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Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system

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Abstract

Nausea and vomiting (emesis) are important elements in defensive or protective responses that animals use to avoid ingestion or digestion of potentially harmful substances. However, these neurally-mediated responses are at times manifested as symptoms of disease and they are frequently observed as side-effects of a variety of medications, notably those used to treat cancer. Cannabis has long been known to limit or prevent nausea and vomiting from a variety of causes. This has led to extensive investigations that have revealed an important role for cannabinoids and their receptors in the regulation of nausea and emesis. With the discovery of the endocannabinoid system, novel ways to regulate both nausea and vomiting have been discovered that involve the production of endogenous cannabinoids acting centrally. Here we review recent progress in understanding the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system, and we discuss the potential to utilize the endocannabinoid system in the treatment of these frequently debilitating conditions.

Keywords

Cannabis; serotonin; emesis; brainstem; insular cortex; CB_1 receptor; CB_2 receptor

1. Introduction

Reflex mechanisms that serve to protect a host from injury and disability represent important and frequently well-conserved adaptations to a hostile external environment. Rarely do these adaptations, such as blinking or sneezing, become “hijacked” by physiological or pathophysiological processes in the body, not involving the organ they evolved to protect. Unfortunately, that is not the case for nausea and vomiting. Nausea is an aversive experience that often precedes emesis (vomiting), but is distinct from it (Borison and Wang, 1953; Carpenter, 1990; Horn, 2008; Andrews and Horn, 2006; Stern et al., 2011). Retching and vomiting lead to the forceful expulsion of gastric and/or upper intestinal contents, the

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primary function of which is to remove ingested materials or food that may be contaminated or potentially harmful. Nausea associated with emesis serves as an unconditioned stimulus for learning and memory; food that becomes associated with nausea and vomiting will be avoided in future encounters (Borison and Wang, 1953; Carpenter, 1990; Horn, 2008; Andrews and Horn, 2006; Stern et al., 2011).

In the natural environment, as a protective reflex, nausea and vomiting are very important adaptations found in most vertebrate species (Borison et al., 1981). However, possibly because of its importance, the sensitivity of this reflex is very low, making it easily activated. In various disease states, e.g. diabetes and labyrinthitis (Koch, 1999; Schmäl, 2013), the inappropriate activation of this reflex leads to severe and debilitating symptoms. Many central nervous system conditions, including elevated intracranial pressure, migraine headache and concussion also cause nausea and vomiting (Edvinsson et al., 2012; Mott et al, 2012; Stern et al., 2011). Nausea and vomiting are frequent, unwanted, side-effects of a range of medications used to treat a variety of conditions, notably cancer chemotherapeutic agents (Hesketh, 2005; Rojas and Slusher, 2012). Pregnancy-induced nausea and vomiting are reportedly adaptive mechanisms, but hyperemesis gravidarum can severely compromise both the health of the mother and the developing fetus (Patil et al, 2012; Sanu and Lamont, 2011; Sherman and Flaxman, 2002). Finally, motion sickness, which results from a sensory conflict between visual and vestibular stimuli, can be of immense discomfort, and severely limit certain activities (Schmäl, 2013; Yates et al., 1998). Nausea and vomiting are significant in our society and understanding them represents both an important goal and a major challenge; the former because of the substantial health implications, but the latter because it is hard to judge if an experimental animal is nauseated and commonly used laboratory animals are some of the few species that do not vomit! Nevertheless, significant progress has been made in our understanding of the processes of nausea and vomiting, which has led to new and improved pharmacological treatments for these disorders in the last 20–30 years, as described in many of the accompanying articles in this volume and previous reviews (Rojas and Slusher, 2012; Sanger and Andrews, 2006; Schmäl, 2013).

One of the oldest pharmacological remedies for nausea and vomiting is the plant cannabis (Kalant, 2001). In clinical trials, cannabis-based medicines have been found to be effective anti-emetics and even surpass some modern treatments in their potential to alleviate nausea (Cotter, 2009; Tramèr et al., 2001). However, it was not until the early 1990s that the mechanism of action of cannabis was established following the cloning of the “cannabinoid” (CB) receptors (Howlett et al., 2002; Pertwee et al., 2010). The significance of this discovery was enhanced when it was realized that these receptors were part of an endogenous cannabinoid (endocannabinoid) system in the brain and elsewhere in the body (Di Marzo and De Petrocellis, 2012; Izzo and Sharkey, 2010; Mechoulam and Parker 2013; Piomelli, 2003). The endocannabinoid system serves to modulate the expression of nausea and vomiting when activated by central or peripheral emetic stimuli (Darmani and Chebolu, 2013; Parker et al., 2011).

In this article we will outline the endocannabinoid system and then describe what is known about this system in relation to the neural circuits of nausea and vomiting. We will describe recent findings on the anti-emetic effects of cannabinoids and show how manipulation of elements of the endocannabinoid system can modify the expression of emesis. We will discuss at some length the evidence that cannabinoids and the endocannabinoid system can regulate nausea, because this is an area that has been not been considered so fully in the past. We will then briefly describe the paradoxical effect of chronic exposure to high doses of cannabis that in some people causes a cyclic vomiting syndrome. Finally, we will conclude with some future directions for this research by identifying gaps in our knowledge of the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system.

2. The endocannabinoid system

The isolation of Δ^9-tetrahydrocannabinol (Δ^9-THC) as the major psychoactive ingredient in cannabis was an important milestone in neuropharmacology (Howlett et al., 2002; Pertwee et al., 2010). This discovery provided the impetus for extensive investigations that led to an understanding of many of the central and peripheral sites of action of cannabis and ultimately to the cloning of the two G-protein coupled cannabinoid receptors; CB_1 and CB_2. CB_1 receptors are distributed throughout the central and peripheral nervous system, but also in many other sites throughout the body (Howlett et al., 2002; Pertwee et al., 2010). In the brain they are frequently expressed in high density on presynaptic nerve terminals of both inhibitory and excitatory nerves, depending on the region (Katona and Freund, 2012). CB_2 receptors are expressed on cells and organs of the immune system, but they are also found in the brain and at other sites in the body (Onaivi et al., 2012; Pacher and Mechoulam, 2011). The actions of cannabinoids can largely be accounted for by these two receptors, however, there are some well-described non-cannabinoid$_1$-, non-CB_2 receptor-mediated actions of cannabinoids. To date there is limited evidence for a third cannabinoid receptor, though some cannabinoids act at the GPR55 receptor (Pertwee et al., 2010). Whether GPR55 has any role in nausea and vomiting is not known and has not been examined to date.

Both cannabinoid receptors signal through $G_{i/o}$ proteins, inhibiting adenylyl cyclase and activating mitogen-activated protein kinase. Activation of the cannabinoid receptors limits calcium entry into cells by inhibiting N- and P/Q-type calcium currents and further inhibits cellular excitability by activating A-type and inwardly rectifying potassium channels (Howlett et al., 2002; Pertwee et al., 2010).

Shortly after the discovery of the CB_1 receptor, two endogenous cannabinoid receptor ligands, *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) were isolated (Di Marzo and De Petrocellis, 2012). Unlike many preformed intercellular mediators, endocannabinoids are made on demand when cells are stimulated with either an increase in intracellular calcium (Alger and Kim, 2011), or following metabotropic receptor activation involving $G_{q/11}$ or possibly G_s proteins (Gyombolai et al., 2012). These ligands are found in the brain and in the periphery, for example, in the gastrointestinal tract (Izzo and Sharkey, 2010), where they act at cannabinoid and other receptors (see below).

