NOVEL INSIGHTS ON THE IMPLICATION OF THE CANNABINOID SYSTEM ON GASTRIC PHYSIOLOGY AND PATHOPHYSIOLOGY. THERAPEUTIC POTENTIAL IN PREVENTION OF EMESIS

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Abstract

Cannabinoid system is a relatively recently described as an endogenous component of the systems that control gastric secretion and motility. The cannabinoid system comprises two types of receptors as well as an array of mediators, whose chemical structures are highly variable. It might represent a new target for drugs used in ulcer, in gastroesophageal reflux disease or emesis (with either central or peripheral mechanisms). Preventing emesis, especially after cytotoxic treatments, could be an important clinical use of cannabinoids, but further studies are needed.

Keywords: cannabinoid system, gastric secretion and motility, emesis, tetrahydrocannabinol, nabilone.

Introduction

Although psychotropic properties and some therapeutic actions of natural cannabinoids (extracted from Cannabis sativa) are well known since thousands of years, it was only in 1964 when Ganoi and Mechoulam identified Δ9 tetrahydrocannabinol (Δ9 THC), being the main psychotropic agent from this plant [1]. It was followed by the discovery of cannabinoid receptors and endogenous cannabinoids, about twenty years later [2]. The therm "endocannabinoids" was then introduced by Di Marzo and Fontana in 1995 [3]. Various researches in this field discovered many important roles of the endocannabinoid system in central nervous system but also in periphery. The gastrointestinal cannabinoids and their array of receptors and mechanisms for synthesis and degradation might be an important part of this peripheral endocannabinoid system.

The cannabinoid receptors and endocannabinoids

The human cannabinoid receptor type 1 (CB1 receptor)

was cloned by Gerrard et al. (1991) [4]. CB1 receptors are coupled with Gi/Go proteins and are serpentine receptors. The level of cAMP is reduced as the activity of adenylyl-cyclase is diminished by the action of G protein. In the same time the activity of different channels is modulated [5].

The cannabinoid receptors type 2 (CB2 receptors) were first identified in man in 1993 [6].

CB2 receptors are coupled with Gi/Go type proteins. Unlike CB1 receptors, the CB2 ones didn't seem to be coupled to ionic channels. They are coupled with intracellular signalization pathways associated to mitogen-activated protein kinase (MAP kinase) [5].

Another two serpentine receptors, being classified among orphan receptors because when discovered there did not exist a specific ligand to bind them, are supposed to be cannabinoid receptors. These two receptors are still named GPR55 and GPR119 [7]. Another receptor for anandamide is the transient receptor potential vanilloid 1 receptor (TRPV1 receptor), the receptor for capsaicine.

Endogenous ligands for CB receptors discovered until now are eicosanoids: N-arachidonoylethanolamide (anandamide), 2-arachidonoyl glycerol, noladin ether,

O-arachidonoylethanolamine (virodhamide) and N-arachidonoyldopamine [8] and some peptides (hemopressin) [9].

Anandamide, 2-arachidonoyl glycerol, and N-arachidonoyldopamine are susceptible to degradation by fatty acid amide hydrolase (FAAH), although a second enzyme, monoacylglycerol lipase (MGL), catalyzes hydrolysis of 2-arachidonoylglycerol in vivo [8].

Numerous substances with cannabinoid properties were described, with or without selectivity to one cannabinoid receptor, with different intrinsic activity such as full or partial agonist, antagonists or inverse agonists, substances that increase the endocannabinoids level (FAAH inhibitors, cellular uptake of cannabinoids inhibitors) [10].

Some of them are presented in table I.

Anatomical and functional evidence of the presence of cannabinoid receptors in the gastrointestinal tract

Autoradiography showed the presence of CB1 receptors in the rat, and immunohistochemistry identified CB1 receptor immunoreactivity in neural plexuses in pig gastrointestinal tract. The colocalisation of CB1 receptor immunoreactivity with vasoactive intestinal peptide (non-cholinergic) and neuropeptide Y (cholinergic) secretomotorneurones in the submucous plexus were demonstrated. In the guinea-pig myenteric plexus, sensory, interneuronal and motoneuronal cell bodies and nerve fibres express of CB1 receptors.

