Expert Opinion

Ashley Publications
www.ashley-pub.com

Monthly Focus: Pulmonary-Allergy, Dermatological, Gastrointestinal & Arthritis

Cannabinoids for gastrointestinal diseases: potential therapeutic applications

Giulia Di Carlo & Angelo A Izzo†
Department of Experimental Pharmacology, University of Naples Federico II, via D. Montesano 49, 80131 Naples, Italy

Δ^9-Tetrahydrocannabinol (the active ingredient of marijuana), as well as endogenous and synthetic cannabinoids, exert many biological functions by activating two types of cannabinoid receptors, CB_1 and CB_2 receptors. CB_1 receptors have been detected on enteric nerves, and pharmacological effects of their activation include gastroprotection, reduction of gastric and intestinal motility and reduction of intestinal secretion. The digestive tract also contains endogenous cannabinoids (i.e., the endocannabinoids anandamide and 2-aracidonylglycerol) and mechanisms for endocannabinoid inactivation (i.e., endocannabinoids uptake and enzymatic degradation). Cannabinoid receptors, endocannabinoids and the proteins involved in endocannabinoids inactivation are collectively referred as the 'endogenous cannabinoid system'. A pharmacological modulation of the endogenous cannabinoid system could provide new therapeutics for the treatment of a number of gastrointestinal diseases, including nausea and vomiting, gastric ulcers, irritable bowel syndrome, Crohn's disease, secretory diarrhoea, paralytic ileus and gastroesophageal reflux disease. Some cannabinoids are already in use clinically, for example, nabilone and Δ^9-tetrahydrocannabinol are used as antiemetics.

Keywords: 2-AG, ACEA, anandamide transport, anandamide, cannabinoid agonists/antagonists, cannabinoid receptors, cannabis, Crohn's disease, diarrhoea, emesis, endocannabinoids, FAAH, gastric secretion, gastric ulcer, GERD, inflammatory bowel disease, intestinal motility, intestinal secretion, intestine, irritable bowel syndrome, noladin ether, paralytic ileus, rimonabant, SR141716A, transient lower oesophageal sphincter relaxation, VDM11

Expert Opin. Investig. Drugs (2003) 12(1):39-49

1. Introduction

Cannabis has a long medical history ranging from its anecdotal use in ancient times and through medical prescribing in the nineteenth and twentieth centuries to modern, usually illicit, self-medication [1-3]. Extracts of cannabis were indicated for gastrointestinal (GI) pain, gastroenteritis and diarrhoea a century ago in the US and there are anecdotal reports suggesting that marijuana may be effective in alleviating symptoms of Crohn's disease and diabetic gastroparesis [2]. The major active constituents of the plant cannabis are a group of C_{21} monoterpenoid derivatives, named cannabinoids. Approximately 70 naturally occurring cannabinoids are known today but of these, the most important representative is Δ^9-tetrahydrocannabinol (Δ^9-THC), which has psychotropic properties and is responsible for many of the pharmacological actions of cannabis [1-3].

Molecular targets of Δ^9-THC consist of at least two types of receptors, the CB_1 and CB_2 receptors, both of which are coupled to $G_{i/o}$ proteins [4-8]. CB_1 receptors (identified pharmacologically in 1988 and cloned in 1990) [9,10] are mostly expressed by central and peripheral neurons, while CB_2 receptors (cloned in 1993) [11] are expressed mostly by immune cells. The discovery of cannabinoid receptors was followed in

 ISSN 1354-3784

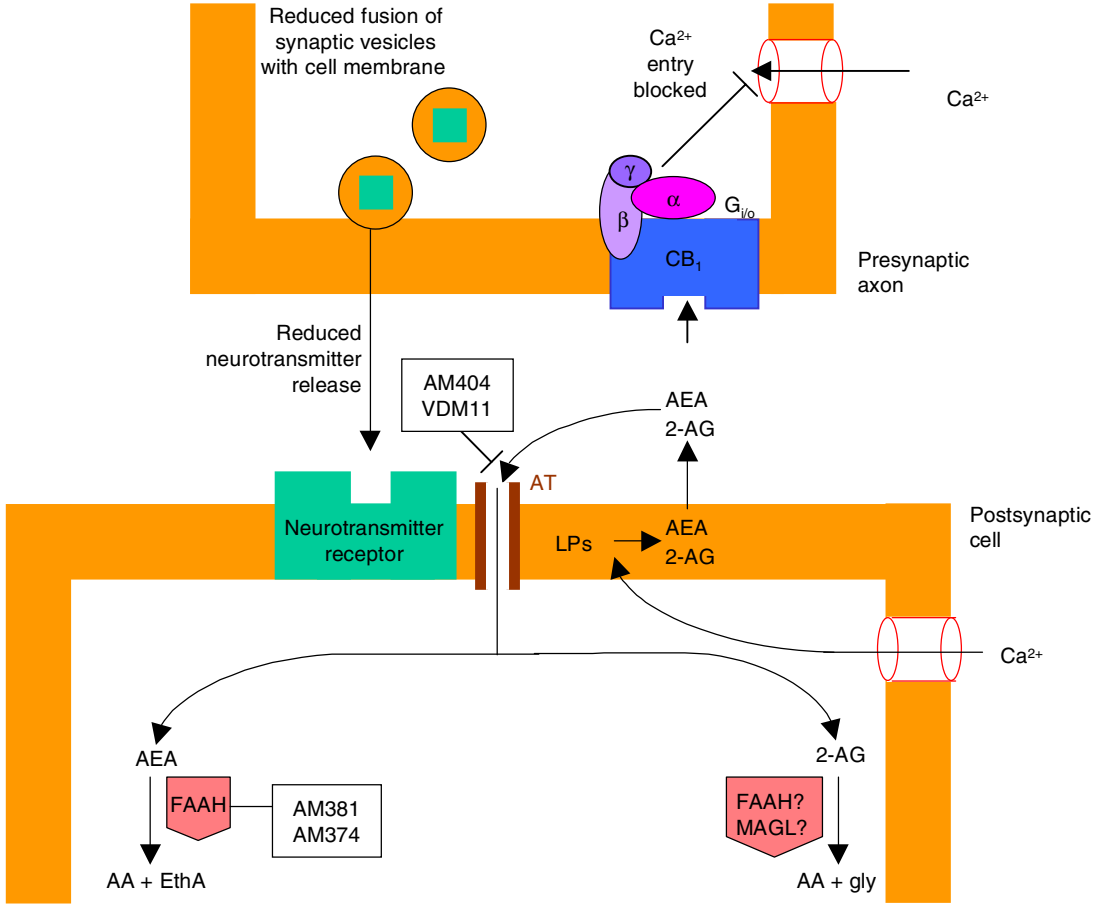

Figure 1. Retrograde signalling by endocannabinoids and their inactivation. Postsynaptic depolarisation opens voltage-dependent Ca^{2+} channels, causing an increase in the concentration of intracellular Ca^{2+}. Elevated Ca^{2+} levels promote activation of enzymes that synthesise the endocannabinoids AEA and 2-AG from membrane LPs. Once synthesised, anandamide and 2-AG leave the postsynaptic cell and activate presynaptic CB_1 receptors (which are coupled to $G_{i/o}$) leading to inhibition of Ca^{2+} influx into the presynaptic axon. The decreased Ca^{2+} levels reduce the probability of fusion of synaptic vesicles with the cell membrane of the presynaptic axon and hence neurotransmitter release into the synapse is reduced. After cannabinoid CB_1 receptor activation, anandamide and 2-AG are removed from the synaptic cleft through a carrier-mediated transport, which can by inhibited by AM404 and VDM11. Once inside the cell, anandamide may be hydrolysed to AA and EthA by a membrane-bound FAAH (also called anandamide amidohydrolase); 2-AG is metabolised to yield AA and glycerol by a MAGL and/or FAAH.

