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REVIEW

Regulation of nausea and vomiting by cannabinoids

Linda A Parker, Erin M Rock and Cheryl L Limebeer

Department of Psychology and Collaborative Neuroscience Program, University of Guelph, Guelph, Ontario, N1G 2W1, Canada

Correspondence
Linda A. Parker, Department of Psychology, University of Guelph, Guelph, ON N1G 2W1, Canada. E-mail: parkerl@uoguelph.ca

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Considerable evidence demonstrates that manipulation of the endocannabinoid system regulates nausea and vomiting in humans and other animals. The anti-emetic effect of cannabinoids has been shown across a wide variety of animals that are capable of vomiting in response to a toxic challenge. CB_1 agonism suppresses vomiting, which is reversed by CB_1 antagonism, and CB_1 inverse agonism promotes vomiting. Recently, evidence from animal experiments suggests that cannabinoids may be especially useful in treating the more difficult to control symptoms of nausea and anticipatory nausea in chemotherapy patients, which are less well controlled by the currently available conventional pharmaceutical agents. Although rats and mice are incapable of vomiting, they display a distinctive conditioned gaping response when re-exposed to cues (flavours or contexts) paired with a nauseating treatment. Cannabinoid agonists (Δ^9-THC, HU-210) and the fatty acid amide hydrolase (FAAH) inhibitor, URB-597, suppress conditioned gaping reactions (nausea) in rats as they suppress vomiting in emetic species. Inverse agonists, but not neutral antagonists, of the CB_1 receptor promote nausea, and at subthreshold doses potentiate nausea produced by other toxins (LiCl). The primary non-psychoactive compound in cannabis, cannabidiol (CBD), also suppresses nausea and vomiting within a limited dose range. The anti-nausea/anti-emetic effects of CBD may be mediated by indirect activation of somatodendritic $5\text{-}HT_{1A}$ receptors in the dorsal raphe nucleus; activation of these autoreceptors reduces the release of 5-HT in terminal forebrain regions. Preclinical research indicates that cannabinioids, including CBD, may be effective clinically for treating both nausea and vomiting produced by chemotherapy or other therapeutic treatments.

LINKED ARTICLES

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Abbreviations

2-AG, 2-arachidonolylglycerol; 5-HT, 5-hydroxytryptamine; $5\text{-}HT_3$, 5-hydroxytryptamine receptor 3; $5\text{-}HT_{1A}$, 5-hydroxytryptamine receptor 1A; 5-HTP, 5-hydroxytryptophan; 5,7-DHT, 5,7-dihydroxytryptamine; 8-OH-DPAT, 8-hydroxy-*N*,*N*-dipropyl-2-aminotetralin; Δ^9-THC, Δ^9-tetrahydrocannabinol; AN, anticipatory nausea; AP, area postrema; CB_1,cannabinoid receptor 1; CB_2, cannabinoid receptor 2; CBD, cannabidiol; DMNX, doral motor nucleus of the vagus; DRN, dorsal raphe nucleus; DVC, dorsal vagal complex; FAAH, fatty acid amide hydrolase; G_i, inhibitory G protein subunit; LiCl, lithium chloride; MAGL, monoacylglycerol-lipase; M6G, morphine-6-glucuronide; MRN, medial raphe nucleus; NADA, n-arachidonoyl-dopamine; NTS, nucleus of the solitary tract; *S. murinus*, *Suncus murinus*; TRPV1, transient receptor potential vanilloid 1

Introduction

A major advance in the control of acute emesis in chemotherapy treatment was the finding that blockade of one subtype of the 5-hydroxytryptamine (5-HT) receptor, the $5\text{-}HT_3$ receptor, could suppress the acute emetic response (retching and vomiting) induced by cisplatin in the ferret and the shrew (Costall *et al.*, 1986; Miner and Sanger, 1986; Ueno *et al.*, 1987; Matsuki *et al.*, 1988; Torii *et al.*, 1991). In clinical trials with humans, treatment with $5\text{-}HT_3$ antagonists often combined with the corticosteroid dexamethasone during the first chemotherapy treatment reduced the incidence of acute vomiting by approximately 70% (e.g. Bartlett and Koczwara, 2002; Aapro *et al.*, 2003; Ballatori and Roila, 2003; Hickok *et al.*, 2003; Andrews and Horn, 2006). However, the $5\text{-}HT_3$ antagonists are less effective at suppressing acute nausea than

they are at suppressing acute vomiting (Morrow and Dobkin, 1988; Bartlett and Koczwara, 2002; Hickok *et al.*, 2003) and they are ineffective at reducing instances of delayed (24 h later) nausea and vomiting (Morrow and Dobkin, 1988; Grelot *et al.*, 1995; Rudd *et al.*, 1996; Rudd and Naylor, 1996; Tsukada *et al.*, 2001; Hesketh *et al.*, 2003) and anticipatory (conditioned) nausea and vomiting (Nesse *et al.*, 1980; Morrow and Dobkin, 1988; Hickok *et al.*, 2003).

More recently, NK_1 receptor antagonists (e.g. aprepitant) have been developed that not only decrease acute vomiting, but also decrease delayed vomiting induced by cisplatin-based chemotherapy (Van Belle *et al.*, 2002); however, these compounds alone and in combination with 5-HT_3 antagonist/dexamethasone treatment are also much less effective in reducing nausea (e.g. Hickok *et al.*, 2003; Andrews and Horn, 2006; Slatkin, 2007), which is the symptom reported to be the most distressing to patients undergoing treatment with 5-HT_3 antagonists (deBoer-Dennert *et al.*, 1997). Considerable evidence suggests that another system that may be an effective target for treatment of chemotherapy-induced nausea, delayed nausea/vomiting and anticipatory nausea (AN)/vomiting is the endocannabinoid system (e.g. for review, Parker and Limebeer, 2008).

