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Gastric acid inhibitory and gastric protective effects of *Cannabis* and cannabinoids

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ABSTRACT

Cannabis sativa has long been known for its psychotropic effect. Only recently with the discovery of the cannabinoid receptors, their endogenous legends and the enzymes responsible for their synthesis and degradation, the role of this 'endocannabinoid system' in different pathophysiologic processes is beginning to be delineated. There is evidence that CB_1 receptor stimulation with synthetic cannabinoids or *Cannabis sativa* extracts rich in Δ^9-tetrahydrocannabinol inhibit gastric acid secretion in humans and experimental animals. This is specially seen when gastric acid secretion is stimulated by pentagastrin, carbachol or 2-deoxy-D-glucose. *Cannabis* and/or cannabinoids protect the gastric mucosa against noxious challenge with non-steroidal anti-inflammatory drugs, ethanol as well as against stress-induced mucosal damage. *Cannabis*/cannabinoids might protect the gastric mucosa by virtue of its antisecretory, antioxidant, anti-inflammatory, and vasodilator properties.

1. Introduction

Cannabis is the most commonly abused illicit substance worldwide. The two commonly used *Cannabis* preparations are herbal *Cannabis* or marijuana (prepared from the dried flowering tops and leaves) and hashish (consists of dried *Cannabis* resin and compressed flowers). Both are derived from the female plant of *Cannabis sativa* Linn (family *Cannabidaceae*) [1]. Research into *Cannabis* led to discovery of its active constituents or cannabinoids, a terpeno-phenol compounds; more than 70 of which have been isolated. The most studied cannabinoids are Δ^9-tetrahydrocannabinol (THC), cannabinol, cannabidiol, cannabigerol, cannabichromene, Δ^9-tetrahydrocannabivarin, cannabidivarin and others [2,3]. Δ^9-THC is the primary constituent that is responsible for the psychotropic properties of recreational *Cannabis* [4].

Cannabinoids mediate their biological effects through interaction with cannabinoid receptors, which belong to the superfamily of G protein-coupled receptors. There are at least two cannabinoid receptor subtypes: the CB_1 receptor, essentially located in the central nervous system, but also in peripheral tissues, and the CB_2 receptor, found only at the periphery especially on immune cells [5]. Most of *Cannabis* effects in the central nervous system are mediated by CB_1 receptors. These are expressed at brain areas that control movements, memory, cognition and emotion and in the spinal cord [6,7] where they mediate retrograde inhibition of neuronal activity [8].

Cannabinoid receptors can also be activated by a number of endogenous ligands, the endocannabinoids. The main endocannabinoids, arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG) are selective agonists at the CB_1 and CB_2 receptors, respectively. Both are derivatives of arachidonic acid, that are produced and released 'on demand' by cleavage of membrane lipid precursors and are hydrolysed by the fatty acid amide hydrolase anandamide or monoglyceride lipase, respectively. Other endocannabinoids are noladin ether and virodhamine [9–11]. The cannabinoid receptors, endocannabinoids as well as the enzymes responsible for their synthesis or degradation, collectively constitute the 'endocannabinoid system' [12].

Cannabis sativa has a wide-world reputation as a psychotropic drug [1]. *Cannabis* is usually smoked, but may also be eaten, mixed in cakes or cookies or drunk in a liquid infusion [13]. Only recently, did *Cannabis* and cannabinoid-based medicines come to attention as a remedy for different medical conditions. The sublingual oromucosal spray Sativex, composed of whole plant extract containing both Δ^9-THC and cannabidiol (CBD) [THC:CBD = 1:1] have recently been approved for the treatment of pain and spasticity in multiple sclerosis [14].

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Dronabinol (Marinol) and nabilone (Cesamet) are two oral formulations of a synthetic THC approved for the treatment of nausea and vomiting that complicate chemotherapy and which are refractory to conventional antiemetic therapy. These agents are also being used to improve appetite to treat weight loss associated with human immunodeficiency virus infection and cancer [15]. Medicinal *Cannabis* is also being used for a variety of medical conditions including chronic pain, depression, arthritis, and neuropathy [16–18]. The endocannabinoid system is a target for the treatment of neurodegenerative disease *e.g.*, tics in Tourette syndrome, levodopa-induced dyskinesia in Parkinson s disease and some forms of tremor and dystonia [19,20].

Cannabinoid receptors and their endogenous ligands (anandamide and 2-arachidonoyl glycerol) have been identified in the gastrointestinal tract and are involved in mediation of several gastrointestinal functions *e.g.*, relaxation of the lower oesophageal sphincter, gastric acid secretion, gastric emptying, gastrointestinal motility and fluid secretion [21,22]. Evidence thus suggests that cannabinoid-based medicines might be beneficial in a number of gastrointestinal disorders.

The aim of this review is to compile and discuss the available data pertaining to the effect of *Cannabis* and/or cannabinoids on gastric acid secretion and gastric mucosal integrity.