2-AG: 2-Arachidonilglycerol; AA: Arachidonic acid; AEA: Anandamide; AT: Anandamide transporter; EthA: Ethanolamine; FAAH: Fatty acid amide hydrolase; gly: Glycerol; LPs: Lipid precursors; MAGL: Monoacylglycerol lipase.

1992 by the demonstration that anandamide (arachidonyl ethanolamide) is an endogenous ligand for these receptors [12]. Other endogenous cannabinoids identified include 2-arachidonoyl glycerol (2-AG), isolated in 1995 [13,14], and noladin ether (2-arachidonyl glyceryl ether), isolated in 2001 [15]. Anandamide is also an endogenous ligand for vanilloid VR_1 receptors [16]. An endogenous compound, virodhamine (an arachidnoic acid and ethanolamine joined by an ester linkage), with antagonist activity at the CB_1 receptors and full agonistic activity at the CB_2 receptor, has been also described [17].

Endocannabinoids have been identified as retrograde signalling molecules in the brain [18-19]. The synthesis of endocannabinoids from membrane lipid precursors is triggered by calcium influx into postsynaptic cells. Endocannabinoids then leave the postsynaptic cell and activate presynaptic CB_1 receptors, resulting in inhibition of neurotransmitter release (**Figure 1**). After leaving the receptor, endocannabinoids are removed from the extracellular space by a carrier (anandamide membrane transporter, [AMT])-mediated, saturable uptake process [20,21]. Within the cell, anandamide is hydrolysed to arachidonic acid and ethanolamine by fatty acid amide hydrolase (FAAH, also named anandamide amidohydrolase) [8,22]. Furthermore, FAAH can catalyse the hydrolysis of 2-AG, an indication that it has esterase as well as amidase

activity [8,22]. Cannabinoid receptors, their endogenous ligands (endocannabinoids) and the proteins participating in the inactivation of these compounds are components of the so-called 'endogenous cannabinoid system'.

Although pharmacological manipulation of the endogenous cannabinoid system could have potential therapeutic applications in the treatment of pain, neurodegenerative and musculoskeletal disorders, obesity, liver cirrhosis, glaucoma, inflammation and cancer [3], this review will deal with the potential therapeutic applications of cannabinoids in GI disorders. Detailed reviews on the GI physiology and pharmacology of cannabinoids have recently been published [23-25].

2. The endogenous cannabinoid system in the gastrointestinal tract

The densities of CB_1 receptors in peripheral tissues are lower than those found in areas of the brain, such as the cerebellum or cerebral cortex. This is because some peripheral tissues may contain high concentrations of CB_1 receptors localised in discrete regions, such as nerve terminals, but which form only a small part of the total tissue mass [23-25]. Immunohistochemical studies have shown the presence of CB_1 receptors on enteric nerves of various animal species, including mice, rats, guinea-pigs and pigs [26-31]. CB_1 immunoreactivity is highly co-localised with immunoreactivity for choline acetyltransferase (ChAT; a cholinergic marker) in neurons and fibres of the myenteric and submucosal plexus of the stomach, small intestine and colon. This association of CB_1 receptors with cholinergic neurons supports functional studies which have described the inhibitory (CB_1-mediated) effects of cannabinoid agonists on intestinal motility (via suppression of acetylcholine release from myenteric nerves) and acid gastric and intestinal secretion (presumably via suppression of acetylcholine release from submucosal plexus neurons) [28-31]. CB_1 is occasionally associated with substance P immunoreactive intestinal neurons but not with nitric oxide synthase (NOS)-immunoreactive neurons or fibres [28-31]. CB_1 immunoreactive neurons were found in close proximity to ileal Peyer's patches and were localised in some submucosal blood vessels [30]. This pattern of distribution is consistent with the well-documented actions of cannabinoid in suppressing systemic immune function and producing vasorelaxation.

The first evidence regarding the presence of endocannabonoids in the GI tract was given by Mechoulam and colleagues [13], who detected 2-AG, but not anandamide in the canine small intestine. More recently, high amounts of both anandamide and 2-AG (compatible with a tonic activation of CB_1 receptors) have been detected in the mouse small intestine and colon [28,32]. Consistently, the CB_1 receptor antagonist SR141716A, administered alone, has an effect on intestinal motility and secretion which is opposite to that of the cannabinoid agonists [23-25]. Other molecular targets for anandamide in the gut are the vanilloid VR_1 receptors, potentially resulting in stimulation of intestinal motility [33] and a non-CB_1, non-CB_2 site, through which anandamide or the cannabinoid receptor agonist WIN 55,212-2 can inhibit GI motility [33-34]. The third endocannabinoid noladin ether, which selectively activates CB_1 receptors, has so far not been detected in the gut.

There is also evidence for the presence of anandamide transport and metabolising mechanisms in rodent gut [22]. The presence of FAAH has been demonstrated in the rat [35] and mouse intestine [28,29,32] and functional studies indicate that the nonspecific FAAH inhibitor phenylmethylsulfonyl fluoride (PMFS) markedly increased anandamide-induced reduction in motility *in vitro* [36]. In addition, the anandamide transport inhibitor VDM11, administered alone, decreased mouse colonic motility *in vivo*, which is consistent with a functional role of anandamide transport in terminating the biological actions of anandamide in the colon [28].

3. Cannabinoid drugs

Three main classes of cannabinoid drugs exist:

- cannabinoid receptor agonists
- inhibitors of endocannabinoids inactivation (indirect agonists)
- cannabinoid receptor antagonists

More comprehensive analysis on cannabinoid ligands can be found elsewhere [5,6,37,38].

3.1 Cannabinoid receptor agonists

Cannabinoid receptor agonists are usually classified by chemical structure into four main groups: classical; non-classical; aminoalkylindoles and eicosanoids [3,5,37] (**Figure 2**).

The classical cannabinoids are dibenzopyrane derivatives that include plant-derived cannabinoids and synthetic analogues of these compounds. Of these, Δ^9-THC, Δ^8-THC and cannabinol are constituents of marijuana, whereas HU-210 (11-hydroxy-Δ^8-THC-demethylheptyl) is a synthetic cannabinoid. Δ^9-THC and Δ^8-THC bind both CB_1 and CB_2 receptors at submicromolar concentrations and behave as partial agonists at CB_1 receptors; cannabinol is a weaker cannabinoid receptor agonist [5,37]. The synthetic analogue HU-210 binds CB_1 and CB_2 receptors at subnanomolar concentration and its pharmacological effects *in vivo* are exceptionally long lasting [5].

The second, non-classical group, developed by Pfizer, consists of bicyclic and tricyclic analogues of Δ^9-THC that lack a pyran ring [3]. The most utilised compound of this group, CP55,940, binds to CB_1 and CB_2 receptors with similar affinity, as well as displaying high activity *in vivo*, being 10 – 50 times more potent than Δ^9-THC in the mouse tetrad model (a well know bioassay system for cannabinoid activity) [5,37]. CP55,940 behaves as a full agonist for both receptor types. Its maximal effects in CB_1 and CB_2 receptor assay systems often match or exceed the maximal effects of several other cannabinoid agonists [5,6].