Anti-emetic effects of cannabinoids in human clinical trials

The cannabis plant has been used for several centuries for a number of therapeutic applications (Mechoulam, 2005), including the attenuation of nausea and vomiting. Ineffective treatment of chemotherapy-induced nausea and vomiting prompted oncologists to investigate the anti-emetic properties of cannabinoids in the late 1970s and early 1980s, before the discovery of the 5-HT_3 antagonists. The first cannabinoid agonist, nabilone (Cesamet), which is a synthetic analogue of Δ^9-THC was specifically licensed for the suppression of nausea and vomiting produced by chemotherapy. Furthermore, synthetic Δ^9-THC, dronabinol, entered the clinic as Marinol in 1985 as an anti-emetic and in 1992 as an appetite stimulant (Pertwee, 2009). In these early studies, several clinical trials compared the effectiveness of Δ^9-THC with placebo or other anti-emetic drugs. Comparisons of oral Δ^9-THC with existing anti-emetic agents generally indicated that Δ^9-THC was at least as effective as the dopamine antagonists, such as prochlorperazine (Carey *et al.*, 1983; Ungerleider *et al.*, 1984; Crawford and Buckman, 1986; Cunningham *et al.*, 1988; Tramer *et al.*, 2001; Layeeque *et al.*, 2006).

There is some evidence that cannabis-based medicines may be effective in treating the more difficult to control symptoms of nausea and delayed nausea and vomiting in children. Abrahamov *et al.* (1995) evaluated the anti-emetic effectiveness of Δ^8-THC, a close but less psychoactive relative of Δ^9-THC, in children receiving chemotherapy treatment. Two hours before the start of each cancer treatment and every six hours thereafter for 24 h, the children were given Δ^8-THC as oil drops on the tongue or in a bite of food. After a total of 480 treatments, the only side effects reported were slight irritability in two of the youngest children (3.5 and 4 years old); both acute and delayed nausea and vomiting were controlled.

Surprisingly, only one reported clinical trial (Meiri *et al.*, 2007) has compared the anti-emetic/anti-nausea effects of cannabinoids with those of the more recently developed 5-HT_3 antagonists and none has compared cannabinoids with the NK_1 antagonist, aprepitant. Meiri *et al.* (2007) compared the efficacy and tolerability of dronabinol, ondansetron or the combination for delayed chemotherapy-induced nausea and vomiting in a 5 day, double-blind, placebo-controlled study. Patients that were receiving moderately to highly emetogenic chemotherapy were all given both dexamethasone and ondansetron, with half also receiving placebo and half receiving dronabinol prechemotherapy on Day 1. On Days 2–5, they received placebo, dronabinol, ondansetron or both dronabinol and ondansetron. The results of the study indicated that the efficacy of dronabinol alone was comparable with ondansetron in the treatment of delayed nausea and vomiting, for the total response of no vomiting/retching and nausea less than 5 mm on a visual analogue scale. Rates of absence of nausea were 71% with dronabinol, 64% with ondansetron and 15% with placebo; also the dronabinol group reported the lowest nausea intensity on a visual analogue scale (10.1 mm vs. 24 mm with ondansetron and 48.4 mm with placebo). However, the combined treatment (ondansetron and dronabinol) was no more effective than either agent alone. The dose of dronabinol used in the present study was at least 50% less than in previous studies resulting in a low incidence of CNS-related adverse effects, which did not differ from the incidence in the ondansetron-treated group. Although the study was not explicitly designed to evaluate the effects of combined therapy on acute nausea and vomiting, the combined active treatment group reported less nausea and vomiting on the chemotherapy treatment day than the placebo group.

All reported clinical trials for the effectiveness of cannabinoid compounds on chemotherapy-induced nausea and vomiting have involved oral use of cannabinoids, which may be less effective than sublingual or inhaled cannabinoids, given the need to titrate the dose (Hall *et al.*, 2005). Recently, in 2005, Sativex (GW Pharmaceuticals), a combination of Δ^9-THC and the non-psychoactive plant cannabinoid, cannabidiol (CBD), was made available as a sublingual spray for the relief of neuropathic pain in patients with multiple sclerosis and in cancer patients with advanced pain (Johnson *et al.*, 2010). However, to the best of our knowledge, the effectiveness of this compound in reducing nausea and vomiting has not been evaluated. Many patients have a strong preference for smoked marijuana over the synthetic cannabinoids delivered orally (Tramer *et al.*, 2001). Several reasons for this have been suggested: (i) advantages of self-titration with the smoked marijuana; (ii) difficulty in swallowing the pills while experiencing emesis; (iii) faster speed of onset for the inhaled or injected Δ^9-THC than oral delivery; (iv) a combination of the action of other cannabinoids with THC that are found in marijuana. Although many marijuana users have claimed that smoked marijuana is a more effective anti-emetic than oral THC, no controlled studies have yet been published that evaluate this possibility.

Effects of cannabinoids on vomiting in animal models

To evaluate the anti-emetic potential of drug therapies, animal models have been developed. Since rats and mice do not vomit in response to a toxin challenge, it is necessary to use other animal models of vomiting. There is considerable evidence that cannabinoids attenuate vomiting in emetic species (reviewed in Parker *et al.*, 2005; Parker and Limebeer, 2008). Cannabinoid agonists have been shown to reduce vomiting in cats (McCarthy and Borison, 1981), pigeons (Feigenbaum *et al.*, 1989; Ferrari *et al.*, 1999), ferrets (Simoneau *et al.*, 2001; Van Sickle *et al.*, 2001; 2003; 2005), least shrews, *Cryptotis parva* (Darmani, 2001a,b,c; 2002; Darmani and Johnson, 2004; Darmani *et al.*, 2005; Ray *et al.*, 2009; Wang *et al.*, 2009) and the house musk shrew, *Suncus murinus* (Kwiatkowska *et al.*, 2004; Parker *et al.*, 2004). As well as attenuating acute vomiting produced by cisplatin, Δ^9-THC also attenuates delayed vomiting in the least shrew (Ray *et al.*, 2009).