Both endocannabinoids are made by enzymatic pathways that have specific localization patterns in the brain that give important clues to their functional roles. Best characterized are the biosynthetic and degradative pathways for the formation and hydrolysis of 2-AG (Blankman and Cravatt, 2013; Long and Cravatt, 2011; Ueda et al., 2010, 2011). The most important pathway for the synthesis of 2-AG begins with activation of a phosphoinositol (PI)-phospholipase C (PLC) which hydrolyzes inositol phospholipids at the *sn-2* position producing diacylglycerol (DAG). The hydrolysis of DAG via *sn*-1-selective diacylglycerol lipases (DAGL)-α and DAGL-β then leads to the formation of 2-AG. Alternatively, but less well characterized, is the sequential hydrolysis of PI by phospholipase A_1 to make lyso-PI which is then further hydrolysed to 2-AG by lyso PI-specific PLC. In the brain, endocannabinoid signaling is abolished in DAGL-$\alpha^{-/-}$ mice (Gao et al., 2010), suggesting this form of the enzyme is the key physiological rate limiting enzyme for 2-AG biosynthesis. The metabolism of 2-AG is complex and potentially can involve enzymatic oxygenation, acylation, or phosphorylation; but probably the most important pathway for 2-AG metabolism is hydrolysis (Blankman and Cravatt, 2013; Ueda et al., 2011). Using a functional proteomic approach, Blankman *et al.* (2007) showed that the majority (~85%) of the 2-AG hydrolyzing activity in the brain was due to the serine hydrolase, monoacylglycerol lipase (MAGL) (Dinh et al., 2002). The remaining hydrolytic activity was due to the enzymes α/β-hydrolase domain-containing protein-6 (ABHD-6) and ABHD-12

(Marrs et al., 2010; Savinainen et al., 2012). MAGL is located presynaptically (Gulyas et al., 2004), but ABHD6 is found in postsynaptic sites (Marrs et al., 2010), suggesting their roles in the regulation of 2-AG are distinct, and possibly important for the establishment of different pools of 2-AG in cellular compartments in the brain. The distribution of these enzymes elsewhere in the body is not well understood.

The major biosynthetic enzyme for the formation of 2-AG in the brain, DAGL-α, was identified in the plasma membranes of postsynaptic dendritic spines in various brain regions (Yoshida et al., 2006). In contrast, as noted above, CB_1 receptors are located presynaptically. This anatomical arrangement is entirely consistent with 2-AG being a retrograde synaptic neurotransmitter in the CNS: being synthesized and released from a postsynaptic site and acting to limit neurotransmitter release from presynaptic terminals via CB_1 receptor activation, and then having its action terminated by hydrolysis (Alger and Kim, 2011; Castillo et al., 2012). There is some evidence for a basal pool of 2-AG in neurons, since DAGL inhibitors do not block all the synaptic endocannabinoid signaling in some situations, whereas endocannabinoid signaling is completely blocked in $DAGL^{-/-}$ mice (Min et al., 2010). However, the significance of this observation remains to be determined.

Anandamide is the other major endocannabinoid ligand. Anandamide acts not only at CB_1 receptors but strong evidence supports the idea that it is also an “endovanilloid”, acting on the ligand-gated transient receptor potential (TRP) vanilloid 1 receptor, and possibly other TRP receptor ion channels (Di Marzo and De Petrocellis, 2012). It should be noted that both anandamide and 2-AG might also be natural ligands for receptors other than the cannabinoid receptors, as data is accumulating that they can modulate receptor binding at a variety of receptors including the G protein-coupled muscarinic cholinergic and mu opioid receptors, nuclear peroxisome proliferator-activated receptors and ligand-gated ion channels such as the $5\text{-}HT_3$ receptor, albeit with relatively low potency and/or efficacy in many cases (Pertwee et al., 2010).

An important route of anandamide synthesis begins with the membrane phospholipid precursor, N-arachidonoylphosphatidylethanolamine (NAPE), which is formed by the transfer of arachidonic acid from the *sn*-1 position of a donor phospholipid to phosphatidylethanolamine by N–acyltransferase. Hydrolysis of NAPE by an N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) produces anandamide (Blankman and Cravatt, 2013; Di Marzo and De Petrocellis, 2012; Ueda et al., 2010). That said, the levels of anandamide in $NAPE\text{-}PLD^{-/-}$ mice are very similar to those of wild type animals and the increase in anandamide seen in the brain after blocking its degradation *in vivo* is also similar, suggesting that another biosynthetic pathway can completely compensate for the NAPE-PLD pathway or that there are at least two parallel pathways for anandamide synthesis in the brain (Leung et al., 2006). These additional enzymatic pathways for the production of anandamide include the sequential deacylation of NAPE by the enzyme alpha beta-hydrolase 4 and the cleavage of glycerophosphate to yield anandamide, and a PLC-mediated hydrolysis of NAPE which produces phosphoanandamide, which is then dephosphorylated to produce anandamide (Blankman and Cravatt, 2013; Di Marzo and De Petrocellis, 2012; Liu et al., 2006, 2008; Ueda et al., 2010). Little is known about the distribution of these additional biosynthetic enzymatic pathways in the brain, but the distribution of NAPE-PLD has recently been described.

NAPE-PLD has been localized in many regions of the brain, and its distribution is similar to the distribution of the CB_1 receptor, but unlike DAGL-α, it has been localized in both pre- and post-synaptic structures (Egertová et al., 2008). Furthermore, it appears to be localized intracellularly on organelles including the smooth endoplasmic reticulum, suggesting that

anandamide may act as both an anterograde signaling molecule and/or as an intracellular regulator. Since the binding site for anandamide on TRPV1 receptors is intracellular (Di Marzo and De Petrocellis, 2012), and anandamide is a full agonist of TRPV1 (whereas it is only a partial agonist at the CB_1 receptor; Howlett et al., 2002; Pertwee et al., 2010) it seems possible that its primary function in the brain may be distinctly different from that of the synaptic retrograde signaling function of 2-AG (Alger and Kim, 2011; Castillo et al., 2012). In support of this idea, anandamide has been shown to be released tonically in the hippocampus and seems to be responsible for regulating inhibitory network activity in a homeostatic manner (Kim and Alger, 2010). In this case, its actions appear to be retrograde in nature, and so given the distribution of NAPE-PLD noted above, perhaps this is not the source of the anandamide, which has still to be resolved. Much more work is needed to establish the enzyme systems responsible for the production of endocannabinoids in specific brain regions. But as we will see later, both CB_1 and TRPV1 receptors are responsible for the antiemetic actions of the endocannabinoid anandamide and the related compound N-arachidonoyl-dopamine (Sharkey et al., 2007).

The principal enzyme for the degradation of anandamide is fatty acid amide hydrolase (FAAH). FAAH is found in neurons throughout the brain, where its postsynaptic distribution is consistent with the idea that the function of anandamide may be primarily to mediate anterograde or intracellular signaling (Gulyas et al., 2004; Tsou et al., 1998). A surprising finding is that levels of anandamide are not only regulated by FAAH, but are reduced in DAGL-$\alpha^{-/-}$ mice, pointing to a convergence in endocannabinoid signaling pathways where 2-AG production regulates the levels of anandamide (Gao et al., 2010). Exactly how this is occurs is not known. Convergence of endocannabinoid signaling was also revealed using dual FAAH and MAGL inhibitors and MAGL inhibitors in $FAAH^{-/-}$ mice (Long et al., 2009; Wise et al., 2012). These studies suggest there is significant cross-talk between these ligand systems and the cannabinoid receptors.