The third group, developed by Sterling-Winthrop, is given by aminoakyllindoles which are structurally different from

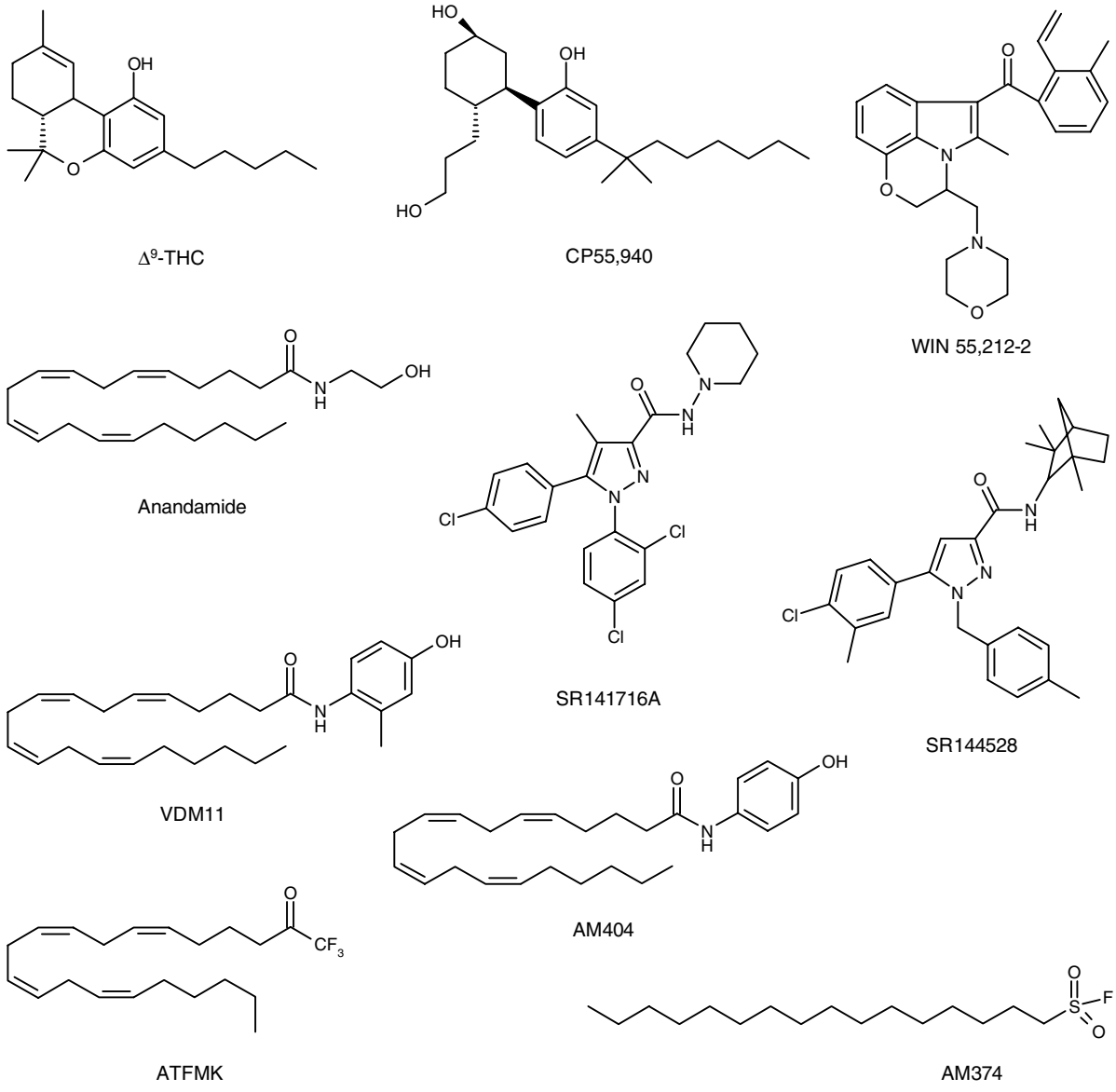

Figure 2. Chemical structures of the main cannabinoid drugs. Δ^9-THC, CP55,940, WIN 55,212-2 and anandamide are non-selective cannabinoid receptor agonists. Δ^9-THC is a classical cannabinoid, CP55,940 is a non-classical cannabinoid, WIN 55,212-2 is an aminoalkylindoles derivative and anandamide is a member of the eicosanoid group. VDM11 and AM404 are inhibitors of anandamide transport (anandamide re-uptake) and ATFMK and AM374 are FAAH (anandamide amidohydrolase) inhibitors.
ATFMK: Arachidonyltrifluoromethyl-ketone; FAAH: Fatty acid amide hydrolase; THC: Tetrahydrocannabinol.

members of the first two groups [3,5]. WIN 55,212-2 is the most highly studied, commercially available compound of the series. It displays high affinity for both cannabinoid receptors, with moderate selectivity in favour of the CB_2 receptors. Some of the new aminoalkylindoles (e.g., JWH-015) have been found to display significant selectivity for the CB_2 receptor [5,6,37].

The eicosanoids group contains several arachidnoic acid derivatives (animal-derived cannabinoids and their analogues) and the prototypic member of this family is the endogenous ligand anandamide, which belongs to the 20:4, n = 6 series of fatty acid amides [5-7]. Anandamide resembles Δ^9-THC in behaving as a partial agonist at CB_1 receptors and in exhibiting less relative intrinsic activity at CB_2 than CB_1 receptors [5,35]. Structural modification of the anandamide molecule has led to the development of the first generation of CB_1-selective agonists. Notable examples are methanandamide, arachidonyl-2′-chloroethylamide (ACEA) and arachidonylcyclopropylamide (ACPA). In contrast to methanandamide, ACEA and ACPA do not show any sign of reduced susceptibility to enzymatic hydrolysis by FAAH, presumably because they lack a methyl substituent [5,6]. The second endogenous cannabinoid,

2-AG, is an agonist for both CB_1 and CB_2 receptors and exhibits higher relative intrinsic activity than anandamide at both CB_1 and CB_2 receptors [6,7,38]. Like anandamide, 2-AG has marginally higher affinity for CB_1 than CB_2 receptors [6,7]. Few pharmacological experiments have been performed with noladin ether, the third endocannabinoid. These have generated data indicating that in contrast to anandamide and 2-AG, noladin ether has much higher affinity for CB_1 receptors than for CB_2 receptors [15].

3.2 Inhibitors of anandamide inactivation

Cannabinoid receptors can be activated indirectly by drugs which, by inhibiting endocannabinoids inactivation, can increase the concentration of endocannabinoids at cannabinoid receptors. Although the indirect activation of cannabinoid receptors is expected to be more selective than direct receptor agonists, as it would produce effects only at sites where ongoing production of endocannabinoids is taking place, this approach has generally not been favoured to date [8].

AM404 and VDM11 are two inhibitors of anandamide transport [8,20,39,40] (**Figure 2**). AM404 has been reported to inhibit anandamide transport by rat cultured cortical neurons (effector concentration for half-maximum response [EC_{50}] = 1 µM) and astrocytes (EC_{50} = 5 µM), to potentiate anandamide both *in vitro* and *in vivo* and to exert some cannabimimetic effects (e.g., decrease in locomotor activity and amelioration in spasticity in mice) when administered alone [8,39]. AM404 elevates the levels of circulating anandamide and its direct interaction with cannabinoid receptors is poor [39]. VDM11 exhibits the same potency as AM404, but exhibits markedly lower efficacy than AM404 at vanilloid receptors [40]. Notably, VDM11, when administered alone, reduces motility in the colon, an effect prevented by the CB_1 receptor antagonist SR141716A [38].

FAAH is blocked reversibly by anandamide analogues, such as arachidnonyltrifluoromethyl-ketone (ATFMK, half-maximal inhibitory concentration [IC_{50}] = 700 nM), and irreversibly by a variety of compounds including palmitylsulfonyl fluoride (AM374, IC_{50} = 7 nM) and stearylsulfonyl fluoride (AM381, IC_{50} = 4 nM) [8,19,40]. FAAH inhibitors share the ability of anandamide transport inhibitors to potentiate some anandamide responses and to produce, in some bioassays, anandamide-like effects when administrated alone [8,40].