CB1 receptor staining is present in cell bodies within the dorsal vagal complex (i.e. the area postrema, nucleus of the solitary tract).

Noxious stimuli, food deprivation, colorectal cancer increased the expression of CB1 receptors, FAAH expression/activity or the endocannabinoid levels [11].

Influence of cannabinoids on gastric secretion and motility

Gastric secretion

In rats Adami et al., 2002 showed that two cannabinoid receptor agonists HU-210 and WIN 55212-2 decreased the acid secretion induced by cholinergically mediated secretagogues, such as 2-deoxy-D-glucose, but not that induced by histamine. Bilateral cervical vagotomy and ganglionic blockade, but not atropine treatment, significantly reduced (but did not abolished) the inhibitory effect of HU-210 [12]. These data suggest a predominant location for CB1 receptors on central vagal component.

In man, CB1 receptors were found on gastric parietal cells, as cannabinoids may directly inhibit acid secretion (Pazos et al., 2008) [13].

Gastric emptying

In rats, intravenous Δ9 THC can reduce both the contractile activity of stomach and duodenum and the intragastric pressure. Δ9-THC may produce its inhibitory effects on the stomach partly by acting on the dorsal vagal complex of the brain stem to modulate vagal outflow to gastric smooth muscle. Δ9 THC may also alter gastric motility by acting directly on the vagus nerves and on the gastrointestinal myenteric plexus. The inhibitory action of CB receptor agonists was counteracted only by CB1 receptor antagonists, suggesting a selective involvement of CB1 receptors [14].

Table I. Some substances that influence the endocannabinoid system (CB1R-CB1 receptors; CB2R-CB2 receptors, FAAH- fatty acid amide hydrolase) [10].

Cannabinoid receptor agonists:		
Classical cannabinoids	Δ9 THC	partial agonist of CB1R and CB2R
Non-classical cannabinoids	CP-55,940	complete agonist of both CB1R and CB2R
Specific CB-2 receptor agonist	AM 1241	
Aminoalkylindoles	WIN-55,212-2	complete agonist of both CB1R and CB2R, slighty selective for CB2R
Eicosanoids	anandamide	partial agonist of both CB1R and CB2R and TRPV1 agonist
	R-(+)-methanandamide arachidonoyl- 2'-chloroethylamide (ACEA).	
Cannabinoid receptor antagonists/inverse agonists:		
Diarylpyrazoles	SR141716A [rimonabant]	selective CB1R blocker
	SR144528	selective CB2R blocker
Uptake blockers: AM 404		
Carbamate FAAH inhibitors: URB 597		

In man, Δ9 THC delays gastric emptying of solid food [15].

Influence of cannabinoids on lower esophageal sphincter pressure

Functional studies have shown that intravenous administration of the cannabinoid agonists WIN55 212-2 and Δ9 THC inhibited (via CB1 activation) lower esophageal sphincter relaxation in dogs, the effect being associated with inhibition of gastroesophageal reflux [16].

Transient lower oesophageal sphincter relaxations (TLESRs) are the main mechanism underlying gastro-oesophageal reflux and are a potential pharmacological target. In healthy volunteers, Δ9 THC significantly reduced the number of TLESRs and caused a non-significant reduction of acid reflux episodes in the first postprandial hour. In addition, lower oesophageal sphincter pressure and swallowing were significantly reduced by Δ9 THC [17].

Influence of cannabinoids on emesis

CB1 receptors, as well as FAAH, have been found in areas of the brain involved in emesis, including the dorsal vagal complex (area postrema and the dorsal motor nucleus of the vagus). The CB1 receptors are also present in peripheral endings of abdominal vagal efferents. Cannabinoids (nabilone, Δ9THC and levonantradol) are effective antiemetics in humans. The CB1 antagonist SR141716A caused nausea or emesis, or potentiated emetic stimuli, when given alone, suggesting a possible involvement of endocannabinoids in the emetogenic mechanism[11]. Endocannabinoids inhibit emesis through CB1, CB2 and TRPV1 receptors [18].

Because chemosensors of the area postrema are located outside the blood–brain barrier, cannabinoids that do not cross this barrier might have antiemetic actions devoid of psychotropic side effects [11].