Anti-emetic effect of cannabinoids: mechanisms of action

The mechanism of action of the suppression of nausea and vomiting produced by cannabinoids has recently been explored with the discovery of the endocannabinoid system and the development of animal models of nausea and vomiting. Recent reviews on the gastrointestinal effects of cannabinoids have concluded that cannabinoid agonists act mainly via peripheral CB_1 receptors to decrease intestinal motility (Pertwee, 2001), but may act centrally to attenuate emesis (Van Sickle *et al.*, 2001). The dorsal vagal complex (DVC) is involved in the vomiting reactions induced by either vagal gastrointestinal activation or several humoral cytotoxic agents. The DVC is considered to be the starting point of a final common pathway for the induction of emesis in vomiting species. The DVC consists of the area postrema (AP), nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus (DMNX) in the brainstem of rats, ferrets and the least shrew. CB_1 receptors, as well as the catabolic enzyme of anandamide, fatty acid amide hydroxyslase (FAAH), have been found in areas of the brain involved in emesis, including the DMNX (Van Sickle *et al.*, 2001).

CB_1 receptors in the NTS are activated by Δ^9-THC and this activation is blocked by the selective CB_1 antagonist/inverse agonists, SR-141716, known as rimonabant (Darmani *et al.*, 2005) and AM251 (Van Sickle *et al.*, 2003). In fact, at higher doses than those required to reverse the anti-emetic effects of Δ^9-THC, rimonabant produces emesis on its own in the least shrew (Darmani, 2001c) and AM-251 potentiates cisplatin-induced emesis in the ferret (Van Sickle *et al.*, 2001). Molecular markers of activation also implicate the role of central CB_1 receptors in the anti-emetic effects of Δ^9-THC. Cisplatin pretreatment results in *c-fos* expression in the DMNX, specific subnuclei of the NTS and AP, which is significantly reduced by pretreatment with Δ^9-THC (Van Sickle *et al.*, 2001; 2003). Endogenous cannabinoid ligands, such as anandamide and 2-arachidonyol glycerol (2-AG), as well as synthetic cannabinoids, such as WIN 55,212–2, also act on these receptors (Simoneau *et al.*, 2001). However, Darmani and Johnson (2004) provide evidence that both central and peripheral mechanisms contribute to the actions of Δ^9-THC against emesis produced by 5-hydroxytryptophan (5-HTP), the precursor to 5-HT in the least shrew. At lower doses, Δ^9-THC acts centrally as an anti-emetic, but at higher doses (10 mg·kg^{-1}) it acts peripherally.

Although anandamide has been reported to have anti-emetic properties in the ferret (Van Sickle *et al.*, 2001) and the least shrew (Darmani, 2002), the role of 2-AG in the regulation of nausea and vomiting is less clear. Darmani (2002) found that 2-AG (2.5–10 mg·kg^{-1}, i.p.) produces emesis in the least shrew, most likely via its downstream metabolites, because its emetic activity can be blocked by both rimonabant and the the COX inhibitor, indomethacin. An evaluation of changes in endocannabinoid levels elicited by cisplatin revealed that cisplatin increased levels of 2-AG in the brainstem, but decreased intestinal levels of both 2-AG and anandamide (Darmani *et al.*, 2005). Darmani *et al.* (2005) suggested that the central elevation of 2-AG may contribute to the emetic potential of cisplatin (in addition to mobilizing the release of known emetic stimuli such as 5-HT, dopamine and substance P). On the other hand, Van Sickle *et al.* (2005) reported that 2-AG is anti-emetic in ferrets treated with the emetogenic agent morphine-6-glucuronide (M6G). CB_2 receptors in the brainstem may play a role in the regulation of emesis by 2-AG, at least when CB_1 receptors are co-stimulated. The anti-emetic effects of 2-AG (0.5–2.0 mg·kg^{-1}) in ferrets were reversed by both CB_1 (AM251) and CB_2 (AM630) antagonists, but the anti-emetic effects of anandamide were only reversed by AM251. Therefore, 2-AG, unlike anandamide, may selectively activate these brainstem CB_2 receptors (Van Sickle *et al.*, 2005). Finally, consistent with the anti-emetic effects of 2-AG in the ferret, the monoacylglycerol-lipase (MAGL) inhbitior, JZL-184 (Long *et al.*, 2009a,b), which elevates endogenous 2-AG, dose-dependently suppresses vomiting in the *S. murinus* (Sticht *et al.*, 2010). Furthermore, *in vitro* data revealed that JZL 184 inhibited MAGL expression in shrew tissue.

The FAAH inhibitor, URB597, alone and in combination with exogenously administered anandamide has been shown to interfere with vomiting produced by M6G in the ferret (Van Sickle *et al.*, 2005; Sharkey *et al.*, 2007) and with nicotine and cisplatin in *S. murinus* (Parker *et al.*, 2009a). Although inhibition of FAAH elevates multiple endocannabinoid-like molecules that show activity at multiple target receptors, the anti-emetic effects of URB 597 were reversed by pretreatment with rimonabant, indicating a CB_1 mechanism of action. There may be a species difference in this effect, because URB597 (5 or 10 mg·kg^{-1}) administered to the least shrew did not modify toxin-induced vomiting (Darmani *et al.*, 2005); yet in this latter study URB597 was administered only 10 min prior to cisplatin at a time that may not have produced sufficient inhibition of FAAH prior to the onset of the toxin effect (Fegley *et al.*, 2005). In experiments with the *S. murinus*, a much lower dose (0.9 mg·kg^{-1}) administered 2 h prior to the toxin challenge suppressed vomiting.