3.3 Cannabinoid receptor antagonists

Studies from Sanofi Recherché elucitated two cannabinoid receptor antagonist, SR141716A (rimonabant) and SR144528, which are potent and selective antagonists for the CB_1 and CB_2 receptors, respectively [5-6]. There are many reports indicating that, by itself, SR141716A can act on CB_1 receptors, including those in the gut, to produce effects that are opposite to those produced by cannabinoid receptor agonists. These effects are not unequivocally attributable to displacement of endocannabinoids, as SR141716A behaves as an inverse agonist at the human cannabinoid CB_1 receptors [4-6]. SR141716A is not commercially available. However, it is possible to purchase two structural analogues of SR141716A, AM251 and AM281, which have been found to be three and eight times less potent than SR141716A, respectively [5,6].

4. Potential therapeutic applications

4.1 Emesis

In the early 1970s, a number of anecdotal reports from young cancer patients suggested that smoking marijuana could alleviate the nausea and vomiting caused by chemotherapeutic agents. Since then, both government- and industry-sponsored clinical trials with synthetic cannabinoids, as well as smoked marijuana, provided proof of their effectiveness as antiemetic agents [4]. The synthetic cannabinoid nabilone, developed by Eli Lilly, and dronabinol (Δ9-THC) are available by prescription in some countries as antiemetics for coadministration with cancer chemotherapeutic agents [1,4]. Nabilone has also been shown to be useful in treating nausea and vomiting associated with anaesthesia after abdominal surgery, as well as radiation therapy [4], although the effect seems to be less pronounced [1].

Evidence from a recent systematic review (30 randomised comparisons of cannabinoids with placebo or antiemetics with a total of 1336 patients) shows that oral nabilone and dronabinol and intramuscolar levonantradol (a synthetic cannabinoid) are slightly superior to conventional antiemetics (such as prochlorperazine or metoclopramide) for treating chemotherapy-induced emesis [41]. Side effects are common with cannabinoids and although some may be potentially beneficial (euphoria, 'high', sedation), others are harmful (dysphoria, depression, hallucinations). Nevertheless, many patients have a strong preference for cannabinoids [41].

Though cannabinoids appear to be a more efficacious class of antiemetics than dopamine D2 receptor antagonists for the prevention of chemotherapy-induced vomiting, the efficacy of tested cannabinoids to date does not appear to be as high as the more potent antiemetics, such as the selective 5-HT_3 receptor antagonists [42]. However, one interesting advantage of cannabinoids is that many of the patients who are protected from the acute phase of emesis also respond well during the delayed phase of chemotherapy-induced emesis, which 5-HT_3 receptor antagonists poorly control [43].

Unlike the relatively large body of clinical reports, only a few published animal studies on the antiemetic effects of cannabinoids are available. These indicate that the antiemetic activity of cannabinoids is mediated by the CB_1 receptor and that the endogenous cannabinoid system may play an important regulatory role in emesis [43-46]. Van Sickle and colleagues [46] have recently shown that the cannabinoid receptor agonists Δ^9-THC, WIN 55,212-2 and methanandamide, reduced morphine-induced emesis in ferrets and their action was reversed by the selective CB_1 receptor antagonist AM251. CB_1 receptors and FAAH were localised in the dorsal vagal complex, consisting of the area postrema, the nucleus of the solitary tract and

Table 1. Potency (ED_{50}) of cannabinoid receptor agonists in reducing electrically-induced contractions in the guinea-pig ileum, upper gastrointestinal transit and colonic motility in the mouse *in vivo* (intraperitoneal administration).

Cannabinoid	Guinea-pig ileum IC_{50} (95 confidence limits) (nM)	Mouse colon ED_{50} ± s.e.m (mg/kg)	Mouse UGT ED_{50} ± s.e.m (mg/kg)	Ref.
Anandamide	8823*	4.73 ± 0.59	4.24 ± 0.51	[28,48,62]
WIN 55,212-2	5.54 (4.35 – 7.08)	0.375 ± 0.04	0.262 ± 0.035	[28,49,63]
ACEA	Not studied	0.174 ± 0.03	0.203 ± 0.024	[28]
Cannabinol	3913 (2902 – 5278)	11.203 ± 1.124	7.784 ± 0.853	[6,28,49]
Δ^9-THC	214 (125 – 368)	Not studied	1.3 ± 0.8‡	[49,78]
CP55,940	3.46 (2.3 – 5.21)	Not studied	0.047 ± 0.0051§	[46,64]

*The IC_{50} was 289 nM in the presence of a FAAH inhibitor; confidence limits not reported in the original paper. ‡After i.v. administration. §Data refer to the rat.
ED_{50}: Effective dose for half-maximum response; IC_{50}: Half-maximal inhibitory concentration; UGT: Upper gastrointestinal transit.

the dorsal motor nucleus of the vagus in the brainstem. Given alone, the cannabinoid receptor antagonsits AM251 potentiated vomiting in response to an emetic stimulus in ferrets [46], while SR141716A, another CB_1 receptor antagonist, caused emesis in shrews [43]. On the basis of these data it has been hypothesised that cannabinoids act centrally to inhibit emesis, although it is possible that this central site might exist outside the blood–brain barrier (BBB). The undesirable psychoactive effects of Δ^9-THC could be avoided by targeting Δ^9-THC analogues to central sites, such as the area postrema and nucleus of the solitary tract that lie outside of the BBB.

4.2 Irritable bowel syndrome

Irritable bowel syndrome (IBS) is the most common condition that a physician faces in the GI clinic. It is a functional bowel disorder associated with abdominal discomfort or pain and altered bowel habits. Abnormal intestinal motility, including increased contractility and accelerated transit, is often associated with many IBS symptoms. Hence, antispasmodics (e.g., anticholinergic agents) and drugs that decrease intestinal transit (e.g., the opioid loperamide) are currently used in the treatment of IBS [47].

Cannabinoid receptor agonists affect isolated intestinal segments in a manner that resembles the action of μ opioid receptor agonists [24], Thus, a number of cannabinoid receptor agonists (via CB_1 activation) have been shown to reduce or inhibit excitatory transmission, neural acetylcholine release and peristalsis efficiency in isolated intestinal segments [48-52]. A functional evidence for the presence of prejunctional CB_1 in the human isolated ileum and colon, through which the cannabinoid receptor agonist WIN 55,212-2 inhibited electrically-evoked contractile responses, has also been demonstrated [53-54].

Consistent with these *in vitro* studies, cannabinoid receptor agonists reduce gastric [55-57], small intestinal [57-64] and colonic [28] motility in rodents (**Table 1**), an effect which is due, at least in part, to activation of peripheral (enteric) CB_1 receptors [28,57,63]. Notably, McCallum and colleagues have found Δ^9-THC to delay gastric emptying in humans [65].

A recent study [28] reports strong evidence for the existence of a local endocannabinoid tone controlling propulsion in the mouse colon *in vivo*. The evidence is based on the findings that:

- unusually high amounts of endocannabinoids are present in the mouse colon
- a stimulatory action on colonic propulsion occurs after selective blockade of CB_1 receptors with SR141716A
- an inhibitory effect on colonic propulsion occurs after inhibition of endocannabinoid re-uptake with VDM11

These findings open the way to use of non-psychotropic drugs that activate enteric CB_1 receptors or selectively reduce endocannabinoid inactivation for the treatment of the motility disorders associated with IBS.