In summary, the endocannabinoid system is responsible for shaping and refining synaptic signaling in the brain and the peripheral nervous system. There is considerable complexity to this system and in only a few areas have systematic studies of all of its many components been conducted. To date, the endocannabinoid system in the peripheral and central neural circuits responsible for the nausea and vomiting have not been extensively studied. In the next section we will outline what is known of the functional neuroanatomy of this system in relation to the reflex circuitry of the brain-gut circuit mediating emesis.

3. The endocannabinoid system at sites in the brain and gastrointestinal tract involved in nausea and vomiting

The key components of the brain-gut circuitry mediating emesis have been well described (Andrews and Horn, 2006; Hornby, 2001). As outlined above, emesis can be initiated peripherally or centrally. However, most commonly, emesis is evoked from the gastrointestinal tract by ingestion of toxins, including bacteria or bacterial products, or food that is not tolerated. It may also be caused by drugs such as the cancer chemotherapeutic agent cisplatin and radiation. In most of these examples, the initial trigger for emesis is the release of serotonin (5-HT) from enterochromaffin cells that are distributed throughout the epithelium of the gastrointestinal tract (Andrews and Bhandari, 1993; Naylor and Rudd, 1996; Rojas and Slusher, 2012). Serotonin activates 5-HT_3 and/or 5-HT_4 receptors on vagal primary afferent nerves, whose cell bodies are located in the nodose ganglia. Vagal afferents innervating the proximal gastrointestinal tract may also be activated by distension and/or the release of enteric neurotransmitters in the vicinity of vagal afferent endings in the mucosa, myenteric plexus or muscle layers of the wall of the gut. When effectively stimulated, vagal afferents activate circuits in the dorsal vagal complex of the brainstem (Boissonade et al.,

1994; Hornby, 2001; Miller and Ruggiero, 1994). The dorsal vagal complex consists of the nucleus of the solitary tract, area postrema and dorsal motor nucleus of the vagus. Circulating emetogens can also directly activate neurons in the area postrema, which is a circumventricular organ that lies outside of the blood-brain barrier (Miller and Leslie, 1994). Cerebral and vestibular inputs are also integrated at the level of the nucleus of the solitary tract. The integrative circuitry of the nucleus of the solitary tract initiates appropriate motor responses that involve activation of the respiratory, gastric, salivatory, esophageal, laryngeal and hypoglossal neural centres in the brainstem and spinal cord (Carpenter, 1990; Miller, 1999). These motor centres elicit the characteristic and stereotyped behaviours of emesis.

The brain centres that elicit nausea are far less clearly defined than those involved in emesis. They are clearly distinct from those involved in emesis and are certainly localized in the forebrain. Early studies from Penfield and Faulk (1955) revealed that stimulation of the insular cortex elicited nausea in some patients undergoing surgery for intractable epilepsy. As well, stimulation of the insular cortex has been shown to produce vomiting in humans (Fiol et al., 1988; Catenoix et al., 2008) and other animals (Kaada, 1951). In rats, inactivation of the visceral insular cortex (granular) reduced lithium chloride (LiCl)-induced malaise (Contreras et al., 2007). Contreras et al. (2007) suggested that this region of the insular cortex (which is also involved in craving for drugs; Naqvi and Bechara, 2009; Forget et al., 2010) may be responsible for sensing strong deviations from a “well-being state” (e.g., Craig, 2002). However, recent functional magnetic resonance imaging studies have revealed an extensive network of brain regions activated by visually-evoked nausea (Napadow, 2013). Phasic and sustained increases in BOLD signals were identified with increasing degrees of nausea. Increasing nausea was associated with increasing phasic activation in the ventral putamen, amygdala and the locus coeruleus; brain regions known to process emotion, stress and fear conditioning. With higher levels of nausea intensity, sustained activation was noted in the insular, anterior cingulate, premotor, and orbitofrontoal cortices and the primary and secondary somatosensory cortices. In addition, subcortical activation was noted in the putamen, ventral tegmental area and nucleus accumbens; a broad network of interoceptive, limbic, somatosensory, and cognitive processing brain areas (Napadow, 2013). Some of these regions are also important in integrating vestibular inputs, and so are likely the common centres for the development of nausea, but further experimental studies are required to substantiate whether nausea evoked from different stimuli activate the same brain regions. Of particular relevance to this paper are findings discussed in more detail below that the anti-nausea effects of a CB_1 receptor agonist are mediated by an action in the insular cortex (Limebeer et al, 2013), suggesting it may have a prominent role as a central substrate for nausea.

CB_1 receptors are widely distributed in the brain and periphery and are in essence found in all the brain regions and peripheral neural structures described above. Direct evidence for the presence of CB_1 receptors on 5-HT containing enterochromaffin cells is lacking, but in both rats (that do not vomit) and the house musk shrew (that does vomit) CB_1 receptor agonists reduce intestinal 5-HT release, suggesting that enterochromaffin cells express functional CB_1 receptors (Hu et al., 2007; Rutkowska and Gliniak, 2009). Of particular interest are the observations that the CB_1 agonist WIN 55,212-2 reduced 5-HT release evoked by the emetogenic Staphylococcal enterotoxin (Hu et al., 2007). These results suggest that 5-HT release from enterochromaffin cells might be selectively targeted to reduce emesis triggered by peripheral stimuli, cancer chemotherapeutics or radiation treatment. It remains to be determined if this strategy would be effective. CB_1 receptors are found on the vagal afferent neurons in the nodose ganglion (Burdyga et al., 2004; Partosoedarso et al., 2003). Of interest is the fact that these receptors are regulated by the feeding state of the animal. Fed animals have low levels of CB_1 expression whereas the levels of CB_1 receptor increase with fasting (Burdyga et al., 2004). The expression of these

receptors are not only regulated by circulating hormones such as leptin, but also cannabinoid receptor agonists including anandamide (Burdyga et al., 2004, 2010; Jelsing et al., 2009). Whether CB_1 receptors on vagal afferent neurons are involved in the control of nausea and vomiting is not well understood.

CB_1 receptors are found in the forebrain, midbrain and brainstem regions described above, in differing densities and in varying locations in the cell. For example, in the locus coeruleus, CB_1 receptors were not only found presynaptically, as expected, but also on postsynaptic somatodendritic compartments (Scavone et al., 2010). The highest density of CB_1 receptors are in the cortex, amygdala and basal ganglia, with lower densities in the nucleus accumbens, ventral tegmental area and brainstem regions (Mackie, 2005). In the cortex the density of distribution of CB_1 receptors varies according the different layers. Throughout the brain there are varying degrees of colocalization with the two main classical transmitters; CB_1 seems universally to colocalize with GABA, where it regulates inhibitory transmitter release, but in only some locations does it colocalize with glutamate to regulate excitation (Freund et al., 2003; Kano et al., 2009; Mackie, 2005). Moreover, in neurons the efficiency of the coupling of CB_1 receptor to the G protein signaling molecules differs: in GABA neurons it is weakly coupled, whereas in glutamate neurons this coupling is far stronger (Steindel et al., 2013). This implies that lower doses of cannabinoids may elicit effects on glutamatergic synapses whilst GABA synapses may require higher doses of cannabinoids to be effective. Currently, the specific synaptic pathways regulating nausea have not been defined well enough to know which neuronal populations control this sensory experience. Likewise for vomiting, whilst the synaptic circuitry of the dorsal vagal complex is well understood, the specific synaptic events underlying this behavior have not yet been defined. CB_1 receptors are nevertheless found in the DVC (Derbenev et al., 2004; Moldrich and Wenger, 2000; Partosoedarso et al., 2003; Sharkey et al., 2007; Suárez et al., 2010; Van Sickle et al., 2001; 2003). CB_1 receptors are also found on dopaminergic, noradrenergic and other transmitter containing neurons in the brain regions involved in the control of nausea and vomiting (Freund et al., 2003; Kano et al., 2009; Mackie, 2005).

