Syndrome:

The CB1 cannabinoid receptor has specifically been found to inhibit motility of the intestine in a variety of laboratory and farm animals. The effect is specific, indicating that endogenous cannabinoids to be responsible for regulating smooth muscle tone in the intestine, and the rate of peristalsis.

Rosell et al[iv] first demonstrated that cannabinoids inhibit contractions of the small intestine in the rat. Pertwee et al[v] established the presence of cannabinoid (CB1) receptors within the guinea-pig intestine, Kazuhisa et al[vi] established the presence of enzymes which break down anandamide (the endogenous cannabinoid CB1-agonist) within the small intestine, and in rats Katayama et al[vii] also found "a high content of anandamide hydrolase in small intestine". The smooth muscle-relaxant properties of cannabinoids are so well established that preparations of guinea-pig intestine are routinely used as an in vitro screening tool to test the potency and function of novel cannabinoids[viii][ix].

Shook & Burks[x] found that THC reduced the frequency of intestinal contractions, and reduced the flow of food in the small intestine, without altering basal tone, and concluded "...delta 9-THC, delta 9,11-THC, cannabinal and nabilone (but not cannabidiol) exert an inhibitory effect on GI transit and motility in rats". Cadas et al[xi] reported that a gut enzyme (vasoactive intestinal peptide) may regulate the precursor chemical to anandamide (which activates cannabinoid CB1 receptors) and N-palmitoylethanolamine (which activates a CB2-like receptor subtype), suggesting that endogenous cannabinoids may play a role in regulating the activity of the gut.

Studying guinea-pigs & rats, Coutts et al[xii] report "Activation of cannabinoid CB(1) receptors inhibits gastrointestinal motility, propulsion, and transit, whereas selective antagonism of these receptors has the opposite effects, suggesting the presence of endocannabinoid tone." Lopez-Redondo et al[xiii] reported "cannabinoid-induced inhibition of fast cholinergic synaptic transmission occurred by reversible activation of both presynaptic and postsynaptic CB1 receptors and that slow excitatory synaptic transmission can also be reversibly depressed by cannabinoids." In mice, Pinto et al[xiv] found endogenous and exogenous CB1-receptor agonists reduced gut motility, whereas CB1 antagonists increased motility, concluding "endocannabinoids acting on myenteric CB1 receptors tonically inhibit colonic propulsion in mice." Izzo et al[xv] concluded "inflammation of the gut increases the potency of cannabinoid agonists possibly by 'up-regulating' CB(1) receptor expression; in addition, endocannabinoids, whose turnover is increased in inflamed gut, might tonically inhibit intestinal motility", finding CB2 receptor antagonists did not reverse the effect[xvi], and Mancinelli et al[xvii] concluded "cannabinoids perform a neuromodulatory role in various tracts of gastrointestinal system".

Ueda et al[xviii] established the presence of anandamide hydrolase - an enzyme which breaks down endogenous cannabinoids, in the rat, as well as other enzymes inhibiting its activity, suggesting close regulation of endocannabinoid levels in the gut. They noted "The anandamide hydrolase and synthase activities were detected in a variety of rat organs, and liver showed by far the highest activities. A high anandamide hydrolase activity was also detected in small intestine but only after the homogenate was precipitated with acetone to remove endogenous lipids inhibiting the enzyme activity."

In an in vitro study of human tissue preparations, Croci et al[xix] reported "These results provide functional evidence of the existence of prejunctional cannabinoid CB1-receptors in the human ileum longitudinal smooth muscle. Agonist activation of these receptors prevents responses to electrical field stimulation, presumably by inhibiting acetylcholine release. SR 141716 is a potent and competitive antagonist of cannabinoid CB1 receptors naturally expressed in the human gut."

Tyler et al[xx] found CB1 agonists inhibited, and CB1 antagonists increased, small intestinal secretion, concluding "cannabinoids may have therapeutic potential for diarrhea unresponsive to available therapies." However, after finding humans using cannabis produced more voluminous diarrhoea when challenged with cholera or E.Coli, Nalin et al[xxi] warned "Cannabis use may be an important factor predisposing to severe diarrhoea." Izzo et al[xxii] found SR141716A (CB1 antagonist) increased, whereas WIN 55,212-2 (CB1 agonist) decreased, defaecation,

gastrointestinal transit and fluid accumulation. Winn et al[xxiii] found "Ten new delta6a,10a-THC analogs with arylalkyl side chains... showed pharmacological activity as analgesics, tranquilizers, antihypertensives, and hypnotics and as antisecretory, antiulcer, and antidiarrheal agents."

