The Veterinary Journal 203 (2015) 36–43

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Review

Nausea: Current knowledge of mechanisms, measurement and clinical impact

Hannah Kenward [a,*], Ludovic Pelligand [a,b], Karine Savary-Bataille [c], Jonathan Elliott [a]

[a] Department of Comparative Biomedical Sciences, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Herts AL9 7TA, UK
[b] Department of Clinical Sciences and Services, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Herts AL9 7TA, UK
[c] Zoetis International Services, 23-25 Av du Dr Lannelongue, Paris 75014, France

ARTICLE INFO

Article history:
Accepted 9 October 2014

Keywords:
Biomarker
Emesis
Maropitant
Nausea
VAS

ABSTRACT

Nausea is a subjective sensation, which often acts as a signal that emesis is imminent. It is a widespread problem that occurs as a clinical sign of disease or as an adverse effect of a drug therapy or surgical procedure. The mechanisms of nausea are complex and the neural pathways are currently poorly understood. This review summarises the current knowledge of nausea mechanisms, the available animal models for nausea research and the anti-nausea properties of commercially available anti-emetic drugs. The review also presents subjective assessment and scoring of nausea. A better understanding of the underlying mechanisms of nausea might reveal potential clinically useful biomarkers for objective measurement of nausea in species of veterinary interest.

Introduction

Nausea is an unpleasant subjective experience, colloquially defined as feeling queasy or sick to the stomach (Koch, 1995). The experience of nausea is linked with the urge to vomit (Jenns, 1994; Kowalski et al., 2006; Holmes et al., 2009), but nausea does not always result in emesis (Shelke et al., 2004) and is reported by human patients to be a worse experience and more disabling than the act of vomiting itself.

The origins and mechanisms of nausea have yet to be fully elucidated, but it continues to be a common problem in both human and veterinary medicine. Nausea is a frequent indication of disease and an adverse effect of many drug therapies; it is reported in human patients receiving cancer chemotherapy as the most distressing side effect (Morrow et al., 2002b). This could also be the case in veterinary medicine but, as nausea is a subjective sensation reported by human patients, its detection in veterinary species relies on observation of signs that are the animal's response to this sensation. These are variably expressed depending on individual susceptibility, extent of disease and drug treatments administered. By analogy to pain (Stern et al., 2011), nausea has a protective function and could therefore be perceived by animals (Schwartz et al., 1996). Humans describe nausea as a multidimensional experience including physical, emotional and psychological components (Muth et al., 1996), making it challenging to quantify accurately in non-verbal species. Lack of an objective measure of nausea greatly impedes the assessment of nausea in veterinary practice. Current behavioural assessments are subjective, entirely based on the observer's opinion and are, therefore, liable to large inter-observer variation. A better understanding of the mechanisms that lead to the sensation of nausea might reveal potential clinically useful biomarkers for nausea.

Our inability to positively identify animals experiencing nausea in clinical practice with certainty makes it difficult to understand the extent of the phenomenon and its clinical consequences for veterinary patients. It could be speculated that the experience of nausea in response to drugs and disease states leads to subtle signs, which are often missed, by veterinarians, veterinary technicians and pet owners. Nausea could underlie the inappetence that afflicts our veterinary patients under a number of circumstances. Thus, a more complete understanding of nausea in veterinary patients is important and the goal of finding a suitable biomarker of nausea is highly desirable. Such a biomarker would help us to recognise those animals affected by nausea and could be used to assess the response of veterinary patients to anti-nausea medications, ultimately allowing us to improve the quality of life of the animals in our care.

Mechanism of emesis

Causes of emesis are numerous but all initiate the emetic reflex universally coordinated by the vomiting centre (VC) located in the brainstem (Elwood et al., 2010). The VC can receive pro-emetic stimuli from the following sources: chemical emetogens in the circulation via the area postrema (also known as the chemoreceptor trigger zone), abdominal vagal and glossopharyngeal afferents, the

* Corresponding author. Tel.: +44 1707 333666.
E-mail address: hkenward@rvc.ac.uk (H. Kenward).

http://dx.doi.org/10.1016/j.tvjl.2014.10.007

central nervous system, and the vestibular system (Sanger and Andrews, 2006). On receiving stimuli which surpass the emetic threshold, the VC acts as a central pattern generator, producing controlled stimulation of output nuclei located in the brainstem to induce the emetic reflex (Hornby, 2001).