In general, a detailed description of the other components of the endocannabinoid system in the brain regions regulating nausea and vomiting is lacking. Van Sickle *et al.* (2005) made the discovery that CB_2 receptors were present in the dorsal vagal complex of the ferret and were involved in the regulation of emesis. These functional and neuroanatomical studies have not been extended with regard to nausea. Nevertheless, CB_2 receptors are more widely distributed in the brain, including in some of the regions identified above that are involved in nausea, such as the amygdala, striatum, nucleus accumbens and cortex (Brusco et al., 2008; Gong et al., 2006). Interestingly, they have also been described in the vestibular nuclei (Baek et al., 2008), but the functional implications of this for motion sickness remain to be determined. It is not yet clear if they are present in the insular cortex of emetic species. Unlike CB_1 receptors, CB_2 receptors appear to be postsynaptically localized and may regulate neuronal excitability by unique mechanisms, as well as through more traditional cannabinoid signaling. For example, CB_2 receptors were recently described in the prefrontal cortex to be intracellular, regulating neuronal excitability though calcium-activated chloride channels (den Boon et al., 2012). Another interesting feature of the CB_2 receptor in the brain is that it may form functional heteromers with the CB_1 receptor (Callén et al., 2012). One specific characteristic of these heteromeric receptors is that they are bidirectionally cross-antagonized with both CB_1 and CB_2 receptor antagonists. This opens up interesting possibilities for therapeutics, but needs to be examined more thoroughly since clearly both receptors need to be in the same anatomical location for this to be happening – and in many brain regions they appear distinct.

Far less is known of the other components of the endocannabinoid system, namely the biosynthetic and degradative enzyme systems involved in the production and breakdown of the endocannabinoids. FAAH was described in neurons of the dorsal motor nucleus of the vagus and it appears also to be expressed in the ferret area postrema (Van Sickle et al., 2001), but not that of the rat (Suárez et al., 2010). MAGL is expressed in the area postrema in the rat (Suárez et al., 2010), but has not been anatomically localized in species that vomit, but it is present in brain of house musk shrews by whole brain analysis (Sticht et al., 2012). DAGLα is not found in the area postrema, and NAPE-PLD and DAGLβ are only weakly expressed, suggesting endocannabinoids are not major transmitters in this region of the brain (Suárez et al., 2010). In other brainstem nuclei involved in emesis, DAGL and NAPE-PLD have not been examined. In the brain regions involved in nausea there have not been extensive examinations of the distribution of the enzymes of endocannabinoid biosynthesis, though FAAH and MAGL are present in some of these regions, such as the nucleus accumbens and the amygdala (Dinh et al., 2002; Gulyas et al., 2004; Tsou et al., 1998).

Much more work is required to examine in detail the endocannabinoid system in the brain regions involved in nausea and vomiting, despite the functional evidence for the effectiveness of this system in regulating these functions, as we shall describe below.

4. Anti-emetic effects of cannabinoids and endocannabinoids

Cannabis is a well-known anti-emetic whose actions have been extensively reviewed (Cotter, 2009; Darmani and Chebolu, 2013; Izzo and Sharkey, 2010; Parker et al., 2011; Tramèr et al., 2001). Following the isolation of Δ^9-THC, the mechanism and site of action of cannabinoids were established. In humans and animal models, plant-derived cannabinoids, synthetic cannabinoids and endocannabinoids inhibit emesis evoked peripherally or centrally with drugs or natural stimuli. Cannabinoids block both acute and delayed emesis. Where it has been examined, these effects are mediated by CB_1 receptors in the DVC (Darmani, 2001a, 2001b; Darmani et al., 2003b; Ray et al., 2009; Van Sickle et al., 2003). Interestingly, there is dissociation between the antiemetic doses of Δ^9-THC and effects of Δ^9-THC on impairing motor function (Darmani, 2001b; Darmani and Crim, 2005).

The role of CB_2 receptors in the anti-emetic actions of cannabinoids is less well established. Van Sickle *et al*. (2005) demonstrated that in the ferret the anti-emetic actions of the endocannabinoid 2-AG were blocked by a CB_2 receptor antagonist, which did not block the anti-emetic effects of anandamide or Δ^9-THC. Neither were the effects of the synthetic cannabinoid WIN55,212-2 blocked by a CB_2 receptor antagonist in the ferret or Δ^9-THC and synthetic cannabinoids CP55,940 and WIN55,212-2 in the least shrew (Darmani, 2001c; Darmani et al., 2003b; Simoneau et al., 2001). Because they lack psychotropic effects, CB_2 receptor agonists represent potential anti-emetic therapeutics, but this has yet to be tested clinically.

We will focus the rest of this section on compounds that alter the levels of endogenous cannabinoids and the role of the endocannabinoid system in the regulation of emesis. Administration of CB_1 receptor antagonists to humans is frequently associated with nausea and vomiting (Després et al., 2009; Kipnes et al., 2010; Pi-Sunyer et al., 2006). In animals that vomit, CB_1 receptor antagonists either initiate vomiting or potentiate emesis evoked by an emetogen (Darmani, 2001a; Sharkey et al., 2007; Van Sickle et al., 2001). Taken at face value, these results initially suggested that there is a tonic release of endocannabinoids giving rise to anti-emetic tone, presumably in the brainstem sites that regulate emesis. However, in these studies the receptor antagonists used are in fact “inverse agonist / receptor antagonists” (Bergman et al., 2008; Pertwee et al., 2010) and these findings were subsequently challenged when it was shown that the centrally acting “neutral” CB_1 receptor

antagonist AM4113 did not potentiate emesis (and similar compounds do not cause nausea, as we discuss below) (Chambers et al., 2007). Exactly what property of the inverse agonists is responsible for their pro-emetic action has not been discovered, although they do release serotonin and dopamine in the brainstem of the least shrew (Darmani et al., 2003a), which may contribute to these actions. Assuming it is the inverse agonist activity that causes this effect, these data are consistent with the notion that there is constitutive receptor activity in the brainstem. But it still remains to be determined where in the synaptic circuitry CB_1 receptors are acting and whether or not this is the case, because, as we shall illustrate below, further evidence supports the notion of an anti-emetic endocannabinoid tone.

Compounds that increase the availability of endogenous cannabinoids have the potential to harness the anti-emetic power of the endocannabinoid system in a locally restricted manner, given the “on demand” nature of endocannabinoid release (Alger and Kim, 2011). That is, when the emetic circuitry is activated the local release of endocannabinoids acting at cannabinoid receptors would limit the extent of this activation. This concept has been tested and whilst it holds true in some circumstances, there are some conflicting data.