A relative of the cannabinoid system, vanilloid TRPV1 receptors have recently been shown to regulate emesis in the ferret (Sharkey *et al.*, 2007). The TRPV1 receptor is targeted by capsaicin (the burning component of chili peppers) as well as resiniferatoxin, which can produce pro-emetic and anti-

emetic effects at similar doses in *S. murinus* (Andrews *et al.*, 2000), but produces anti-emetic effects in ferrets (Andrews and Bhandari, 1993; Andrews *et al.*, 2000; Yamakuni *et al.*, 2002). Recent evidence indicates that anandamide and the endovanniloid, N-arachidonoyl-dopamine (NADA), are endogenous agonists for both CB_1 and TRPV1 receptors (Di Marzo and Fontana, 1995; van der Stelt and DiMarzo, 2004). Extensive colocalization of CB_1 and TRPV1 receptors have been demonstrated (Cristino *et al.*, 2006). Both endogenous (anandamide, NADA) and synthetic (arvanil or O-1861) 'hybrid' agonists of CB_1 and TRPV1 receptors have been shown to exert more potent pharmacological effects *in vivo* (Di Marzo *et al.*, 2001) than 'pure' agonists of each receptor type, particularly when acting on cells co-expressing the two receptor types (Hermann *et al.*, 2003). Sharkey *et al.* (2007) found that anandamide, NADA and arvanil were all anti-emetic in the ferret; these effects were attenuated by the CB_1 receptor inverse agonist AM251 and the TRPV1 antagonists iodoresiniferatoxin and AMG9810. TRPV1 receptors were localized in the ferret NTS and were co-localized with CB_1 in the mouse brainstem.

CB_1/5-HT interactions

Recent findings indicate that the cannabinoid system interacts with the 5-hydroxytryptaminergic system in the control of emesis (e.g. Kimura *et al.*, 1998). The DVC not only contains CB_1 receptors, but is also densely populated with 5-HT_3 receptors (Himmi *et al.*, 1996; 1998), potentially a site of anti-emetic effects of 5-HT_3 antagonists. Cannabinoid receptors are co-expressed with 5-HT_3 receptors in some neurones in the CNS (Hermann *et al.*, 2002). The first evidence of an interaction between cannabinoids and 5-HT_3 receptors was revealed by the finding that anandamide, WIN55 212 and CP55940 inhibit 5-HT_3 receptor-mediated inward currents with IC_{50} values in the nanomolar concentration range in rat nodose ganglion cells (Fan, 1995). Subsequently, Δ^9-THC, anandamide and several synthetic cannabinoids were shown to directly inhibit currents through human 5-HT_{3A} receptors (Barann *et al.*, 2002). Since WIN 55,212–2 did not displace a 5-HT_3 antagonist ([^{3}H]-GR65630) from the ligand binding site, the results suggest that cannabinoids inhibit 5-HT_{3A} receptors noncompetitively by binding to an allosteric modulatory site of the receptor (Barann *et al.*, 2002). Indeed, anandamide produced analgesia in CB_1/CB_2 knockout mice that was prevented by pretreatment with the 5-HT_3 antagonist, ondansetron (Racz *et al.*, 2008). In the regulation of vomiting, low doses of Δ^9-THC and ondansetron that were ineffective alone completely suppressed cisplatin-induced vomiting in the *S. murinus* (Kwiatkowska *et al.*, 2004) and the combination of low doses of tropisetron and Δ^9-THC were more efficacious in reducing emesis frequency in the least shrew than when given individually (Wang *et al.*, 2009). Additionally, cannabinoids have been shown to reduce the ability of 5-HT_3 agonists to produce emesis (Darmani and Johnson, 2004) and this effect was prevented by pretreatment with rimonabant. Cannabinoids may act at CB_1 presynaptic receptors to inhibit the release of newly synthesized 5-HT (Schlicker and Kathmann, 2001; Howlett *et al.*, 2002; Darmani and Johnson, 2004). Indeed, Darmani *et al.* (2003) reported that rimonabant (which produces vomiting in the least shrew) increases brain 5-HT levels and turnover at doses that induce vomiting in the shrew.

CBD: a special case

Another major cannabinoid found in marijuana is CBD. Unlike Δ^9-THC, CBD does not produce intoxicating effects and has a low affinity for the CB_1 and CB_2 receptors (Mechoulam *et al.*, 2002). At a low dose, CBD (5 mg·kg^{-1}, i.p.) inhibits cisplatin-induced (Kwiatkowska *et al.*, 2004) and LiCl-induced (Parker *et al.*, 2004) vomiting and anticipatory retching (Parker *et al.*, 2006) in *S. murinus*. As has been reported by others (e.g. Pertwee, 2004), the effects of CBD are biphasic with high doses (20–40 mg·kg^{-1}, i.p.) potentiating toxin-induced vomiting in the *S. murinus* (Parker *et al.*, 2004; Kwiatkowska *et al.*, 2004), but a dose as high as 20 mg·kg^{-1} of CBD had no effect on 2-AG-induced emesis in the least shrew (Darmani, 2002). A wide range of doses was not effective in reducing motion-induced emesis in the *S. murinus* (Cluny *et al.*, 2008), which may reflect a different mechanism of action of motion and toxin-induced vomiting (Cluny *et al.*, 2008).