Exploration of nausea mechanisms

Nausea, much like pain, is a perceptual experience involving not only a physiological but also an affective response (Schwartz et al., 1996). Nausea can be induced by an emotional state such as fear or anticipation. Anxiety levels in human patients prior to cancer chemotherapy treatment are predictive of chemotherapy-induced nausea and vomiting (CINV; Yap et al., 2012). In our experience, dogs experience anticipatory nausea with repeated pairing of a specific context to emetic stimuli. However, the ability of animals to experience nausea in the same way as humans is a topic for debate, due to their inability to verbalise the experience. While we cannot know the emotional response of animals to nausea, it is a protective physiological response and is undoubtedly aversive in order to discourage future exposure to potentially damaging scenarios or toxins.

Identification of nausea mechanisms in animals is complicated by its subjective nature and the inability of animals to self-report the sensation of nausea experienced. Unlike studies of emesis, which can be carried out in anaesthetised animal models, nausea studies must be carried out in conscious subjects.

Emesis is controlled in the brainstem but the sensation of nausea is thought to arise from the activation of cortical structures involved in conscious perception (Sanger and Andrews, 2006; Horn, 2008; Holmes et al., 2009). Rostral projections from emetic regions of the brainstem or direct input from the vestibular system may stimulate the cortical nausea centre (Sanger and Andrews, 2006). Prodromal signs of vomiting, such as salivation, cutaneous vasoconstriction and tachycardia, controlled by the autonomic nervous system, are activated at the same time as the sensation of nausea is reported. These add to the overall unpleasantness of nausea (Morrow et al., 2002b; Sanger and Andrews, 2006). The onset of nausea has been linked to changes in the levels of hormones controlled by the HPA axis, such as arginine vasopressin (AVP; Cubeddu et al., 1990c; Kim et al., 1997) and cortisol (Fredrikson et al., 1992; Morrow et al., 2002a). The release and relevance of these hormones in relation to nausea are discussed in more detail elsewhere in this review.

A variety of experimental techniques have been employed in an attempt to locate the area of the cortex responsible for the genesis of nausea sensation. Electroencephalographic recordings of human volunteers experiencing motion sickness identified activity in the temporo-frontal region, which resembled that of a partial seizure (Chelen et al., 1993). Magnetic source imaging (MSI) has been employed in the study of nausea, as it combines functional data from magnetoencephalography and the structural data from magnetic resonance imaging (MRI). MSI has demonstrated increased neuronal activation in the inferior frontal gyrus, which correlated with self-reported nausea scores in human volunteers following vestibular stimulation or the ingestion of syrup of ipecac (Miller et al., 1996). Horn et al. (2007) studied the activity of forebrain areas following intraperitoneal administration of cisplatin in rats. In these rats, c-fos expression, a marker of neuronal activity, was significantly increased in both the central amygdala and the bed nucleus of the stria terminalis, which implicates these areas in conscious perception of nausea (Horn et al., 2007).

A study by Napadow et al. (2013) suggests that the brain regions involved in the evolution of nausea are numerous. Motion sickness was induced in human volunteers by the use of an optokinetic drum and functional magnetic resonance imaging (fMRI) was conducted while they self-reported nausea scores. Increased activity was recorded in the left amygdala, the ventral putamen and the putative locus coeruleus prior to the subject reporting an increasing nausea score (i.e. these two events were associated, but there was a time lag between them). Increased nausea was also associated with increased activity in the following cortical regions: insula, cingulate, somatosensory, orbitofrontal, prefrontal and premotor cortices and in subcortical structures including the putamen, nucleus accumbens and ventral tegmental area. These brain regions encompass areas involved with fear, emotion and stress (Napadow et al., 2013), which are involved with the perception of nausea in humans.

Manifestations of nausea in experimental models and in clinical settings

Rats are a non-emetic species, as their nibbling style of food intake allows for food to be sampled and avoided should a nausea-like state occur (Andrews and Horn, 2006). Despite their inability to vomit, rats have been used extensively to study of the neurochemistry of nausea using a number of behavioural models. Conditioned taste avoidance (CTA) uses this innate nibbling behaviour as a measure of nausea. If a novel flavour (e.g. saccharin) is paired with an emetogen (e.g. lithium chloride), avoidance of the novel flavour can then be tested (Yamamoto et al., 1995). CTA is attenuated by lesions to the area postrema (Ritter et al., 1980) and is reversed by some antiemetic agents (Coil et al., 1978); however, CTA is also induced when the flavour is paired with non-nausiogenic drugs which have reinforcing properties such as amphetamine or LSD. This suggests that CTA measures the rat's defensive avoidance of any flavour paired to an altered physiological state rather than specifically measuring a nausea-like response.