Results of clinical studies on the therapeutic potential of cannabinoids for prevention of emesis

The benefic therapeutic effects of cannabinoids could be: analgesia, attenuation of nausea and vomiting in cancer chemotherapy, reduction of intraocular pressure, appetite stimulation in wasting syndromes, relief from muscle spasms/spasticity in multiple sclerosis and decreased intestinal motility. Adverse reactions like alterations in cognition and memory, dysphoria/euphoria, and sedation also appear [10].

Ben Amar (2006) [19]; Hazekamp and Grotenhermen (2010)[20] wrote two important reviews on the therapeutic potential of cannabinoids for prevention of emesis in properly controlled clinical trials.

The first review was a meta analysis conducted on articles written up to July 1, 2005.

Various controlled studies evaluated the antiemetic effects of nabilone and dronabinol and described their efficacy. Nabilone is a synthetic analog of Δ9 THC and dronabinol is synthetic THC. The two substances were administered orally in clinical trials.

15 controlled studies analysed the effect of nabilone as compared to a placebo or an antiemetic drug from the neuroleptic group and to domperidone on a total of 600 patients suffering from various types of cancers. Nabilone turned out to be significantly superior to prochlorperazine, domperidone and alizapride for treating nausea and vomiting associated with cancer chemotherapy. On the other hand, the patients preferred nabilone for continuous use. After these studies nabilone is marketed as oral 1 mg pulvules named Cesamet®. The recommended dosage is 2–6 mg per day.

14 controlled studies analysed the effect of dronabinol as compared to antiemetic drugs from the neuroleptic class and to metoclopramide on a total of 681 patients suffering from various types of cancers. Dronabinol proved to have an antiemetic effect equivalent to or significantly greater than chlorpromazine and equivalent to metoclopramide, thiethylperazine and haloperidol. After these studies dronabinol is marketed as capsules of 2.5, 5 and 10 mg under the name of Marinol®. The recommended dosage is 5–15 mg/m2/dose, without exceeding 4–6 doses per day.

Levonantradol, a synthetic cannabinoid administered intramuscularly, has also proved its antiemetic efficacy in a controlled study. In 108 patients suffering from various tumors, it turned out to be significantly superior to chlorpromazine to relieve nausea and vomiting related to antineoplasic chemotherapy.

Anyway, adverse central effects of these three drugs limit their utility.

The results of the three controlled studies using smoked marijuana to alleviate nausea and vomiting accompanying cancer chemotherapy were ambiguous. The treatments only turned out to be effective in 25% of the patients.

Despite the existence of many clinical trials with cannabinoids against nausea and vomiting associated with cancer chemotherapy, none (until 2005) have compared their efficacy against newer generation agents such as the 5-HT3 receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron and tropisetron) and the more recent neurokinin-1-receptor-antagonists (aprepitant).

The second review, wrote by Hazekamp and Grotenhermen (2010), used the same protocol and found one randomized controlled trial that match with their criteria for the period 2005-2009.

Delayed chemotherapy-induced nausea and vomiting (CINV), defined as nausea and vomiting occurring more than 24 hours after chemotherapy and lasting for up to 1 week, is common, with at least 50% of patients experiencing it following moderately emetogenic chemotherapy.

Meiri 2007 evaluated the efficacy of dronabinol versus ondansetron in delayed chemotherapy-induced

nausea and vomiting (nausea and vomiting occurring more than 24 hours after chemotherapy and lasting for up to 1 week). Over the course of 2-5 days after receiving chemotherapy, subjects received an increasing dose of up to 20 mg dronabinol daily, either alone, or in combination with ondansetron. Efficacy of dronabinol alone was comparable with ondansetron, and combination therapy did not provide benefit beyond that observed with either agent alone. Active treatments were well tolerated.

Conclusions

1. The cannabinoid system comprises two types of receptors as well as an array of mediators, whose chemical structures are highly variable.

2. The cannabinoid system represents a novel opportunity for researchers to influence the complex pattern of gastric secretion and motility with possible implications in the treatment of ulcer and gastroesophageal reflux disease.

3. An important clinical utility of cannabinoids could be the prevention of emesis especially after cytostatic treatments, but further studies are needed.

4. New compounds with cannabinomimetic properties but devoid of psychotropic adverse effects could be an alternative for current treatment of emesis.

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