The anti-emetic effect of CBD does not appear to be mediated by its action at CB_1 receptors, because it is not reversed by the CB_1 antagonist, rimonabant (Kwiatkowska *et al.*, 2004; Parker *et al.*, 2004). Recent evidence indicates that CBD may act as an indirect agonist on the 5-HT_{1A} autoreceptors, to reduce the availability of 5-HT (Russo *et al.*, 2005; E.M. Rock *et al.*, unpubl. obs.). Known 5-HT_{1A} autoreceptor agonists such as 8-OH-DPAT, buspirone, and LY228729, have been found to suppress vomiting in emetic species such as pigeons (Wolff and Leander, 1994; 1995; 1997), shrews (Okada *et al.*, 1994; Andrews *et al.*, 1996; Javid and Naylor, 2006), cats (Lucot and Crampton, 1989; Lucot, 1990) and dogs (Gupta and Sharma, 2002). Indeed, Russo *et al.* (2005) reported that CBD displaces the agonist [^{3}H]-8-OH-DPAT from a cloned human $5HT_{1A}$ receptor in a concentration-dependent manner. Furthermore, CBD was shown to act as an agonist at the $5HT_{1A}$ receptor, because, like 5HT, it increased GTP binding to the receptor coupled G protein, Gi, characteristic of a receptor agonist. Finally, the agonist CBD was shown to reduce cAMP production, characteristic of Gi activation.

Recently, our laboratory has investigated the mechanism of action for the anti-emetic effects of CBD. Consistent with previous results, CBD (5 mg·kg^{-1}, s.c.) was shown to be effective in suppressing vomiting in the *S. murinus* induced by either nicotine, LiCl or cisplatin (20 mg·kg^{-1}, but not 40 mg·kg^{-1}). Interestingly, this CBD-induced suppression of vomiting was reversed by systemic pretreatment with the 5-HT_{1A} antagonist WAY100135 (E.M. Rock *et al.*, unpubl. obs.), suggesting that the anti-emetic effect of CBD may be mediated by activation of somatodendritic autoreceptors. This activation of the 5-HT_{1A} receptors results in a reduction of the rate of firing of 5-HT neurones, ultimately reducing the release of forebrain 5-HT (Blier and de Montigny, 1987). It is this reduction in 5-HT release that is probably mediating CBD's anti-emetic effects. In addition, a recent finding suggests that CBD may also act as an allosteric modulator of the 5-HT_3 receptor (Yang *et al.*, 2010); CBD reversibly inhibited 5-HT-evoked currents in 5-HT_{3A} receptors expressed in *Xenopus laevis* oocytes in a concentration-dependent manner (1 μM), but did not alter the specific binding of a 5-HT_{3A} antagonist. These findings

suggest that allosteric inhibition of 5-HT_3 receptors by CBD may also contribute to its role in the modulation of emesis.

Effects of cannabinoids on nausea in animal models

Nausea is more resistant to effective treatment with new anti-emetic agents than is vomiting (e.g. Andrews and Horn, 2006) and therefore remains a significant problem in chemotherapy treatment and as a side effect from other pharmacological therapies, such as anti-depressants. Even when the cisplatin-induced emetic response is blocked in the ferret by administration of a 5-HT_3 receptor antagonist, *c-fos* activation still occurs in the AP, suggesting that an action here may be responsible for some of the other effects of cytotoxic drugs, such as nausea or reduced food intake (Reynolds *et al.*, 1991). In rats, the gastric afferents respond in the same manner to physical and chemical (intragastric copper sulphate and cisplatin) stimulation that precedes vomiting in ferrets, presumably resulting in nausea that precedes vomiting (Hillsley and Grundy, 1998; Billig *et al.*, 2001). Furthermore, 5-HT_3 antagonists that block vomiting in ferrets also disrupt this preceding neural afferent reaction in rats. That is, in the rat the detection mechanism of nausea is present, but the vomiting response is absent. Nauseogenic doses of cholecystokinin and LiCl induce specific patterns of brainstem and forebrain *c-fos* expression in ferrets that are similar to *c-fos* expression patterns in rats (Reynolds *et al.*, 1991; Billig *et al.*, 2001). In a classic review paper, Borrison and Wang (1953) suggest that the rats' inability to vomit can be explained as a species-adaptive neurological deficit and that, in response to emetic stimuli, the rat displays autonomic and behavioural signs corresponding to the presence of nausea, called the prodromata (salivation, papillary dilation, tachypnoea and tachycardia).

Conditioned taste avoidance: a nonselective measure of nausea in rats

The typical measure used in the literature to evaluate the nauseating potential of a drug is conditioned taste avoidance. However, taste avoidance is not only produced by nauseating doses of drugs, it is also produced by drugs that animals choose to self-administer or that establish a preference for a distinctive location (e.g. Berger, 1972; Wise *et al.*, 1976; Reicher and Holman, 1977). In fact, when a taste is presented prior to a drug self-administration session, the strength of subsequent avoidance of the taste is a direct function of intake of the drug during the self-administration session (Wise *et al.*, 1976; Grigson and Twining, 2002). This paradoxical phenomenon was initially interpreted as another instance of taste aversion learning. Because Garcia *et al.* (1974) had developed a model to account for taste aversion produced by emetic agents, it was reasonable for early investigators to assume that rewarding doses of drugs also produce taste avoidance because they produce a side effect of nausea that becomes selectively associated with a flavour (Reicher and Holman, 1977). However, in an animal capable of vomiting, the *S. murinus*, rewarding drugs do not produce a conditioned taste avoidance, in fact they produce a conditioned taste preference and a conditioned place preference (Parker *et al.*, 2002a). Since rats are incapable of vomiting, it is likely that conditioned taste avoidance produced by rewarding drugs in this species is based upon a learned fear of anything that changes their hedonic state (e.g. Gamzu, 1977) when that change is paired with food previously eaten.