Conditioned gaping in rats mimics the orofacial reactions seen during the emetic reflex in emetic species. This has been argued to provide a more robust measure for nausea than CTA (Limebeer et al., 2006; Parker and Limebeer, 2006). Gaping appears to be selectively induced by emetic drugs (Parker, 1998) and is reversed by the anti-emetics ondansetron (Limebeer and Parker, 2000) and Δ^9-tetrahydrocannabinol (Δ^9-THC) (Limebeer and Parker, 1999).

Although rat models have been useful in identifying the neurotransmitters involved in nausea pathways, they are better described as measuring a 'nausea-like' response, as the existence of the sensation of nausea in non-emetic species is uncertain. In this respect, the term nausiception could be coined from *nausia*, the Greek origin of the nausea. By analogy to nociception, nausiception would be used to describe the afferent neural response to emetic stimuli but would not encompass the emotional elements of nausea, in much the same way as nociception is the neural component of pain (Table 1; Le Bars et al., 2001). Nocifensive behaviours are observed after nociceptive stimulation (Fan et al., 1995) and are the defensive response associated with protection against the insult. Similarly, nausifensive behaviours occur as a defensive response to a nausiceptive stimulus. In rodents, this would describe the conditioned gaping behaviour and in other species the prodromal responses (salivation, sweating, changes in pallor) associated with nausea that precede the emetic reflex. Pain and nausea are only experienced in the conscious subject or animal but, like nociception, nausiception could be evaluated in the anaesthetised animal by the measurement of neuronal activity.

In emetic animal species such as the dog, cat, ferret and *Suncus murinus* (house musk shrew), nausea and emesis can be induced by

Table 1
Characteristics of nociceptive and posited nausiceptive responses.

Sensation	Requires conscious subject	Neural encoding and ascending processing	Elicited protective behaviours
Pain	Yes	Nociception	Nocifensive behaviours
Nausea	Yes	Nausiception	Nausifensive behaviours

Table 2
Stimulus or drugs associated with nausea and emesis in small animal practice.

Stimulus/drug	Representative example	Reference
Purgative emetogen	Apomorphine, syrup of ipecac	(Sedlacek et al., 2008)
Cytotoxic drugs	Cisplatin, doxorubicin, methotrexate, carboplatin	European Emesis Council[a] (Hahn et al., 1997; Yamakuni et al., 2000; Kristal et al., 2001; de la Puente-Redondo et al., 2007; Rau et al., 2010; Kenward et al., 2014)
Opioids	Morphine, hydromorphone	(Villablanca et al., 1984; Foss et al., 1993; Hay Kraus, 2013)
Alpha-2 adrenoceptor agonists	Xylazine, medetomidine	(Lucot and Crampton, 1986; Vaha-Vahe, 1989; Hikasa et al., 1992; Cullen, 1996)
Antibiotics	Erythromycin and other macrolides, metronidazole, doxycycline	European Emesis Council[a]
Antifungal	Ketoconazole	(Medleau and Chalmers, 1992; Mayer et al., 2008)
Plant alkaloids	Digoxin, lycorine	European Emesis Council[a] (Kretzing et al., 2011a)
Vasopressors	Vasopressin infusion	(Chen et al., 2003; Tatewaki et al., 2005)

[a] See: http://www.emesiscouncil.com/knowledge-hub/nausea (accessed 23 September 2014).

a number of chemical emetogens. These emetogens act peripherally to stimulate vagal afferent fibres due to 5-hydroxytryptamine (5-HT) released in the gastrointestinal tract e.g. after the administration of syrup of ipecac (Soderpalm et al., 2001) or centrally, by stimulating the chemoreceptor trigger zone e.g. after the administration of apomorphine (Andrews et al., 1990). Alternatively, certain emetogens, such as cisplatin, have both a central and peripheral action (Minami et al., 2003). These mechanisms are clinically relevant, as therapeutic agents stimulate these pathways, causing nausea and emesis as side effects. Table 2 presents medicines that give rise to nausea and emesis in small animals.