4.3 Crohn's disease

Crohn's disease is an inflammatory bowel disease typically confined to the lower end of the small intestine. Inflammation from Crohn's disease can cause ulcers, bleeding and scar formation that may lead to intestinal blockage. As a result, patients suffer intestinal cramps and spasm, nausea and vomiting, loss of appetite and weight, severe diarrhoea and rectal bleeding [66]. Therapeutic strategies other than those directed at the underlying inflammatory process need to be considered for certain patients. Some people display improvement with primary therapy and generally feel well but continue to have chronic diarrhoea. In this situation, the use of a nonspecific antidiarrhoeal (e.g., loperamide) agent may be beneficial [66].

Although no specific studies exist examining the effects of cannabis in Crohn's disease, many patients anecdotally report that they experience relief from smoking marijuana. This is not surprising since the ability of cannabis to stimulate appetite, alleviate nausea and control spasms, and potentially reduce inflammation is well documented [2,3].

Croton oil is a well know intestinal irritant used experimentally to induce inflammation in the mouse small intestine. This inflammation is characterised by disruption of the mucosa and an infiltration of lymphocytes into the submu-

cosa. This experimental model of inflammation is associated with an increased CB_1 receptor expression in the small intestine [32]. Consistently, cannabinoid receptor agonists (i.e., CP55,940 and cannabinol) were more potent in reducing intestinal motility in inflamed mice than in control mice [32]. The low doses of cannabinoid agonists that are needed to reduce motility during gut inflammation are of interest in the light of possible therapeutic applications of such compounds in inflammatory bowel diseases.

Even if there is a paucity of preclinical data dealing with the protective effect of cannabinoid drugs in inflammatory bowel diseases, some cannabinoid-based preparations are already being evaluated in clinical trials. GW Pharmaceuticals is developing a broad ratio Δ^9-THC and cannabidiol (CBD, a cannabis-derived cannabinoid which does not bind cannabinoid receptors) product (Δ^9-THC:CBD) for the potential treatment of inflammatory bowel disease. In March 2002, the broad ratio Δ^9-THC:CBD was in Phase I and the company believes the first product will be marketed in 2004. Moreover, Pharmos Company is investigating tricyclic dextrocannabinoids (dibenzopyrane derivatives), of which dexanabinol is the prototype, as a part of its non-psychotropic dextrocannabinoid platform for the potential treatment of a number of disorders, including inflammatory bowel disease. In January 2002, clinical testing of a lead compound was expected to begin later that year.

4.4 Paralytic ileus

Paralytic ileus is defined as long-lasting inhibition of GI motility in response to nociception initiated at the abdominal level. The many situations that can provoke paralytic ileus include peritonitis, trauma to the nerve supplying the gut wall during intra-abdominal surgery, decreased blood supply to the intestinal wall, spinal injury, pneumonia, pancreatitis and myocardial infarction. Patients with this disorder accumulate gas and secretions, leading to bloating, distension, emesis and visceral pain [67].

In vitro and *in vivo* studies indicate that the CB_1 receptor antagonist SR141716A increases intestinal motility in rodents [23,24]. In fact, SR141716A increases choliniergic and non-adrenergic non-cholinergic (NANC) transmission in the guinea-pig ileum [48,51], peristaltic activity in the isolated guinea-pig ileum [51] and mouse colon [28], and defaecation [60,64] and intestinal transit in the mouse small intestine [58-61] and colon [28]. These effects are probably due to the displacement of endocannabinoids rather than to the inverse agonist properties of SR141716A [25].

The authors have recently demonstrated that the impaired intestinal motility associated with the experimental ileus induced by intraperitoneal acetic acid in mice was restored by SR141716A, while it was worsened by the cellular re-uptake inhibitor VDM11 [29]. Ileus was characterised by increased intestinal levels of anandamide and by increased number and density of CB_1 receptors, compared to the small intestine of control mice [29]. These data not only suggest a causative role of the endogenous cannabinoid system in the pathogenesis of ileus, but also open the possibility for the use of selective, non-psychotropic CB_1 receptor antagonists or yet to be developed inhibitors of anandamide biosynthesis as new pharmacological tools for the clinical management of paralytic ileus.

4.5 Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a digestive disorder that affects the lower oesophageal sphincter (LES), the muscle connecting the oesophagus with the stomach [68,69]. GERD occurs when the LES is weak or relaxes inappropriately allowing gastric content to flow up into the oesophagus. Repetitive self-medication with antacids and lifestyle modifications are sensible treatment for the majority of patients with uncomplicated episodic heartburn. When this first-line therapy fails, H_2 histamine receptor antagonists (e.g., nizatidine and ranitidine) or proton pump inhibitors (e.g., omeprazole) are used [68,69]. A different approach to therapy is to increase the strength of the LES with cholinergic agonists, such as bethanechol [69].

Recent data indicate that cannabinoid agonist WIN 55,212-2 inhibits transient LES relaxation (TLESR) and gastroesophageal reflux in dogs, and this effect is counteracted by the selective CB_1 receptor antagonist SR141716A, but not by the CB_2 receptor antagonist SR144528 [70]. WIN 55,212-2 reduced the rate of TLESRs without altering their shape (duration, simultaneous oesophageal contraction). The likely site of action lies within the central pattern generator (dorsal vagal complex) thought to control TLESR, rather than along the motor pathway that determines the extent of LES relaxation.

The clinical relevance of these findings is, at this stage, speculative but potentially relevant. Cannabinoids can have beneficial effect on GERD via two different mechanisms: reduction of gastric acid secretion (see Section 4.8) and reduction of TLESR. The latter effect may be pursued using compounds not penetrating the BBB but which may have access to the dorsal vagal complex through the area postrema.

4.6 Secretory diarrhoea

Secretory diarrhoea (such as that caused by small bowel infections) arises from two basic pathophysiological mechanisms: increased active secretion and decreased absorption of water and electrolytes. In most instances, both processes are simultaneously affected; the resulting net secretion causes the increase in stool volume and weight [71]. Decreased transit time and abnormal motor activity are invariably found in patients with diarrhoea, but they are rarely primary causes [71].

Cannabis extracts have been used for more than a century in the US for the treatment of diarrhoea [2]. Apart from their exaggerated inhibitory effect on motility during diarrhoea [63], cannabinoids may reduce secretory diarrhoea by reducing intestinal secretion or promoting intestinal absorption. Using an enteropooling method, it has been demonstrated that the cannabinoid agonist WIN 55,212-2 decreased basal fluid accumulation in the rat small intestine and this effect was counteracted by the CB_1 receptor antagonist

SR141716A [60]. Activation of CB_1 receptors in isolated rat intestinal sheets consistently produces an antisecretory effect through a neural mechanism, which in all likelihood, involves the inhibition of acetylcholine release from neurons of the submucosal plexus [72]. Thus, cannabinoids can play a neuromodulatory role in the small intestinal mucosal transport function and may prove to be an alternative therapeutic approach for the treatment of secretory diarrhoea that is unresponsive to currently available therapies.