Another approach to understanding the role that nausea plays in the establishment of taste avoidance in rats is to evaluate the potential of anti-nausea treatments to interfere with avoidance of a flavour paired with an emetic treatment. Early work suggested that anti-nausea agents interfered with the expression of previously established taste avoidance produced by LiCl (Coil *et al.*, 1978); however, more recent findings suggest that similar anti-nausea treatments (Goudie *et al.*, 1982; Rabin and Hunt, 1983; Parker and McLeod, 1991) and different anti-nausea treatments (Gadusek and Kalat, 1975; Limebeer and Parker, 2000; 2003; Parker *et al.*, 2002b; 2003) failed to interfere with the expression of LiCl-induced taste avoidance. Furthermore, there is considerable evidence that anti-nausea treatments either do not interfere with the establishment of conditioned taste avoidance learning (Rabin and Hunt, 1983; Rudd *et al.*, 1998; Limebeer and Parker, 2000; Parker *et al.*, 2002b) or at least only interfere with the establishment of very weak LiCl-induced taste avoidance (Wegener *et al.*, 1997; Gorzalka *et al.*, 2003). Two prominent anti-nausea treatments include drugs that reduce 5-HT availability and drugs that elevate the activity of the endocannabinoid system in rats (see Parker *et al.*, 2005; 2009b; Parker and Limebeer, 2008). These treatments interfere with the establishment and/or the expression of conditioned disgust reactions, but not conditioned taste avoidance (for review, see Parker, 2003; Parker *et al.*, 2009b).

Conditioned gaping: a selective measure of nausea in rats

Over the past number of years, our laboratory has provided considerable evidence that conditioned nausea in rats may be displayed as conditioned disgust reactions (Parker, 1982; 1995; 1998; 2003; Limebeer and Parker, 2000; 2003; Limebeer *et al.*, 2004; Parker *et al.*, 2008; 2009b) using the taste reactivity (TR) test (Grill and Norgren, 1978). Rats display a distinctive pattern of disgust reactions (including gaping, chin rubbing and paw treading) when they are intraorally infused with a bitter tasting quinine solution. Rats also display this disgust pattern when infused with a sweet tasting solution (that normally elicits hedonic reactions of tongue protrusions) that has previously been paired with a drug that produces vomiting (such as LiCl or cyclophosphamide) in species capable of vomiting. Only drugs with emetic properties produce this conditioned disgust reaction when paired with a taste.

The most reliable conditioned disgust reaction in the rat is that of gaping (Breslin *et al.*, 1992; Parker, 2003). If conditioned gaping reflects nausea in rats, then anti-nausea drugs should interfere with this reaction. Limebeer and Parker (2000) demonstrated that when administered prior to a saccharin-LiCl pairing, the 5-HT_3 antagonist, ondansetron, prevented the establishment of conditioned gaping in rats, presumably by interfering with LiCl-induced nausea. Since ondansetron did not modify unconditioned gaping elicited by bitter quinine solution, the effect was specific to nausea-

induced gaping. Subsequently, Limebeer and Parker (2003) demonstrated a very similar pattern following pretreatment with the 5-HT_{1A} autoreceptor antagonist, 8-OH-DPAT, that also reduces 5-HT availability and serves as an anti-emetic agent in animal models. Most recently, Limebeer *et al*. (2004) reported that lesions of the dorsal raphe nucleus (DRN) and median raphe nucleus (MRN) that reduced forebrain 5-HT availability interfered with the establishment of LiCl-induced conditioned gaping consistent with reports that reduced 5-HT availability interferes with nausea. Since rats are incapable of vomiting, we have argued that the gape represents an 'incipient vomiting response'. The orofacial characteristics of the rat gape are very similar to those of the shrew retch just before it vomits (Parker, 2003). Indeed, Travers and Norgren (1986) suggest that the muscular movements involved in the gaping response mimic those seen in species capable of vomiting.

Effects of cannabinoids on nausea in rats

Using the conditioned gaping response as a measure of nausea in rats, we have demonstrated that a low dose (0.5 mg·kg^{-1}, i.p.) of Δ^9-THC interferes with the establishment and the expression of cyclophosphamide-induced conditioned gaping (Limebeer and Parker, 1999). The potent agonist, HU-210 (0.001–0.01 mg·kg^{-1}), also suppressed LiCl-induced conditioned gaping (Parker and Mechoulam, 2003; Parker *et al*., 2003) and this suppression was reversed by the CB_1 antagonist/inverse agonist, rimonabant, suggesting that the effect of HU-210 was mediated by its action at CB_1 receptors. When administered 30 min prior to the conditioning trial, rimonabant did not produce conditioned gaping on its own, but it did potentiate the ability of LiCl to produce conditioned gaping. This same pattern has been reported in the emesis literature (Van Sickle *et al*., 2001; Chambers *et al*., 2007). Van Sickle *et al*. (2001) reported that although the CB_1 antagonist/inverse agonist AM251 did not produce vomiting on its own, it potentiated the ability of an emetic stimulus to produce vomiting in the ferret.

More compelling evidence that the endocannabinoid system may serve as a regulator of nausea is the recent finding that prolonging the duration of action of anandamide by pretreatment with URB597, a drug that inhibits the enzyme FAAH, also disrupts the establishment of LiCl-induced conditioned gaping reactions in rats (Cross-Mellor *et al*., 2007). Rats pretreated with URB597 (0.3 mg·kg^{-1}, i.p.) 2 h prior to a saccharin-LiCl pairing displayed suppressed conditioned gaping reactions in a subsequent drug free test. Rats given the combination of URB597 (0.3 mg·kg^{-1}, i.p.) and anandamide (5 mg·kg^{-1}, i.p.) displayed even greater suppression of conditioned gaping reactions. Although inhibition of FAAH produces an elevation of a variety of fatty acids that act at different receptors, the effect of URB597 on conditioned nausea was reversed by AM251, indicating that it was mediated by CB_1 receptors.