In species relevant to veterinary small animal practice, there is a much greater representation of dogs than cats in nausea research and reporting. A search of the literature in PubMed using the terms 'nausea AND (cat/s OR feline)' returned 112 results, of which 24 were relevant after inspection of the abstracts. However, a search for 'nausea AND (dog/s OR canine)' produced 219 results, of which 105 were relevant following inspection of the abstracts. This is probably because the dog is a more common laboratory species than the cat.

Behavioural assessment of nausea

Currently, the measurement of nausea relies on the interpretation of behavioural changes that are thought to be related to nausea. Salivation, lip licking and restlessness are most often observed (Table 3). Behavioural change is quantified using a scoring system such as the visual analogue scale (VAS), a 100 mm line on which a mark is made to denote perceived nausea, where 0 mm represents 'no nausea' and 100 mm 'worst possible nausea'. Such a scoring system has been utilised in dogs (de la Puente-Redondo et al., 2007) and cats (Hickman et al., 2008) based on the following behaviours: exaggerated swallowing, salivation, licking lips, body posture, lethargy, depression and restlessness. It is important that the context is taken into account, as in isolation, or when conflicting conditions such as stress or pain are present, these behaviours might not be a specific measure of nausea. This is a highly subjective method of measurement; scores are allocated by observers and there can be large variations between observers. To limit this variation, observers should be trained to recognise 'nausea' behaviours and, if practicable, the same observer/s, blinded to treatment allocation, should be present for all scoring in a single study (Kenward et al., 2014).

Table 3
Canine behaviours associated with nausea. Behaviours listed in table are as observed by authors during pre-clinical studies and clinical practice or as reported in the nausea knowledge statement produced by the European Emesis Council.[a]

Behaviour	Clinical signs
Salivation	Hypersalivation, increase in swallowing frequency, gulping, chewing movements
Gastro-intestinal disturbances	Pica, belching, productive or non-productive vomiting, defecating
Lip smacking	Lip licking, licking the nose, nictation (the action of winking)
Excitement behaviours	Apprehension, restlessness, rapid breathing
Vocalisation	Murmuring, groaning, whining
Withdrawal behaviours	Standing with the head drooping, closing eyes, yawning, drowsiness, lethargy and excessive sleeping
Appetite	Decreased appetite, avoidance of food bowl

[a] See: http://www.emesiscouncil.com/knowledge-hub/nausea (accessed 23 September 2014).

Rau et al. (2010) used a simplified VAS scoring system in dogs consisting of a five-point scale with descriptions of behaviour. The narrowed criteria of this system might reduce inter-observer variation, but can also result in the exclusion of pertinent 'nausea' behaviours, not mentioned in the description. Further drawbacks of the VAS system are also evident in the context of a clinical study. In a busy veterinary hospital or practice it is often not practical for animal care staff to constantly observe canine patients, and therefore periods of nausea might be missed. If observations continue in the home environment, the same problem occurs and furthermore, owners are not trained to recognise nausea behaviours. The construction of a composite scale including weighted quantitative behavioural changes and validated nausea biomarkers could increase the objectivity and validity of nausea scoring.

Several self-reporting scales have been designed for use in humans. Some, such as the Melzack questionnaire (Melzack et al., 1985, inspired by the McGill pain scale), attempt to capture the multidimensional experience of nausea. Muth et al. (1996) designed a nausea profile questionnaire which recognises that nausea is probably manifested differently in each patient as a complex syndrome with several dimensions, each of which could be measured individually (somatic distress, gastro-intestinal distress and emotional distress).

Neurotransmitters involved in nausea and potential nausea biomarkers

The ideal nausea biomarker would be a specific physiological variable, easily measured without bias, which is released in proportion to the severity of nausea experienced by the animal. Such a biomarker would be important in clinical research where there is a need to measure nausea, in conditions not conducive to behavioural measurement, and when quantifying the effect of anti-nausea treatment in particular clinical settings (Table 4). While the evidence presented below for potential nausea biomarkers is mainly based on studies in humans, it is the opinion of the authors that these also have the potential to be validated in animals.