4.7 Gastric ulcer

The gastric antisecretory and antiulcer activity of cannabis and its main active ingredient Δ^9-THC was first observed in the late 1970s, before the discovery of cannabinoid receptors and endocannabinoids [73]. It was found that the Δ^9-THC reduced gastric juice volume and ulcer formation associated with the ligation of the pylorus in the rat (Shay rat test). In recent years, the gastric acid antisecretory effect of cannabinoids has been related to their ability to activate CB_1 receptors located on pre- and postganglionic cholinergic pathways [26,74]. Indeed, it has been demonstrated that the non-selective cannabinoid agonists WIN 55-212-2 and HU-210 markedly inhibited (in a SR141716A-sensitive manner) gastric acid secretion induced by indirectly acting secretagogues, such as 2-deoxy-D-glucose (which stimulated acid secretion by increasing the efferent activity of the vagus nerve) and pentagastrin (which acts in part through a cholinergic pathway) in anaesthetised rats without affecting the secretion induced by histamine (which stimulates secretion by activating histamine H_2 receptors located on parietal cells) [26]. WIN 55,212-2 consistently reduced stress-induced gastric ulcers in rats in a SR141716A-sensitive manner [75]. In view of these findings, it is noteworthy that Nalin and colleagues [76] found a link between the self-reported heavy smoking of cannabis by 90 human subjects (more than 2 days per week) and low gastric acid output. Finally, it should be noted that cannabinoids possess analgesic, anti-inflammatory and antiulcer activities, which could be of particular therapeutic importance given the ulcerogenic effects of many of the anti-inflammatory drugs, such as aspirin, used in modern medicine.

5. Expert opinion

There is anecdotal evidence for the therapeutic benefit of cannabinoids in a variety of human disease conditions, that spans over many centuries. Recently, however, in-depth research efforts have begun to document the biological mechanism involved. In addition, it is becoming clear that a pharmacological manipulation of the endogenous cannabinoid system could have important therapeutic applications, including for the pathologies of the digestive system.

The future should involve the study of strategies for reducing or abolishing the adverse effect of cannabinoid agonists without attenuating their beneficial clinical effects. The unwanted central effects of cannabinoid agonists are probably mediated largely (although not exclusively) by CB_1 receptors in the brain. These include sedation, cognitive dysfunction, ataxia and immunosuppressant effects, as well as psychotropic effects. The side-effect profile of cannabinoid antagonists is less understood. There are different possible strategies for minimising the unwanted side effects. The first being the design of selective CB_1 receptor agonists that do not readily cross the blood barrier (in a manner similar to the antidiarrhoeal opiate loperamide), as a drug of this kind might be able to reduce intestinal motility and secretion by acting on the CB_1 receptors located on enteric nerves. The second strategy would be to adopt the approach often used for the management of depression: drugs that block endocannabinoids inactivation should magnify their physiological effects in the same way as serotonin re-uptake or monoamine oxidase (MAO) inhibitors heighten the mood-regulating actions of endogenous biogenic amines. Indirect activation of cannabinoid receptors is expected to be more advantageous than direct-acting cannabinoid receptor drugs, because inhibitors of anandamide inactivation are unlikely to affect endocannabinoid levels at one time, producing instead effects only at sites where ongoing production of endocannabinoids is taking place. If the released endocannabinoids participate in the modulation of specific gut disease, it is likely that this strategy will be successful. This approach would also abolish the peripheral (e.g., tachycardia, hypotension) side effects associated with activation of peripheral CB_1 receptors.

A third strategy would be to focus on non-CB_1-mediated effects, as there is evidence from *in vitro* studies that anandamide [33] and WIN 55,212-2 [34] exert inhibitory effects on intestinal and gastric motility, respectively, via activation of non-CB_1, non-CB_2 receptors. This strategy is more promising because it is likely devoid of psychotropic effects. However, to validate such an approach, this mechanism needs to be fully elucidated.

Finally, animal studies suggest that the cannabimimetic substance palmitoylethanolamide (a fatty acid ethanolamide coreleased with anandamide from nerves) possesses anti-inflammatory and antimotility actions which are not mediated by cannabinoid receptor activation [77]. These effects open up the possibility that this compound, which, unlike anandamide, has weak psychotropic effects, can be used as a possible therapeutic drug for the treatment of intestinal hypermotility during inflammatory bowel diseases.

Acknowledgements

Supported by Cofinanziamento MURST. The authors wish to thank SESIRCA (Regione Campania) and Enrico and Enrica Sovena Foundation (Rome, Italy).

Bibliography

Papers of special note have been highlighted as (•).

1. WILLIAMSON EM, EVANS FJ: Cannabinoids in clinical practice. *Drugs* (2000) **60**:1303-1314.
2. GRINSPOON L, BAKALAR JB: *Marihuana - the Forbidden Medicine*. Yale University Press, New Haven, CT, USA (1997).
3. NOCERINO E, AMATO M, IZZO AA: Cannabis and cannabinoid receptors. *Fitoterapia* (2000) **71**:S6-S12.
4. PORTER AC, FELDER CC: The endocannabinoid nervous system: unique opportunities for therapeutic intervention. *Pharmacol. Ther.* (2001) **90**:45-60.
5. PERTWEE RG, ROSS RA: Cannabinoid receptors and their ligands. *Prostaglandins Leucotr. Essent. Fatty Acids* (2002) **66**:101-121.
6. HOWLETT AC, BARTH F, BONNER TJ *et al.*: International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol. Rev.* (2002) **54**:161-202.

• **This review summarises the main features of the structure, pharmacology and function of cannabinoid receptors that provide the basis for the classification of these receptors.**

7. MECHOULAM R: Discovery of endocannabinoids and some random thoughts on their possible roles in neuroprotection and aggression. *Prostaglandins Leucotr. Essent. Fatty Acids* (2002) **66**:93-99.
8. GIUFFRIDA A, BELTRAMO B, PIOMELLI D: Mechanisms of endocannabinoid inactivation: biochemistry and pharmacology. *J. Pharmacol. Exp. Ther.* (2001) **298**:7-14.
9. DEVANE WA, DYSARZ FAI, JOHNSON MR, MELVIN LS, HOWLETT AC: Determination and characterization of a cannabinoid receptor in rat brain. *Mol. Pharmacol.* (1988) **34**:605-613.
10. MATSUDA LA, LOLAIT SJ, BROWNSTEIN BJ, YOUG AC, BONNER TL: Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* (1990) **346**:561-564.
11. MUNRO S, THOMAS KL, ABU-SHAAR M: Molecular characterization of a peripheral receptor for cannabinoids. *Nature* (1993) **365**:61-65.
12. DEVANE WA, HANUS L, BREUER A *et al.*: Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* (1992) **258**:1946-1949.
13. MECHOULAM R, BEN-SHABAT S, HANUS L *et al.*: Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to a cannabinoid receptor. *Biochem. Pharmacol.* (1995) **50**:83-90.
14. SUGIURA T, KONDO S, SUKAGAWA A *et al.*: 2-arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem. Biophys. Res. Commun.* (1995) **215**:89-97.
15. HANUS L, ABU-LAFI S, FRIDE E *et al.*: 2-Arachidonyl glyceryl ether, an endogenous agonists of the cannabinoid CB_1 receptor. *Proc. Natl. Acad. Sci. USA* (2001) **98**:3662-3665.
16. ZYGMUNT PM, PETERSSON J, ANDERSSON DA *et al.*: Vanilloid receptors on sensory nerves mediate the vasodilatator action of anandamide. *Nature* (1999) **400**:452-457.
17. PORTER AC, SAUER JM, KNIERMAN MD *et al.*: Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB_1 receptor. *J. Pharmacol. Exp. Ther.* (2002) **301**:1020-1024.
18. WILSON RI, NICOLL RA: Endocannainoid signaling in the brain. *Science* (2002) **296**:678-682.