Early studies using the compound VDM11 that was initially reported as an endocannabinoid transport inhibitor revealed efficacious anti-emetic actions in both ferrets and the least shrew against morphine 6-glucuronde and apomorphine, respectively (Darmani et al., 2005; Van Sickle et al., 2005). In the ferret, this effect was interestingly inhibited by both CB_1 and CB_2 receptor antagonists (Van Sickle et al., 2005). Similarly, AM404, an analogous compound to VDM11, blocks acute but not delayed emesis induced by cisplatin, but not that caused by copper sulphate or apomorphine (Chu et al., 2010); the receptor mechanism of action of AM404 was not examined. These compounds and others like them were recently shown to inhibit the association of anandamide with fatty acid binding proteins, rather than a membrane transporter (Kaczocha et al., 2012). So exactly where it is having an effect and how this action occurs remains an enigma. One possible explanation is that they are acting as FAAH inhibitors and raising the local levels of endocannabinoids. The FAAH inhibitor, URB597, is a particularly promising compound in treatment of nausea and vomiting, because it has no known psychoactive effects (Fegley et al, 2003; Gobbi et al, 2005). URB597 was shown to be anti-emetic against morphine 6 glucuronide in the ferret (Van Sickle et al., 2005), but not against apomorphine in this species (Percie du Sert et al., 2010); but in the least shrew, it is pro-emetic and does not prevent vomiting evoked by cisplatin or apomorphine (Darmani et al., 2005), which argues against this possibility in this species.

More recently, URB597 was tested in the house musk shrew against cisplatin- and nicotine-induced emesis (Parker et al., 2009). URB597 given alone or together with anandamide blocked cisplatin-induced emesis, whilst anandamide (5mg/kg) was ineffective when given alone. Nicotine-induced emesis was also attenuated by URB597 and this effect was reversed by the CB_1 receptor antagonist rimonabant, in a dose that alone was not pro-emetic (Parker et al., 2009). Further support for the role of endocannabinoids in the regulation of emesis was obtained by blocking MAGL. Raising 2-AG levels with the selective inhibitor JZL184 was also an effective strategy to block LiCl-induced vomiting in the house musk shrew (Sticht et al., 2011). As before, this was shown to be sensitive to CB_1 receptor antagonists, but in neither case were the effects of CB_2 receptor antagonists examined with either JZL184 or URB597 (Parker et al., 2009; Sticht et al., 2011). These data tell us that FAAH and MAGL inhibitors, and drugs like VDM11 offer the potential for new anti-emetic strategies. Why the least shrew behaves differently in response to these treatments remains slightly unclear. It may be that endocannabinoids are metabolized differently in this species or that for some reason the emetic circuitry is subtly different in these animals. However, it should also be said, that in most of the studies noted above in the ferret and the house musk shrew, full dose-response curves for the various cannabinoid agonists and antagonists, as

well as enzyme inhibitors have not be performed. Different conclusions might be drawn depending on the nature of the results obtained conducting such studies.

Before moving on to discuss the anti-nausea effects of cannabinoids and endocannabinoids, it is important to consider possible synergistic actions with other receptor systems, notably 5-HT_3 and TRPV1. As noted above, anandamide is an intracellular TRPV1 agonist and acts at these receptors to inhibit emesis in the ferret (Sharkey et al., 2007). Similarly, Δ^9-THC at low doses was more efficacious against cisplatin-induced emesis in the house musk shrew when combined with a low dose of a 5-HT_3 antagonist, than when given alone (Kwiatkowska et al., 2004), but full dose-response studies were not conducted. In the least shrew, limited potentiation at low doses of Δ^9-THC was also observed (Wang et al., 2009). These studies suggest there is a potential that some of the actions of the endocannabinoid system involve other receptor systems – not limited only to these two. However, the extent to which such interactions actually occur are not clear and future studies should consider them in order to explain more fully the potential of utilizing the endocannabinoid system in novel anti-emetic strategies.

5. Cannabinoids and endocannabinoids in the control of nausea in humans

There is clearly a need of treatments for acute, delayed and anticipatory nausea in chemotherapy treatment (e.g., Poli-Bigelli et al., 2003). One of the first recognized medicinal benefits of cannabis was for the treatment of nausea (Iversen, 2008). The most investigated compound has been Δ^9-THC (see Cotter, 2009; Tramèr et al., 2001 for reviews); however, other nonpsychoactive compounds in the cannabis plant have recently been reported to also have benefits in preclinical models of nausea and vomiting.

Nabilone (Cesamet) an orally active, synthetic analogue of Δ^9-THC, was licensed for management of chemotherapy-induced nausea and vomiting in 1985, but today is only prescribed after conventional anti-emetics fail. To our knowledge, studies have only compared nabilone with dopamine receptor 2 (D_2) receptor antagonists for their anti-emetic/anti-nausea effects in chemotherapy patients. When compared with D_2 receptor antagonists in double blind cross-over designs, such as metoclopramide, nabilone treatment resulted in fewer vomiting episodes (Ahmedzai et al., 1983; Herman et al., 1979; Pomeroy et al., 1986; Steele et al., 1980) and reports of nausea on a 3 point scale of severity (Ahmedzai et al., 1983; Dalzell et al., 1986; Herman et al., 1979) in patients taking moderately toxic chemotherapy treatments; however, when given to cancer patients receiving cisplatin chemotherapy, nabilone was only as effective as the D_2 receptor antagonist in reducing vomiting (Crawford and Buckman, 1986). Therefore, nabilone is superior to D_2 receptor antagonists for the treatment of moderate emesis but probably not for the treatment of severe emesis.

Another orally active, synthetic Δ^9-THC known as dronabinol (Marinol), has also been used as an anti-emetic and was later used as an appetite stimulant (Pertwee, 2009). When compared with Prochlorperazine (a D_2 receptor antagonist) or a combination of dronabinol and the D_2 receptor antagonist, those patients given the combination treatment had less severe nausea and the duration was significantly shorter than with either agent alone, when they were being treated with moderately emetogenic chemotherapy (Lane et al., 1991). Most recently, Namisol, a tablet containing pure Δ^9-THC, was designed to improve absorption after ingestion. Evidence in healthy adults indicates its rapid onset may be beneficial for rapid therapeutic effects, but no clinical trials have yet been completed to demonstrate its clinical efficacy (Klumpers et al., 2012).

In cancer patients, administration of oral Δ^9-THC has been shown to significantly suppress the experience of nausea and vomiting, in comparison to placebo controls (Chang et al.,

1979; Frytak et al., 1979; Orr et al., 1980; Sallan et al., 1975; Sweet et al., 1981) and when compared to the D_2 receptor antagonists available at the time, Δ^9-THC was at least as effective (Carey et al., 1983; Crawford and Buckman, 1986; Cunningham et al., 1988; Frytak et al., 1979; Tramèr et al., 2001; Ungerleider et al., 1984) if not *more* effective (Ekert et al., 1979; Orr and McKernan, 1981) at reducing nausea and vomiting. Clinical evidence suggests that Δ^8-THC suppresses anticipatory nausea in child patients (Abrahamov et al., 1995).

Only one published clinical trial has directly compared the anti-emetic and anti-nausea effects of a cannabinoid with a 5-HT_3 receptor antagonist. Meiri et al. (2007) compared dronabinol, ondansetron, or their combination, for efficacy in reducing delayed chemotherapy-induced nausea and vomiting. Dronabinol and ondansetron alone were equally effective in reducing nausea and vomiting, but the combined therapies were no more effective than either agent alone. When assessing severity of nausea alone, dronabinol was more effective than ondansetron for mildly to moderately severe nausea produced by chemotherapy treatments, but not for severe emetogenic treatments. However, there has been no report of a direct comparison of Δ^9-THC and the current first line treatment of 5-HT_3 receptor antagonist/dexamethasone/neurokinin 1 receptor antagonist on acute or delayed chemotherapy-induced nausea or vomiting in human chemotherapy patients.