Neurotransmitters and hormones involved in the sensation of nausea are diverse and there is evidence that noradrenaline (NA), 5-HT, vasopressin and substance P all have some role in the genesis

Table 4
Circumstances associated with nausea in veterinary clinical practice.

Recognised conditions associated with nausea in animals	Recognised association with nausea in humans but lacking evidence in animals
Pancreatitis (European Emesis Council[a])	Pregnancy (Lacasse et al., 2008)
Uraemia (Krawiec, 1996)	Diabetes-associated nausea (Koch, 1999)
Vestibular disease (Rossmeisl, 2010) and motion sickness (Conder et al., 2008)	Post-operative nausea and vomiting (Koivuranta and Laara, 1998)
Drugs (see Table 2)	
Hormones (vasopressin; Chen et al., 2003)	
Emetogens (ipecac and apomorphine; Sedlacek et al., 2008)	

[a] See: http://www.emesiscouncil.com/knowledge-hub/nausea (accessed 23 September 2014).

of nausea; their potential as nausea biomarkers applicable to the veterinary patient is discussed elsewhere in this review.

5-Hydroxytryptamine

Antagonists of the neurotransmitter 5-HT_3, such as ondansetron, constitute a major class of anti-emetics. They are highly efficacious in the treatment of chemotherapy-induced acute emesis and have some anti-nausea efficacy, thereby implicating 5-HT in the mechanism of nausea. A number of experiments have been carried out in the rat to further investigate the role of 5-HT in nausea. Reduced 5-HT availability leads to the prevention of the development of conditioned gaping in rats (Parker et al., 2010). Pre-treatment of rats with the selective 5-HT_{1A} agonist, 8-OH-DPAT, reduces 5-HT availability due to its auto-receptor function and attenuates the conditioned gaping response in rats (Limebeer and Parker, 2003). Decrease in striatal and hippocampal 5-HT following lesions of the median and dorsal raphe nuclei causes a significant decrease in conditioned gaping in rats (Limebeer et al., 2004).

Although 5-HT release and stimulation of abdominal afferent vagal fibres might be responsible for nausea and emesis, the rapid uptake and metabolism of these compounds limit their potential use as biomarkers. Therefore, it might be more practical to measure a stable metabolite of 5-HT in plasma or urine, such as 5-hydroxyindoleacetic acid (5-HIAA). Urinary excretion of 5-HIAA (corrected by creatinine) is significantly increased from pre-treatment levels in human cancer patients receiving high-dose cisplatin or cyclophosphamide (Cubeddu et al., 1990b, 1992). Cubeddu et al. (1990b) also reported that 5-HIAA excretion rose in parallel to the onset of emesis; however, nausea was not recorded in this study.

Noradrenaline

Catecholamines can play a role in the neurohumoral development of nausea and emesis (Andrews et al., 1988). It has been hypothesised that NA promotes 5-HT release from the gut peripherally, and that this could increase receptor sensitivity centrally, facilitating emetogen detection in the area postrema (Fredrikson et al., 1994). Alpha$_2$-adrenoceptors have been identified in the area postrema (Beleslin and Strbac, 1987) and are thought to be mainly located pre-synaptically to transmit emetic signals (Japundzic-Zigon et al., 1997). Phosphodiesterase (PDE)-4 inhibitors, such as rolipram, which increase NA neurotransmission, cause a dose-dependent increase in conditioned gaping in rats when paired with either a specific flavour or context (Rock et al., 2009). Rolipram-induced nausea is likely to be due to triggering of noradrenergic rostral projections from the brainstem to the cortex.

Urinary NA excretion has been investigated as a marker of nausea in humans with cancer chemotherapy-induced emesis. High pre-treatment NA excretion is predictive of the intensity of delayed nausea of cancer chemotherapy (Fredrikson et al., 1994). Further studies are required to characterise changes in endogenous NA levels in both the brain (or at least cerebrospinal fluid) and plasma during periods of nausea and emesis.

Substance P

The neurokinin$_1$ (NK_1) receptor and its endogenous ligand the peptide neurotransmitter, substance P, have been identified as mediators of emetic responses. NK_1 receptors have been localised in emetic brainstem regions such as the area postrema, the solitary nucleus, and the dorsal motor nucleus of the vagus (Watson et al., 1995; Sanger, 2004). There is also evidence of a secondary peripheral role of NK_1 receptors in emesis involving modulation of abdominal vagal afferent activity (Minami et al., 2001).