• **This review discusses the notion that endogenous cannabinoids can function as retrograde synaptic messengers and affect memory, cognition and pain perception by means of this cellular mechanism.**

19. ELPHICK MR, EGERTOVA M: The neurobiology and evolution of cannabinoid signalling. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* (2001) **356**:381-408.
20. FOWLER CJ, JACOBSSON SOP: Cellular transport of anandamide, 2-arachidonoylglycerol and palmitoylethanolamide – targets for drug development? *Prostaglandins Leucotr. Essent. Fatty Acids* (2002) **66**:193-200.
21. SUGIURA T, KOBAYASHI Y, OKA S, WAKU K: Biosynthesis and degradation of anandamide and 2-arachidonylglycerol and their possible physiological significance. *Prostaglandins Leucotr. Essent. Fatty Acids* (2002) **66**:173-192
22. DEUTSCH DG, UEDA N, YAMAMOTO S: The fatty acid amide hydrolase (FAAH). *Prostaglandins Leucotr. Essent. Fatty Acids* (2002) **66**:201-210.
23. PERTWEE RG: Cannabinoid and the gastrointestinal tract. *Gut* (2001) **48**:859-897.
24. IZZO AA, MASCOLO N, CAPASSO F: The gastrointestinal pharmacology of cannabinoids. *Curr. Opin. Pharmacol.* (2001) **1**:597-603.
25. PINTO L, CAPASSO R, DI CARLO G, IZZO AA: Endocannabinoids and the gut. *Prostaglandins Leucotr. Essent. Fatty Acids* (2002) **66**:333-341.
26. ADAMI M, FRATI P, BERTINI S *et al.*: Gastric antisecretory role and immunohistochemical localisation of cannabinoid receptors in the rat stomach. *Br. J. Pharmacol.* (2002) **135**:1598-606.

• **Pharmacological and immuno-histochemical evidence for an acid gastric antisecretory role of CB_1 receptors.**

27. COUTTS AA, IRVING AJ, MACKIE K, PERTWEE RG, ANAVI-GOFFER S: Localisation of cannabinoid CB_1 receptor immunoreactivity in the guinea pig and rat myenteric plexus. *J. Comp. Neurol.* (2002) **448**:410-422.
28. PINTO L, IZZO AA, CASCIO MG *et al.*: Endocannabinoids as physiological regulators of colonic propulsion in mice. *Gastroenterology* (2002) **123**:227-234.

• **The paper reports the biochemical and pharmacological basis for the possible use of the uptake inhibitor VDM11 in the control of hyperactivated intestinal motility.**

29. MASCOLO N, IZZO AA, LIGRESTI A *et al.*: The endocannabinoid system and the molecular basis of paralytic ileus in mice. *FASEB J.* (2002) **16**:1973-1975.

• **The paper reports the biochemical and pharmacological basis for the possible use of non-psychotropic CB_1 antagonists in paralytic ileus.**

30. KULKARNI-NARLA A, BROWN DR: Localization of CB_1-cannabinoid receptor immunoreactivity in the porcine enteric nervous system. *Cell Tissue Res.* (2000) **302**:73-80.
31. KULKARNI-NARLA A, BROWN DR: Opioid, cannabinoid and vanilloid receptor localization on porcine cultured myenteric neurons. *Neurosc. Lett.* (2001) **308**:153-156.
32. IZZO AA, FEZZA F, CAPASSO R *et al.*: Cannabinoid CB_1-receptor mediated regulation of gastrointestinal motility in mice in a chronic model of intestinal inflammation. *Br. J. Pharmacol. (*2001) **134**:563-570.

33. MANG CF, ERBELDING D, KILBINGER H: Differential effects of anandamide on acetylcholine release in the guinea-pig ileum mediated via vanilloid and non-CB_1 cannabinoid receptors. *Br. J. Pharmacol.* (2001) **134**:161-167.

34. STORR M, GAFFAL E, SAUR D, SCHUSDZIARRA V, ALLESHER HD: Effect of cannabinoids on neural transmission in rat gastric fundus. *Can. J. Physiol. Pharmacol.* (2002) **80**:67-76.

35. KATAYAMA K, UEDA N, KURAHASHI Y, SUZUKI H, YAMAMOTO S, KATO I: Distribution of anandamide amidohydrolase in rat tissues with a special reference to small intestine. *Biochim. Biophys. Acta* (1997) **1347**:212-218.

36. PERTWEE RG, FERNANDO SR, GRIFFIN G, ABADJI V, MAKRIYANNIS A: Effect of phenylmethylsulphonyl fluoride on the potency of anandamide as an inhibitor of electrically evoked contractions in two isolated tissue preparations. *Eur. J. Pharmacol.* (1995) **272**:73-78.

37. REGGIO PH: Endocannabinoid structure-activity relationships for interaction at the cannabinoid receptors. *Prostaglandins Leucotr. Essent. Fatty Acids* (2002) **66**:161-172.

38. PERTWEE RG: Cannabinoid receptor ligands: clinical and neuropharmacological considerations relevant to future drug discovery and development. *Expert Opin. Invest. Drugs* (2000) **9**:1553-1571.

39. PIOMELLI D, GIUFFRIDA A, CALIGNANO A, RODRIGUEZ DE FONSECA F: The endocannabinoid system as a target for therapeutic drugs. *Trends Pharmacol. Sci.* (2000) **21**:218-224.

40. DE PETROCELLIS L, BISOGNO T, DAVIS JB, PERTWEE RG, DI MARZO V: Overlap between the ligand recognition properties of the anandamide transporter and the VR1 vanilloid receptor: inhibitors of anandamide uptake with negligible capsaicin-like activity. *FEBS Lett.* (2000) **483**:52-56.

41. TRAMER MR, CARROL D, CAMPBELL FA *et al.*: Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ (2001)* **323**:16-21.

- **A systematic review on the antiemetic efficacy and adverse effect of cannabis used for nausea and vomiting induced by chemotherapy.**

42. GRALLA RA: Cannabinoids and the control of chemotherapy-induced nausea and vomiting. In: *Marijuana and Medicine*. GC Nahas, KM Sutin, DJ Harvey, S Agurell (Eds), Humana Press, Totowa, NJ, USA (1999).

43. DARMANI NA: The cannabinoid CB_1 receptor antagonist SR141716A reverses the antiemetic and motor depressant actions of WIN55,212-2. *Eur. J. Pharmacol.* (2001) **430**:49-58.

44. DARMANI NA: Delta-9-tetrahydrocannabinol differentially suppresses cisplatin-induced emesis and indices of motor function via cannabinoid CB_1 receptors in the least shrew. *Pharmacol. Biochem. Behav.* (2001) **69**:239-249.

45. DARMANI NA: Delta-9-tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB_1 receptor antagonist/inverse agonist SR141716A. *Neuropsycopharmacology* (2001) **150**:200-207.

46. VAN SICKLE MD, OLAND LD, HO W *et al.*: Cannabinoids inhibit emesis through CB_1 receptors in the brainstem of the ferret. *Gastroenterology* (2001) **121**:767-774.

- **The paper reports that cannabinoids are effective antiemetics and part of an endogenous system that can modulate emesis.**

47. FARHADI A, BRUNINGA K, FIELDS J, KESHAVARZIAN A: Irritable bowel syndrome: an update on therapeutic modalities. *Expert Opin. Investig. Drugs* (2001) **10**:1211-1222.

48. PERTWEE RG, FERNANDO SR, NASH JE, COUTTS AA: Further evidence for the presence of cannabinoid CB_1 receptors in guinea-pig small intestine. *Br. J. Pharmacol.* (1996) **118**:2199-2205.

49. IZZO AA, MASCOLO N, BORRELLI F, CAPASSO F: Excitatory transmission to the circular muscle of the guinea-pig ileum: evidence for the involvement of cannabinoid CB_1 receptors. *Br. J. Pharmacol.* (1998) **124**:1363-1368.

50. HEINEMANN A, SHAHBAZIAN A, HOLZER P: Cannabinoid inhibition of guinea-pig intestinal peristalsis via inhibition of excitatory and activation of inhibitory neurla pathways. *Neuropharmacology* (1999) **38**:1289-1297.