Turker et al[xxiv] found an antihistaminic and anti-inflammatory activity of THC in intestinal tissue. Kulkarni-Narla et al[xxv] noted "Cannabis has been used for centuries in the medicinal treatment of gastrointestinal disorders. Endogenous cannabinimimetic substances such as 2-arachidonylglycerol have been isolated from gut homogenates and CB1-cannabinoid binding sites have been identified in small intestine."

Gastric Emptying & Motility:

Pertwee[xxvi] noted "Cannabinoid receptor agonists delay gastric emptying in humans as well as in rodents and probably also inhibit human gastric acid secretion", Landi et al[xxvii] suggest "primary role of peripheral cannabinoid CB(1) receptor mechanisms in gastrointestinal transit delay by specific agonists". Izzo et al[xxviii] concluded "cannabinoid agonists delay gastric emptying through activation of cannabinoid CB1 receptors, while the endogenous cannabinoid system does not seem to modulate gastric motility", whilst Krowicki et al[xxix] found "THC evoked long-lasting decreases in intragastric pressure and pyloric contractility. ... gastric motor... effects of peripherally administered delta9-THC seem to be mediated through cannabinoid CB1 receptors".

In human volunteers, Bateman[xxx] reported "Despite significant change in pulse rate and psychological parameters consistent with cannabis activity there was no significant effect on the pattern of gastric emptying. It is therefore suggested that an anti-emetic action of delta-9-tetrahydrocannabinol does not involve a change in gastric emptying",

Gastric Acid Secretion & Ulcers:

Studying the effects of cannabinoids on gastric acid secretions, Adami et al[xxxi] found "gastric antisecretory effects of cannabinoids in the rat are mediated by suppression of vagal drive to the stomach through activation of CB(1) receptors" Izzo et al[xxxii] noted "The digestive tract contains endogenous cannabinoids (anandamide and 2-arachidonylglycerol) and cannabinoid CB1 receptors can be found on myenteric and submucosal nerves. Activation of CB1 receptors inhibits gastrointestinal motility, intestinal secretion and gastric acid secretion" and conclude "The enteric location of CB1 receptors could provide new strategies for the management of gut disorders."

Corruzzi et al[xxxiii] concluded "the inhibitory effect of WIN 55,212-2 on pentagastrin-stimulated acid secretion in the anaesthetized rat is mediated by specific cannabinoid receptors. Moreover, the antagonism of WIN 55,212-2-induced effects by the selective CB1 receptor antagonists SR141716A and LY320135 together with the ineffectiveness of both the CB2 receptor agonist JWH-015 and the CB2 receptor antagonist SR144528 indicate that CB1 receptor subtypes are predominantly involved in the antisecretory effect of WIN 55,212-2". In humans, Nalin et al[xxxiv] found "smoking of cannabis greater than 2 days a week was linked with low (stomach) acid output"

Germano et al[xxxv] reported "The cannabinoid receptor agonist WIN 55,212-2... reduced gastric ulceration. The protective effect of WIN 55,212-2 was counteracted by the cannabinoid CB1 receptor antagonist SR141716A... These results indicate that the antiulcer effect of the cannabinoid receptor agonist(s) is mediated by cannabinoid CB1 receptors." De Souza[xxxvi] found acute and long-term cannabis treatment reduced the rate of gastric ulceration in rats subjected to restraint-induced stress.

Summary - Cannabinoids and the GI Tract:

While I am not aware of any published results from controlled human studies of medical use of cannabis in the treatment of conditions such as gastric ulcers or irritable bowel syndrome, there appears to be sufficient animal evidence of the potential efficacy of cannabis in reducing intestinal spasms, ulceration and gastric acid secretion to merit further research into this and related indications.

Any symptomatic relief obtained from smoking cannabis, or use via inhalers or sublingual sprays, would occur far more rapidly than with oral preparations.

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