At doses (greater than 4 mg·kg^{-1}) that effectively suppress feeding in rats, the CB_1 antagonist/inverse agonist AM251 produces conditioned gaping reactions when explicitly paired with saccharin solution (McLaughlin *et al*., 2005) reflective of nausea. This finding suggests that the appetite suppressant effect of the newly marketed CB_1 antagonist/inverse agonist, rimonabant, may be partially mediated by the side effect of nausea, which is the most commonly reported side effect in human randomized control trials (Pi-Sunyer *et al*., 2006). On the other hand, the silent CB_1 antagonists, AM4113 and AM6527, which do not have inverse agonist properties, do not produce conditioned gaping (Sink *et al*., 2007; Limebeer *et al*., 2010). In addition, the peripherally restricted silent CB_1 antagonist, AM6545, which also suppresses feeding at equivalent doses of AM251 (Cluny *et al*., 2010; Randall *et al*., 2010; Tam *et al*., 2010), does not produce the side effect of nausea (Cluny *et al*., 2010). Finally, neither the silent antagonist, AM6527 (which crosses the blood–brain barrier) nor AM6545 (with limited CNS penetration), potentiate LiCl-induced nausea, an effect evident with low doses (2.5 mg·kg^{-1}) of systemic administration of AM-251 (Limebeer *et al*., 2010). AM251-induced conditioned nausea is thus mediated by inverse agonism of the CB_1 receptor. This effect may be mediated peripherally, because intracranial administration of AM251 at doses up to 1/10 the peripheral dose into the lateral ventricle or the 4th ventricle did not potentiate LiCl-induced nausea that is evident with systemic administration of this inverse agonist of the CB_1 receptor.

CBD reduces nausea by a non-cannabinoid mechanism of action

In addition, the non-intoxicating compound found in marihuana smoke, CBD (5 mg·kg^{-1}, i.p.) as well as its synthetic dimethylheptyl homologue (5 mg·kg^{-1}, i.p.), suppresses the establishment and the expression of LiCl-induced conditioned gaping (Parker *et al*., 2002b; Parker and Mechoulam, 2003). Recent research (Rock *et al*., 2010) demonstrates that the anti-nausea effects of CBD (5 mg·kg^{-1}, s.c.) are suppressed by systemic pretreatment with the 5-HT_{1A} receptor antagonist WAY100135 (10 mg·kg^{-1}, i.p.). In addition, the more selective 5-HT_{1A} receptor antagonist, WAY100635, administered systemically (0.1 mg·kg^{-1}, i.p.) or intracranially (21 ng in 0.5 μL) into the DRN, a site of somatodendritic 5-HT_{1A} autoreceptors, interferes with the CBD-induced suppression of LiCl-induced conditioned gaping in rats. This effect was selective to receptors located in the DRN, as those rats with misplaced cannulae that received CBD outside of the DRN did not show a similar effect. In addition, when administered directly into the DRN, CBD (10 μg·μL^{-1}) suppressed LiCl-induced gaping. These results suggest that CBD produces its anti-emetic/anti-nausea effects by activation of somatodentritic autoreceptors located in the DRN, reducing the release of forebrain 5-HT. Since depletion of forebrain 5-HT by 5,7-DHT lesions of the DRN and MRN also prevented the establishment of LiCl-induced conditioned gaping (Limebeer *et al*., 2004), nausea appears to be mediated by 5-HT action in forebrain regions. Research aimed at determining the forebrain regions (e.g. insular cortex) responsible for the sensation of nausea are currently being conducted in our laboratory (Tuerke *et al*., 2010).

Cannabinoids and AN in rats and shrews

AN often develops over the course of repeated chemotherapy sessions (Nesse *et al*., 1980; Morrow and Dobkin, 1988; Reynolds *et al*., 1991; Stockhorst *et al*., 1993; Aapro *et al*., 1994; Ballatori and Roila, 2003; Hickok *et al*., 2003). For instance, Nesse *et al*. (1980) described the case of a patient who had

severe nausea and vomiting during repeated chemotherapy treatments. After his third treatment, the patient became nauseated as soon as he walked into the clinic building and noticed a 'chemical smell', that of isopropyl alcohol. He experienced the same nausea when returning for routine follow-up visits, even though he knew he would not receive treatment. The nausea gradually disappeared over repeated follow-up visits. Nesse *et al*. (1980) reported that about 44% of the patients being treated for lymphoma demonstrated such AN. AN is best understood as a classically conditioned response (CR) (Pavlov, 1927).

Control over AN could be exerted at the time of conditioning or at the time of re-exposure to the conditioned stimulus (CS). If an anti-emetic drug is presented at the time of conditioning, then a reduction in AN would be the result of an attenuated unconditioned response (UCR); that is, reduced nausea produced by the toxin at the time of conditioning thereby attenuating the establishment of the CR. Indeed, when administered during the chemotherapy session, the 5-HT_3 antagonist, granisetron, has been reported to reduce the incidence of AN in repeat cycle chemotherapy treatment (Aapro *et al*., 1994). On the other hand, if a drug is delivered prior to re-exposure to cues previously paired with the toxin-induced nausea, then suppressed AN would be the result of attenuation of the expression of the CR (conditioned nausea); the 5-HT_3 antagonists are ineffective at this stage (Nesse *et al*., 1980; Morrow and Dobkin, 1988; Reynolds *et al*., 1991; Stockhorst *et al*., 1993; Aapro *et al*., 1994; Ballatori and Roila, 2003; Hickok *et al*., 2003).