Another chemical compound in cannabis is cannabidiol (CBD), this non-psychoactive cannabinoid is now available as a sublingual spray called Nabidiolex (GW Pharmaceuticals). There are no reports of any specific evaluation of CBD alone to reduce nausea and vomiting in human chemotherapy patients. Interestingly, there have been no reports of the evaluation of combined Δ^9-THC and CBD on emesis or nausea in animal models. However, in humans, a phase II clinical trial evaluated Sativex (an oromucosally administered cannabis-based medicine containing Δ^9-THC and CBD in a 1:1 ratio), taken in conjunction with standard anti-emetic therapies (5-HT_3 receptor antagonists), for its ability to control delayed chemotherapy-induced nausea and vomiting (Duran et al., 2010). When compared with placebo, Sativex reduced the incidence of delayed nausea and vomiting and was well tolerated by patients. Fifty-seven percent of Sativex patients experienced no delayed nausea compared to 22% in the placebo group. In terms of emesis, 71% of Sativex patients versus 22% of placebo patients experienced no delayed emesis. These results indicate that Δ^9-THC and CBD in combination may be useful in managing delayed nausea and vomiting in human patients.

The role of endocannabinoids in nausea and vomiting has typically been investigated in animal models with human data rather scarce. However, Choukèr et al. (2010) recently reported lower blood endocannabinoid levels among participants experiencing motion sickness while undergoing parabolic flight maneuvers, whereas anandamide and 2-AG levels were higher among participants who did not experience motion sickness. Moreover, CB_1 receptor expression was reduced among participants experiencing motion sickness compared to those unaffected by parabolic flight maneuvers. Interestingly, anandamide increases were observed early during the flight, whereas the 2-AG increases were observed following the flight, suggesting that endocannabinoids may play different roles in reducing both motion sickness and stress induced by parabolic flights (Choukèr et al., 2010).

6. Cannabinoid and endocannabinoid regulation of nausea in animal models

Animal models of vomiting have been valuable in elucidating the neural mechanisms of the emetic reflex (Hornby, 2001); however, the central mechanisms regulating nausea are still not well understood (Andrews and Horn, 2006). Considerably greater progress has been

made toward the control of vomiting than the control of nausea. One reason is that nausea is much more difficult to quantify than is vomiting, and therefore, preclinical model development has been challenging. Although vomiting is a gastrointestinal event under control of brainstem structures (Hornby, 2001), it is generally agreed that activation of central forebrain structures is required to produce the distinct sensation of nausea (see above). The gastrointestinal visceral inputs to the brain are well characterized (Cechetto and Saper, 1987), but the way in which they are processed in the forebrain, leading to the sensation of nausea, is only beginning to be understood. One limitation in the preclinical assessment of nausea has been the lack of a reliable animal model of nausea. Of course, we can never know if an animal experiences nausea in the same manner as humans, however, here we describe the current models used to determine the nauseating potential of compounds and to determine the potential of anti-nausea agents that reverse nausea. Such models are essential if we hope to develop new treatments for this distressing disorder in humans. These models do not require the use of an animal capable of vomiting and have been primarily employed in rodents, which lack an emetic reflex. Although rodents lack an emetic reflex, their 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 (Billig et al., 2001; Hillsley and Grundy, 1998). Indeed, 5-HT_3 receptor antagonists that block vomiting in ferrets also disrupt this preceding neural afferent reaction in rats (Horn et al., 2004), suggesting that the rat detects nausea, but that the vomiting reaction is absent in this species. Indeed, laboratory rats failed to display any of the common coordinated actions indicative of retching or vomiting after emetic stimulation as compared with the musk shrew, using an in-situ brainstem preparation (Horn et al., 2013).

6.1 Pica

Consumption of non-nutritive kaolin clay, an example of pica (the eating of a non-food substance), is a putative direct indicator of nausea in rodents. Pica consumption may ameliorate the effects of toxins in the diet (e.g. Mitchell et al., 1976; Rudd et al., 2002). Pica has been reported in several strains of rats and mice exposed to emetic compounds (e.g. Stern et al., 2011); however, in emetic species, such as the house musk shrew, pica has not been demonstrated (Liu et al., 2005; Stern et al., 2011; Yamamoto et al., 2004). Although Δ^9-THC has not been specifically evaluated for its anti-nausea effects in the pica model of increased intake of kaolin, the synthetic CB_1 receptor agonist, WIN55,212-2 did not modify pica produced by chronic administration of cisplatin (Vera et al., 2007). To our knowledge, there have been no investigations of the potential of endocannabinoid manipulations to modify pica in rats or mice. Pica has the advantage of being a measure of unconditioned nausea, but it has poor temporal resolution (Stern et al., 2011). In addition, it may be difficult to apply to a species when intake is small, and it can be produced by factors other than nausea, such as stress or pain (Burchfield et al., 1977); therefore, it may not be selectively produced by nausea.

6.2 Lying on Belly

Lying on belly in rats (e.g. Bernstein et al., 1992; Parker et al., 1984) or flopping in ferrets (Stern et al., 2011) is another behavior that has been characterised as a nausea-induced response. In rats, this behavior has only been evaluated as a measure of LiCl-induced nausea (e.g. Bernstein et al., 1992; Contreras et al., 2007; Tuerke et al., 2012b). No other emetic agents have been evaluated using this measure. Both area postrema lesions (Bernstein et al. 1992) and interoceptive insular cortex lesions (Contreras et al. 2007) reduce LiCl-induced lying on belly. As well, pretreatment with the 5-HT_3 receptor antagonist, ondansetron, reduces LiCl-induced lying on belly in rats (Tuerke et al., 2012b). There have been no reports of the effect of cannabinoid manipulations on the behavior of lying on belly in rats.

A major limitation in this measure of nausea-induced behavior, however, is the difficulty in discriminating lying on belly from non-specific locomotor suppression (e.g. Tuerke et al., 2012b); therefore, this measure may not be a specific model of nausea-induced behavior.

6.3 Conditioned Flavor Avoidance and Conditioned Gaping

Other commonly employed rodent measures of nausea are conditioned flavor avoidance learning (e.g. Garcia et al., 1974) and conditioned gaping reactions in the taste reactivity test (Grill and Norgren, 1978). These are not direct measures of nausea, but rely upon conditioning. Conditioned flavor avoidance is a measure of an animal's reluctance to consume flavors of foods that have been previously paired with nausea-inducing treatments. Indeed, high doses (8–10 mg/kg) of the CB_1 inverse agonists AM251 (McLaughlan et al., 2005) and rimonabant (DeVry et al., 2004) have been shown to produce conditioned avoidance of flavored solution as well as conditioned gaping reactions (McLaughlan et al., 2005), but lower doses (3 and 5 mg/kg) that are also effective in reducing food intake failed to produce conditioned avoidance of flavored food pellets in a two choice test, even after 4 conditioning trials (Chambers et al., 2006). On the other hand, CB_1 receptor neutral antagonists, AM6545 (Cluny et al., 2010), AM6527 (Limebeer et al., 2010) and AM4113 (Sink et al., 2008) all failed to produce both conditioned flavor avoidance and conditioned gaping at a high dose (10 mg/kg). These results suggest that it is the inverse agonist effect of rimonabant that is responsible for the side effect of nausea in human clinical trials (Després et al., 2009; Kipnes et al., 2010; Pi-Sunyer et al., 2006). Somewhat paradoxically, the CB_1agonists CP55,940 (0.1 mg/kg; McGregor et al., 1996) and Δ^9-THC (1.5 mg/kg −2.5 mg/kg; Parker and Gilles, 1995; Schramm-Sapyta et al., 2007) also produce conditioned flavor avoidance and conditioned place avoidance. Yet, low doses of Δ^9-THC (0.3 and 1 mg/kg) and nabilone (0.01 and 0.03 mg/kg), but not levonantrodol (0.03 an 0.06 mg/kg) have also been reported to attenuate flavor avoidance induced by cyclophosphamide in CD-1 mice (Landauer et al., 1985). Since conditioned flavor avoidance can be produced even by rewarding drugs in non-emetic rodents it is not a particularly selective measure of nausea (see Parker review in current issue).