51. IZZO AA, MASCOLO N, TONINI M, CAPASSO F: Modulation of peristalsis by cannabinoid CB_1 ligands in the isolated guinea-pig ileum. *Br. J. Pharmacol.* (2000) **129**:984-990.

52. MANCINELLI R, FABRIZI A, DEL MONACO S *et al.*: Inhibition of peristaltic activity by cannabinoids in the isolated distal colon of mouse. *Life Sci.* (2001) **69**:101-111.

53. CROCI T, MANARA L, AUREGGI G *et al.*: *In vitro* functional evidence of neuronal cannabinoid CB_1 receptors in human ileum. *Br. J. Pharmacol.* (1998) **125**:1393-1395.

54. MANARA L, CROCI T, GUAGNINI F *et al.*: Functional assessment of neuronal cannabinoid receptors in the muscular layers of human ileum and colon. *Digest. Liver Dis.* (2002) **34**:262-269.

- **The paper reports functional evidence for the presence of CB_1 receptors in the human colon.**

55. IZZO AA, MASCOLO N, CAPASSO R, GERMANÒ MP, DE PASQUALE R, CAPASSO F: Inhibitory effect of cannabinoid agonists on gastric emptying in the rat. *Naunyn-Schmiedebergs Arch. Pharmacol.* (1999) **360**:221-223.

56. KROWICKI ZK, MOERSCBAECHER JM, WINSAUER PJ, DIVAGALLI SV, HORNBY PJ: Δ^9-Tetrahydrocannainol inhibits gastric motility in the rat through cannabinoid CB_1 receptors. *Eur. J. Pharmacol.* (1999) **37**:187-196.

57. LANDI M, CROCI T, RINALDI-CARMONA M, MAFFRAND J-P, LE FUR G, MANARA L: Modulation of gastric emptying and gastrointestinal transit in rats through intestinal cannabinoid CB_1 receptors. *Eur. J. Pharmacol.* (2002) **450**:77-83.

58. CALIGNANO A, LA RANA G, MAKRIAYANNIS A, LIN SY, BELTRAMO M, PIOMELLI D: Inhibition of intestinal motility by anandamide, an endogenous cannabinoid. *Eur. J. Pharmacol.* (1997) **340**:R7-R8.

59. COLOMBO G, AGABIO R, LOBINA C, REALI R, GESSA GL: Cannabinoid modulation of intestinal propulsion in mice. *Eur. J. Pharmacol.* (1998) **344**:67-69.

60. IZZO AA, MASCOLO N, BORRELLI F, CAPASSO F: Defeacation, intestinal fluid accumulation and motility in rodents: implications of cannabinoid CB_1 ligands in the isolated guinea pig ileum. *Naunyn-Scmiedebergs Arch. Pharmacol.* (1999) **359**:65-70.

61. CARAI MAM, AGABIO R, LOBINA C *et al.:* Relationship between cannabinoid CB_1 and dopamine D2 receptors in

intestinal motility in mice. *Pharm. Pharmacol. Commun. (*2000) **6**:287-291.

62. IZZO AA, CAPASSO R, PINTO L, DI CARLO G, MASCOLO N, CAPASSO F: Effect of vanilloid drugs on gastrointestinal transit in mice. *Br. J. Pharmacol.* (2001) **132**:1411-1416.

63. IZZO AA, PINTO L, BORRELLI F, CAPASSO R, MASCOLO N, CAPASSO F. Central and peripheral cannabinoid modulation of gastrointestinal transit in physiological states or during the diarrhoea induced by croton oil. *Br. J. Pharmacol.* (2000) **129**:1627-1632.

64. IZZO AA, MASCOLO N, PINTO L, CAPASSO R, CAPASSO F: The role of cannabinoid receptors in intestinal motility, defaecation and diarrhoea in rats. *Eur. J. Pharmacol.* (1999) **384**:37-42.

65. McCALLUM RW, SOYKAN I, SRIDHAR KR, RICCI DA, LANGE RC, PLANKEY MW: Delta-9-tetrahydrocannabinol delays the gastric emptyng of solid food in humans: a double-blind, randomised study. *Aliment. Pharmacol. Ther.* (1999) **13**:77-80.

66. BITTON A, PEPPERCORN MA: Medical management of Crohn's disease. In: *Gastrointestinal Pharmacology and Therapeutics.* G Friedman, E Jacobson, R McCallum (Eds), Lippincott-Raven, Philadelphia, PA, USA (1997).

67. LIVINGSTON EH, PASSARO EP: Postoperative ileus. *Dig. Dis. Sci.* **35**:121-132.

68. KAHRILAS PJ: Gastroesophageal reflux disease. In: *Gastrointestnal Pharmacology and Therapeutics*. G Friedman, E Jacobson, R McCallum (Eds), Lippincott-Raven, Philadelphia, PA, USA (1997).

69. FASS R, OFMAN JJ: Gastroesophageal reflux disease-should we adopt a new conceptual framework? *Am. J. Gastroenterol.* (2002) **97**:1901-1909.

70. LEHMANN A, ASHLEY BLACKSHAW L, BRANDEN L *et al.*: Cannabinoid receptor agonism inhibits transient lower esophageal sphincter relaxations and reflux in dogs. *Gastroenterology* (2002) **123**:1129-1134.

- **The paper reports that cannabinoid CB_1 agonists may be effective in gastroesophageal reflux by inhibiting transient LES relaxation.**

71. CHANG EB: The pathophysiology of diarrhea and constipation. In: *Gastrointestinal Pharmacology and Therapeutics*. G Friedman, E Jacobson, R McCallum (Eds), Lippincott-Raven, Philadelphia, PA, USA (1997).

72. TYLER K, HILLARD CJ, GREENWOOD-VAN MEERVELD B: Inhibition of small intestinal secretion by cannabinoids is CB_1 receptor-mediated in rats. *Eur. J. Pharmacol.* (2000) **409**:207-211.

73. SOFIA RD, DIAMANTIS W, HARRISON JE *et al.*: Evaluation of antiulcer activity of Δ^9-tetrahydrocannabinol in Shay rat test. *Pharmacology* (1978) **17**:173-177.

74. CORUZZI G, ADAMI M, COPPELLI G, FRATI P, SOLDANI G: Inhibitory effect of the cannabinoid receptor agonist WIN 55,212-2 on pentagastrin-induced gastric acid secretion in the anaesthetised rat. *Naunyn-Schmiedebergs Arch. Pharmacol.* (1999) **360**:715-718.

75. GERMANÒ MP, D'ANGELO V, MONDELLO MR *et al.*: Cannabinoid CB_1-mediated inhibition of stress-induced gastric ulcers in rats. *Naunyn-Schmiedebergs Arch. Pharmacol.* (2001) **363**:241-244.

- **Pharmacological evidence for a protective role of CB_1 receptors in an experimental model of gastric ulcer.**

76. NALIN DR, RHEAD J, RENNELS M *et al.*: Cannabis, hypochlorhydria and cholera. *Lancet* (1978) **2**:859-862.

77. CAPASSO R, IZZO AA, FEZZA F *et al.*: Inhibitory effect of palmitoylethanolamide on intestinal motility in mice. *Br. J. Pharmacol.* (2001) **134**:945-950.

78. SHOOK JE, BURKS TF: Psychoactive cannabinoids reduce gastrointestinal propulsion and motility in rodents. *J. Pharmacol. Exp. Ther.* (1989) **249**:444-449.

Affiliation

Giulia Di Carlo & Angelo A Izzo[†]
[†]Author for correspondence
Department of Experimental Pharmacology, University of Naples Federico II, via D. Montesano 49, 80131 Naples, Italy
Tel: +39 081 678 439; Fax +39 081 678 403;
E-mail: aaizzo@unina.it