Anecdotal evidence suggests that Δ^9-THC alleviates AN in chemotherapy patients (Grinspoon and Bakalar, 1993; Iversen, 2000). Although there has been considerable experimental investigation of unconditioned retching and vomiting in response to toxins, there have been relatively few reports of conditioned retching; that is, emetic reactions elicited by re-exposure to a toxin paired cue. Conditioned retching has been observed to occur in coyotes, wolves and hawks upon re-exposure to cues previously paired with lithium-induced toxicosis (Garcia *et al*., 1977) and ferrets have been reported to display conditional emetic reactions during exposure to a chamber previously paired with lithium-induced toxicosis (Davey and Biederman, 1998).

The *S. murinus* displays conditioned retching when returned to a chamber previously paired with a dose of lithium that produced vomiting (Parker and Kemp, 2001). Furthermore, this conditioned retching reaction is suppressed by pretreatment with Δ^9-THC. This effect was replicated more recently and extended to demonstrate that CBD also interferes with the expression of conditioned retching in the shrew, but the 5-HT_3 antagonist ondansetron was completely ineffective (Parker *et al*., 2006). The doses employed were selected on the basis of their potential to interfere with toxin-induced vomiting in the *S. murinus* (Kwiatkowska *et al*., 2004, Parker *et al*., 2004).

Rats also display conditioned gaping reactions when re-exposed to a context previously paired with LiCl-induced nausea (Limebeer *et al*., 2006; 2008; Rock *et al*., 2008). Following four pairings of a distinctive, vanilla odour-laced chamber with LiCl-induced illness, rats were returned to the context for 30 min and received a 1 min intraoral infusion of novel saccharin solution every 5 min. During the infusions, the rats displayed gaping reactions. Surprisingly, the rats also gaped during intervals when they were not being infused with saccharin while in the LiCl-paired context. It was further demonstrated that Δ^9-THC, but not ondansetron, interfered with the conditioned gaping response during both infusion and inter-infusion intervals.

The finding that rats express conditioned gaping responses when re-exposed to an odour-laced context previously paired with LiCl during inter-infusion intervals (Limebeer *et al*., 2006) suggests that LiCl-paired cues in the absence of the flavour can elicit conditioned nausea. Meachum and Bernstein (1992) had previously shown the re-exposure to a lithium-paired odour cue elicited gaping reactions in rats. Recently, Limebeer *et al*. (2008) found that even in the absence of a flavoured solution or a distinctive odour, rats display conditioned gaping reactions during exposure to a distinctive context previously paired with a high dose of lithium, as well as a low dose of lithium and provocative motion. Most recently, Rock *et al*. (2008) reported that CBD (within a limited dose range 1–5 $mg \cdot kg^{-1}$, but not 10 $mg \cdot kg^{-1}$) and the FAAH inhibitor, URB597, prevented the expression of conditioned gaping elicited by the lithium-paired context. The effect of URB597 was reversed by rimonabant, indicating a CB_1 mechanism of action. Indeed, inhibition of FAAH by URB597 also prevented the establishment of LiCl-induced conditioned gaping elicited by the contextual cues when administered 2 h prior to each conditioning trial. These results suggest that cannabinoid compounds may be effective agents in the treatment of AN in chemotherapy patients.

Conclusions

Since the discovery of the mechanism of action of cannabinoids, our understanding of the role of the endocannabinoid system in the control of nausea and vomiting has greatly increased. In the ferret and shrew models, the site of action has been identified in the emetic area of the brainstem, the DVC. The shrew model, in particular, is cost effective for the evaluation of the anti-emetic properties of agents. The conditioned gaping response in the rat has provided a glimpse into the anti-nausea mechanisms of action of cannabinoids, in the absence of a vomiting response. Since nausea is a more difficult symptom to control than vomiting, the gaping model may serve as a useful tool for the development of new anti-nausea treatments, as well as for the evaluation of the potential side effects of nausea in newly developed pharmacological treatments. Recent work has also supported anecdotal reports that cannabis may attenuate AN. Using the *S. murinus* and the rat models of AN, both Δ^9-THC and CBD effectively prevented conditioned retching and conditioned gaping (respectively) elicited by re-exposure to a lithium-paired chamber.

Although chemotherapy-induced vomiting is well controlled in most patients by conventionally available drugs, nausea (acute, delayed and anticipatory) continues to be a challenge. Nausea is often reported as more distressing than vomiting, because it is a continuous sensation (e.g. deBoer-Dennert *et al*., 1997; Andrews and Horn, 2006). Indeed, this distressing symptom of chemotherapy treatment (even when vomiting is pharmacologically controlled) can become so

severe that as many as 20% of patients discontinue the treatment (Jordan *et al.*, 2005). Both preclinical and human clinical (e.g. Abrahamov et al. 1995; Meiri *et al.*, 2007) research suggests that cannabinoid compounds may have promise in treating nausea in chemotherapy patients.

Animal models of vomiting have been valuable in elucidating the neural mechanisms of the emetic reflex (e.g. Hornby, 2001); however, the neural mechanisms of nausea are still not well understood (Andrews and Horn, 2006). One limitation in the preclinical screening of the nauseating side effect of compounds and the potential of compounds to treat nausea has been the lack of a reliable preclinical rodent model of nausea. For years researchers have been using conditioned taste avoidance in rats as a model of nausea, but it has been well documented that non-nauseating treatments also produce taste avoidance – it is not a selective measure of nausea (e.g. Parker *et al.*, 2008). However, the considerable amount of evidence reviewed above indicates that conditioned disgust in rats elicited by an illness-paired flavour (e.g. Parker *et al.*, 2008) or an illness-paired context (e.g. Rock *et al.*, 2008) represents a selective and sensitive rodent model of nausea. This model may be a useful tool for elucidating the neurobiology of nausea and the role that the endocannabinoid system plays in the regulation of this distressing condition.

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