In contrast to conditioned flavor avoidance, conditioned gapingreactions appear to be more selective measure of conditioned nausea which is only produced by emetic drugs and consistently prevented by anti-emetic drugs (see Grill and Norgren, 1978; Pelchat et al., 1983; Parker review in present volume). Much of the work on the effects of cannabinoids and endocannabinoids on nausea in rodents using this model is reviewed by Parker et al. (2011). Here we update this review.

Clearly, low doses of CB_1 agonists (0.5 mg/kg Δ^9-THC, Limebeer and Parker, 1999; 0.001–0.01 HU-210, Parker et al., 2003) attenuate nausea in the conditioned gaping model, an effect that is reversed by rimonabant (see Parker et al., 2011). At low doses (1–5 mg/kg, i.p.) the nonpsychoactive phytocannabinoid, CBD, also reduces these nausea-induced behaviors (without affecting any measures of motor activity) by its action as an indirect agonist of 5-HT_{1A} receptors in the dorsal raphe nucleus (Rock et al., 2012; Parker et al., 2011). By acting as an agonist of the somatodendritic 5-HT_{1A} autoreceptors located in the dorsal raphe, CBD would be expected to reduce the release of 5-HT in forebrain regions (e.g. possibly the interoceptive insular cortex, Tuerke et al., 2012a) to ultimately suppress toxin-induced nausea. The currently employed anti-anxiety compound buspirone acts as a partial 5-HT1A agonist. In humans, buspirone resulted in a reduction of self-report nausea scores in healthy human patients participating in nutrient drink test to assess gastric functioning (Chial et al., 2003). In this test, participants consume the maximum tolerated volume of a nutrient drink at the rate of 30 ml/min and 30 min later symptoms of bloating, fullness, nausea and pain are assessed. Buspirione (10 mg twice orally) selectively lowered nausea ratings in this test. On

the other hand, intravenously administered busprione was ineffective in preventing postoperative nausea and vomiting (Kranke et al., 2012).

The non-psychoactive carboxylic acidic precursor of CBD, cannabidiolic acid (CBDA), is present in the fresh cannabis plant and slowly loses its acidic function (decarboxylates) in the plant in response to heating (e.g. when cannabis is smoked). Recent evidence indicates that CBDA (0.1 and/or 0.5 mg/kg, i.p.) potently interferes with motion-, LiCl-, and cisplatin-induced vomiting in the house musk shrew (Bolognini et al., 2012). CBDA also reduced acute nausea produced by LiCl, an effect that was prevented by pretreatment with the 5-HT_{1A} receptor antagonist, WAY100635, and not by rimonabant. CBDA also increased the ability of the 5-HT_{1A} receptor agonist, 8-OH-DPAT, to potently stimulate [^{35}S]GTPγS binding to rat brainstem membrane, again without activating CB_1 receptors *in vitro* or *in vivo*. More recently, CBDA has been shown to reduce acute nausea at a dose as low as 0.5 μg/kg (Rock and Parker, 2013a). As well, a subthreshold dose of CBDA (0.1 μg/kg, i.p.) enhanced the ability of a mildly effective dose of ondansetron (1 μg/kg) (Rock and Parker, 2013a) and an ineffective dose (0.3 mg/g) of metoclopramide (Rock and Parker, 2013b) to reduce LiCl-induced acute nausea in the rat flavor induced gaping model. Interestingly, both CBD (Mechoulam et al., 2002) and CBDA (Rock and Parker, 2013a) have no effect on locomotor activity or any of the commonly measured CB_1 mediated psychoactive behaviors.

The carboxylic acidic precursor of Δ^9-THC is tetrahydrocannabinolic acid (THCA, Gaoni and Mechoulam, 1964). In the fresh plant, THCA is decarboxylated to Δ^9-THC by heating or burning. Interestingly, no psychotomimetic activity was observed when THCA was administered to: rhesus monkeys at doses up to 5 mg/kg (intravenously, i.v.), mice at doses up to 20 mg/kg (i.p.), and dogs at doses up to 7 mg/kg (Grunfeld and Edery, 1969). Recent results (Rock et al., 2013) indicate that THCA (0.5 and 0.05 mg/kg, i.p.) reduced LiCl-induced vomiting in the house musk shrew, an effect that was reversed with rimonabant pretreatment. THCA (0.05 mg /kg, i.p.) also reduced conditioned gaping elicited by a flavour, without modifying saccharin palatability or conditioned taste avoidance. The suppression of LiCl-induced gaping was not simply the result of conversion of the THCA to THC once administered, because when administered at a dose of 0.05 mg/kg, i.p., Δ^9-THC did not suppress this nausea induced behaviour.

Endocannabinoids are also effective in reducing conditioned gaping in rats. As reviewed by Parker et al. (2011) inhibition of FAAH-mediated hydrolysis of anandamide by URB597 has been shown to suppress LiCl-induced conditioned gaping in rats, with an even greater suppressive effect when co-administered with exogenous anandamide (Cross-Mellor et al., 2007). As well, most recently, inhibition of anandamide reuptake by ARN272 also suppresses this nausea-induced behavior (O'Brien et al., 2013). Both of these effects were reversed by the rimonabant, indicating a CB_1 mediated effect. More recently, the endocannabinoid, 2-AG, like anandamide, has been shown to reduce nausea in rats. Pretreatment with exogenous 2-AG dose-dependently suppresses the establishment of LiCl induced conditioned gaping (Sticht et al., 2011). However, unlike the anti-nausea effects of anandamide, those of 2-AG do not seem to be entirely dependent on CB_1 receptors since they can be reversed by the cyclooxygenase inhibitor, indomethacin (Sticht et al., 2011), but not by the CB_1 or CB_2 receptor antagonists, AM251 and AM630, respectively. Interestingly, the suppression of conditioned gaping following concomitant pretreatment with the MAGL inhibitor, JZL184, and exogenous 2-AG was partially reversed by a CB_1 receptor antagonist (Sticht et al., 2011), suggesting that decreased 2-AG turnover reduces nausea, in part, through an action at CB_1 receptors. However, since cyclooxygenase inhibition blocks the anti-nausea effects of 2-AG, it appears that 2-AG acts through several mechanisms to modulate LiCl-induced nausea. Further research is necessary to clarify the precise role of downstream endocannabinoid metabolites in the suppression of nausea.