Since substance P has a predominantly central action, its measurement as a biomarker is problematic. Microdialysis can be used to measure substance P concentrations in the brain (André and Caprioli, 1995), but this method is mainly used in rodents and would be impractical in emetic species such as the dog.

Arginine vasopressin

Plasma arginine vasopressin (AVP) is greatly increased by emetic stimuli with up to an 80-fold increase from baseline levels reported (Rowe et al., 1979). In humans, a positive correlation between plasma AVP increase and nausea induced by motion sickness has been documented (Otto et al., 2006). Increased AVP levels in the plasma have also been detected in dogs following cisplatin treatment (Cubeddu et al., 1990c). Infusion of arginine vasopressin induces nausea in humans (Kim et al., 1997) and can induce both nausea and gastric dysrhythmias in dogs (Chen et al., 2003). Characterisation of vasopressin receptor distribution and the use of selective vasopressin antagonists should enable identification of the role of the vasopressin pathway in nausea. It is currently unclear whether AVP has a role in the induction of nausea or is released as a consequence of nausea.

There is potential for plasma AVP to be used as an objective marker of nausea resulting from motion sickness and drug administration. AVP has the closest correlation with onset and offset of nausea of all candidate hormones and neurotransmitters measured during acute nausea related to motion in human volunteers (Stern et al., 2011).

Cortisol

The role of cortisol in the physiology of nausea is currently unknown; however, corticosteroids have some anti-emetic and anti-nausea properties in humans (Aapro and Alberts, 1981). As a result, dexamethasone is often included as a component of anti-emetic regimens for the treatment of CINV in human medicine (Roila et al., 2010).

In human patients, night-time urinary cortisol concentrations prior to cancer-chemotherapy were inversely related to nausea and patients with low baseline cortisol reported significantly higher

nausea scores (Fredrikson et al., 1992). Additionally, serum cortisol concentrations were significantly reduced 1 h following either cisplatin or carboplatin/cyclophosphamide administration (Morrow et al., 2002a). Further studies are required to fully determine the association between cortisol concentrations and the intensity of nausea and to elucidate the role of cortisol in the experience of nausea.

Autonomic activity

Autonomic tone almost certainly plays a role in nausea, since the autonomic nervous system controls many of the prodromal signs of emesis (e.g. salivation, sweating and vasoconstriction), which are activated simultaneously with the sensation of nausea (Morrow et al., 2000, 2002b). Basal autonomic tone has been linked to the likelihood of developing anticipatory nausea and vomiting (ANV) due to cancer chemotherapy (Kvale et al., 1991). In this study, human patients that developed ANV had significantly higher sympathetic reactivity compared to the no-ANV group. An increase in sympathetic activity and a decrease in parasympathetic activity have been associated with motion sickness (Hu et al., 1991; Doweck et al., 1997). Gastric myoelectrical activity was measured in dogs by Yu et al. (2009), who demonstrated that the percentage of normal slow waves were significantly decreased prior to and during cisplatin-induced emesis.

It is not clear whether autonomic activity alone is nausiogenic, or if it is part of a more complex mechanism leading to nausea. Alternatively, it is possible that autonomic activation occurs as a consequence of other nausiogenic mechanisms, rather than driving nausea directly. Nevertheless, measuring autonomic activity through the analysis of heart rate variability (Stern et al., 2011), electrogastrography, or changes in skin conductivity might prove to be useful biomarkers to detect nausea before its peak and measure its intensity.

Brain imaging as a biomarker of nausea

Imaging with fMRI has facilitated non-invasive identification of the activation sequence of brain structures involved in the nausea pathway (Napadow et al., 2013). Functional imaging technology is not widely accessible for veterinary species and the utility of fMRI in animals is limited by the fact that it must be carried out in conscious non-sedated subjects.