2. *Cannabis* and gastric acid secretion

There are no clinical studies on the effect of *Cannabis* on gastric acid secretion. In their study, however, on 90 human volunteers participating in a vaccine development programme, Nalin *et al.* 1978 [23] found that smoking *Cannabis* for more than 2 days a week was associated with low gastric acid output. On the other hand, several preclinical studies suggested inhibition of gastric acid secretion by *Cannabis* or individual cannabinoids. Thus, in rats subjected to pylorus-ligation for (2–4) h (Shay rat), the administration of an ethanolic extract of *C. sativa* raised the gastric pH. Rats treated with 0.1 and 0.3 g/kg of *Cannabis* extract for 4 h had their gastric pH raised from 2 to 4 and 4.5. In the 4 h pylorus-ligated rat, *Cannabis* 1 g/kg raised pH slightly more than 0.05 g/kg of the histamine H-2 receptor blocker ranitidine. In rats subjected to pylorus-ligation for 2 h, ranitidine was more effective than *Cannabis* (pH values were 2.2, 3.5 and 4 for control, *Cannabis* and ranitidine, respectively) [24].

The effect of long-term treatment with *Cannabis* extracts rich in Δ^9-THC on gastric acid secretion was studied in the pylorus-ligated rat model (Shay rat). Rats were treated with 5, 10 and 20 mg/kg of *Cannabis* extract (expressed as Δ^9-THC) subcutaneously for 4 weeks and then subjected to pylorus-ligation (for 4 h) with or without gastric acid stimulation (using pentagastrin, histamine or carbachol). The administration of low doses of *Cannabis i.e.* 5 or 10 mg/kg Δ^9-THC stimulated basal gastric acid output and gastric volume. The high dose of 20 mg/kg, however, had no effect on basal gastric acid secretion. The effect of *Cannabis* on stimulated gastric acid secretion was somehow different in that it inhibited gastric acid secretory responses stimulated by pentagastrin or carbachol in a dose-dependent manner. On the other hand, *Cannabis* pretreatment had no significant effect on acid output stimulated by histamine [25].

Cannabis's most active constituent Δ^9-THC is CB_1 receptor agonist [6,7]. When administered intravenously (i.v.), synthetic CB_1 receptor agonists inhibited gastric acid secretion in the anaesthetized rat preparation. Thus, WIN55, 212-2, which is a non-selective cannabinoid agonist decreased gastric acid secretion stimulated by pentagastrin (10 mg/kg, *i.v.*) in anaesthetized rats. The inhibitory effect of WIN55, 212-2 on gastric acid secretion is likely to be mediated via CB_1 receptors, since selective CB_1 receptor antagonists SR 141716A and LY320135t antagonized its action. WIN55, 212-2, however, failed to affect basal gastric acid secretion [26].

Similar data were provided by Adami *et al.* [27] who reported inhibition of pentagastrin stimulated gastric acid secretion in anaesthetized rats with lumen-perfused stomach by the non-selective cannabinoid agonists WIN55, 212-2 and HU-210. Gastric acid secretion stimulated by 2-deoxy-D-glucose (a centrally acting secretagogue which stimulates gastric acid by increasing efferent vagus activity) is inhibited by the cannabinoid agonists, thereby suggesting a centrally mediated inhibition of gastric acid secretion by these synthetic cannabinoid agonists. But in contrast to their effect on gastric acid stimulation by pentagastrin or 2-deoxy-D-glucose, the two cannabinoid agonists did not affect acid secretion stimulated by histamine. The study pointed again to a role for CB_1 receptors in inhibition of gastric acid secretion by the synthetic cannabinoids since their effect was blocked by a CB_1 but not CB_2 receptor antagonist. Moreover, vagal involvement is suggested by finding that the inhibitory effect of HU-210 on pentagastrin-induced acid secretion decreased following bilateral cervical vagotomy and ganglionic blockade with hexamethonium.

Using rat isolated parietal cells, Rivas and Garcûa [28], however, reported inhibition of gastric acid secretion stimulated by histamine after high concentration of Δ^9-THC (20 μM). Basal gastric acid secretion was unaffected.

Experiments in the isolated mouse stomach indicated the ability of CB_1 antagonism to increase gastric acid secretion. Stimulation with ouabain (an inhibitor of Na^+/K^+-ATPase) increased gastric acid secretion (by releasing acetylcholine from cholinergic nerves). The addition of the CB_1 receptor antagonist SR 141716A further increased the ouabain-stimulated acid secretion. In contrast, the cannabinoid agonist WIN55, 212-2 was without effect [29]. These data suggest a role for CB_1 receptors in inhibiting gastric acid secretion.

The above *in vivo* and *in vitro* studies thus suggest that are CB_1 receptor stimulation with synthetic cannabinoids or *C. sativa* extracts rich in Δ^9-THC inhibits gastric acid secretion. Given the data suggesting that the CB_1 agonist THC reduces transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux [30], cannabinoid-based medicines might find utility in the treatment of peptic ulcer disease including reflux oesophagitis. Interestingly, a study on the symptoms of withdrawal in human marijuana smokers reported ‘Stomach pain’ on the fourth day of abstinence among the abstinence symptoms [31]. One might thus speculate that the stomach pain was due to a rebound increase in gastric acid secretion and/or increased mucosal sensitivity.

3. The site of action of *Cannabis*

The secretion of gastric acid is controlled at different neural, hormonal and paracrine levels. The parietal cells in the gastric glands are the cells secreting and releasing hydrochloric acid. The parietal cell bears receptors for acetylcholine, histamine, and gastrin, the major stimuli for gastric acid secretion. Cholinergic stimulation is carried out by acetylcholine released from