As described above, rimonabant and AM251 produce both vomiting and nausea at high doses by acting as CB_1 inverse agonists. At lower doses than those that produce the nausea-induced behavior of gaping (2.5 mg/kg), both AM251 (Limebeer et al., 2010) and rimonabant (Parker et al., 2003) potentiated the gaping produced by LiCl. On the other hand, the CB_1 receptor neutral antagonists (without inverse agonist effects), AM4113 (Sink et al., 2007), AM6527 (Limebeer et al., 2010) and AM6545 (Cluny et al., 2010; Limebeer et al., 2010) do not produce conditioned flavor avoidance, nausea-induced conditioned gaping or potentiated LiCl-induced conditioned gaping reactions. Therefore, the nausea inducing effects of rimonabant and AM251 appear to be mediated by their inverse agonism effects at the CB_1 receptor.

As indicated above, it is generally understood that nausea is regulated by central forebrain regions. Recent evidence indicates that at least one the forebrain region regulating nausea is the visceral insular cortex. Ablation of this region (Kiefer and Orr, 1992) and selective serotonin lesions of this region (Tuerke et al., 2012a) prevents LiCl-induced conditioned gaping reactions. As well, intracranial administration of ondansetron to this region attenuates nausea induced gaping reactions (Tuerke et al., 2012). Of particular interest, the location of the CB_1 receptors mediating the anti-nausea actions appear to be in the visceral insular cortex (Limebeer et al., 2012). Delivery of the CB_1 agonist, HU-210, to the visceral insular cortex, but not to the gustatory insular cortex, interfered with the establishment of LiCl-induced gaping reactions in rats. Such interference was prevented by co-administration of the CB_1 inverse agonist/antagonist AM251 at a dose that had no effect on its own. Interestingly, however, the nausea-inducing effects of the CB_1 inverse agonist/antagonist AM251 was not evoked by administration into this brain region (Limebeer et al., 2012).

7. Contextually-elicited conditioned gaping reactions: A model of anticipatory nausea

Rats not only display conditioned gaping reactions when re-exposed to a flavor previously paired with a nausea-inducing drug, but they also display conditioned gaping reactions when re-exposed to a context previously paired with a nausea-inducing drug (Chan et al., 2009; Limebeer et al., 2008; Rock et al., 2008;). As well, the house musk shrew also displays conditioned retching when re-exposed to a context previously paired with toxin-induced vomiting (Parker and Kemp, 2001; Parker et al., 2006). These contextually elicited conditioned gaping or retching reactions represent animal models of anticipatory nausea analogous to that experienced by human chemotherapy patients, which can be produced following 3–4 conditioning trials. In human chemotherapy patients, when anticipatory nausea develops, the classic anti-emetic agent ondansetron is ineffective in reducing this symptom (Hickok et al., 2003); likewise rats and shrews pretreated with ondansetron do not show a suppression of contextually-elicited gaping and retching reactions, respectively (Limebeer et al., 2006; Parker and Kemp, 2001; Parker et al., 2006; Rock et al., 2008). On the other hand, Δ^9- THC, URB597 and CBD all reduce these contextually-elicited conditioned nausea reactions (Parker et al., 2011). More recently, it has been shown that CBDA (Bolognini et al., 2012) were more potent than CBD and Δ^9-THC respectively in attenuation of contextually-elicited conditioned gaping in rats. CBDA potently suppresses nausea and vomiting in a $5\text{-}HT_{1A}$ receptor dependent manner (Bolognini et al., 2012). Since these compounds are both non-psychoactive, they are promising candidates for the treatment of anticipatory nausea, as there is no current therapeutic available once anticipatory nausea does develop. Currently, patients are given non-specific anti-anxiety drugs.

Similarly, endocannabinoid enzyme inhibitors reduce contextually-elicited conditioned gaping in rats. The FAAH inhibitor, URB597, interfered with both the establishment and expression of conditioned gaping to an illness-paired context in a dose dependent manner

(Rock et al., 2008). Since rimonabant reversed these effects, they were most likely mediated by elevated anandamide. Recently, Limebeer et al. (2013) evaluated the potential of the dual FAAH /MAGL inhibitor, JZL195, on its own and combined with anandamide and 2-AG, to reduce anticipatory nausea in the rat model. JZL195 suppressed conditioned gaping and by elevation of anandamide, but not 2-AG, an effect that was reversed by rimonabant (Limebeer et al., 2013). The suppressant effect of JZL195 was potentiated by co-administration of anandamide or 2-AG. On its own anandamide, but not 2-AG, also suppressed contextually elicited gaping, again reversed by rimonabant.

8. Cannabis and hyperemesis: the paradoxical effect of chronic exposure to cannabis

Heavy chronic cannabis use in some people, frequently young ones, leads to a constellation of symptoms that include abdominal pain, recurrent nausea and intractable cyclic vomiting (Galli et al, 2011; Nicolson et al., 2012; Simonetto et al., 2012). This syndrome was first reported about 10 years ago (Allen et al., 2004). These symptoms are, of course, exactly the opposite of what has been outlined above and hence represent a paradoxical effect of cannabis. Relief from these symptoms can be obtained from hot baths and showers, but standard anti-emetic treatments are not particularly effective (Galli et al, 2011; Nicholson et al., 2012; Simonetto et al., 2012). The mechanisms underlying these effects are entirely unknown, but are speculated to be either the buildup of a toxic chemical from the cannabis plant, or are due to a downregulation of cannabinoid receptors due to the high exposure to ligand. There are no animal models for this syndrome, which perhaps warrants further investigations. Given the relatively recent appearance of this condition, it would seem likely that recent developments in the horticulture of the plant may be responsible.

9. Future directions in using the endocannabinoid system in the treatment of nausea and vomiting

As can be appreciated from the discussion in the previous sections, we believe that the endocannabinoid system has the potential to be used for the treatment of nausea and likely as an adjunct therapy for the treatment of emesis, particularly delayed emesis, where current therapies are limited in their degree of efficacy. There are, however, many gaps in our knowledge, most of which were highlighted above. One of the biggest limitations is the very widespread nature of the CB_1 receptor and the many critical functions in the synaptic control of neurotransmission that it subserves. Any compounds that either act directly at the receptor or increase (or reduce) ligand availability, have the potential to radically alter brain functions beyond that of nausea and vomiting. So, for example, enhancing endocannabinoid biosynthesis, which would, on the face of it, seem like a good anti-emetic strategy, is unlikely to be specific and might lead to many unwanted side-effects. Reducing endocannabinoid metabolism seems to carry with it a lot of potential and to date, side-effects of FAAH and MAGL inhibitors seem to be rather minimal, at least in animal models. Currently, another major limitation of advancing endocannabinoid therapies for the treatment of nausea and vomiting is actually our knowledge of the specific roles played by the two endocannabinoids anandamide and 2-AG. By inference from use of FAAH and MAGL inhibitors, both seem to be important, but more sophisticated approaches are required to identify the specific functional contributions of each. As noted above, understanding the role of CB_2 receptors, particularly in nausea, also remains an important direction in research. There may be an opportunity to utilize these receptors for treatments, though as for CB_1 receptors, their widespread nature may limit or restrict the use of such therapies.

Nausea and vomiting are frequently debilitating conditions that require substantial effort and cost to manage. Advances in recent progress in understanding the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system have revealed significant potential for therapeutic approaches to be developed. Future efforts aimed at developing new endocannabinoid-based anti-nausea and anti-emetic therapies are clearly warranted.

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