Anti-nausea potential of current and future antiemetic treatments

In human medicine, all anti-emetic drugs have label claims that they reduce nausea since it is accepted that, in most cases, nausea is a prerequisite of emesis. Although there are some stimuli that induce emesis with little nausea, the two are generally associated. However, it is purely assumption that if a drug prevents emesis, it will also prevent nausea. It is recognised that nausea is more difficult to prevent and treat than emesis. Emesis is an all-or-nothing event and an antiemetic drug is effective if it inhibits emetic stimuli to such a degree that the threshold for the emetic reflex is not reached. However, this could still leave the patient feeling somewhat nauseous, since nausea is a graded phenomenon i.e. one can feel mildly, moderately or severely nauseous. This graded phenomenon can also be implied from observations in veterinary patients of the frequency and severity of nausea behaviours. The understanding of the mechanisms and pathways through which the sensation of nausea occurs would enable the prediction of the most effective anti-nausea drugs.

D_2 receptor antagonists

Metoclopramide, a dopamine$_2$ (D_2) and weak 5-HT$_3$ antagonist, is a commonly used antiemetic in veterinary medicine (Mantione and Otto, 2005) and is effective against apomorphine and cisplatin-induced emesis in dogs (Alphin et al., 1986). A search of the published literature provides no evidence for the anti-nausea effects of metoclopramide in the dog. However, in human medicine, metoclopramide is reported to have efficacy against post-operative nausea following abdominal surgery (Davidson et al., 1979) and also reduces the duration of cisplatin-induced nausea (Gralla et al., 1981).

5-HT$_3$ receptor antagonists

As described earlier, 5-HT$_3$ receptors are present on abdominal vagal afferents and are involved in the detection of emetogens in the gastrointestinal tract. Five-HT receptors also have a central role in emesis. Many types of 5-HT$_3$ antagonists are commercially available as antiemetics, and all use the suffix 'setron' e.g. ondanestron, granisetron or tropisetron. Of these, ondansetron is the most widely used and in dogs as in humans; it is efficacious against acute emesis but not delayed emesis occurring from 1 to 3 days following the administration of chemotherapy (Yamakuni et al., 2000).

Like metoclopramide, the anti-nausea effect of ondansetron is well documented in human patients but less so in veterinary species. Ondansetron has been shown to significantly reduce nausea induced by anaesthesia (Leeser and Lip, 1991), cyclophosphamide (Cubeddu et al., 1990a) and cisplatin (Cubeddu et al., 1990b) in humans. Ondansetron delayed emesis and significantly decreased nausea scores compared with placebo in Beagle dogs administered the daffodil alkaloid lycorine by IV injection (Kretzing et al., 2011b). When administered to cats with chronic kidney disease, mirtazapine, a tetracyclic antidepressant with activity as a 5-HT$_3$ antagonist, had antiemetic effects and increased appetite and activity, possibly suggesting an anti-nausea action. However, nausea was not specifically measured in this study (Quimby and Lunn, 2013).

NK_1 receptor antagonists

Aprepitant was the first drug in this class, approved for human use in 2003, to treat chemotherapy-induced and post-operative nausea and vomiting. Aprepitant significantly increased the number of patients that experienced no nausea or no significant nausea (Poli-Bigelli et al., 2003; Diemunsch et al., 2007).

The NK$_1$ antagonist maropitant is an anti-emetic specifically designed for veterinary use and is licensed for use in dogs and cats. Maropitant is effective at preventing emesis induced by apomorphine, ipecac (Sedlacek et al., 2008), chemotherapeutic agents (Rau et al., 2010) and motion (Conder et al., 2008). Maropitant demonstrated anti-nausiogenic efficacy in dogs treated with cisplatin, significantly reducing VAS measurements for nausea when given up to 19 h prior to or following IV cisplatin infusion (de la Puente-Redondo et al., 2007). However, maropitant did not significantly change nausea scores compared with placebo in dogs receiving doxorubicin treatment for cancer (Rau et al., 2010). Both of these studies employed the VAS system of nausea assessment, which, as mentioned earlier, is subjective and prone to wide inter- and intra-observer variability. There is scope to explore the anti-nausiogenic properties of maropitant further using more objective measures, if these can be developed and validated.

CB_1 receptor agonists

Cannabinoids (CB) are involved in the regulation of nausea. The active ingredient of marijuana, delta-9-tetrahydrocannabinol (Δ^9-THC), has been found to be efficacious in CINV (Tramer et al., 2001),

leading to the development of a synthetic Δ^9-THC, dronabinol, for anti-emetic therapy. The CB_1 receptor agonist HU-210 prevents the development of lithium chloride-induced conditioned gaping; this effect is reversible when rats are also treated with the cannabinoid (CB_1) antagonist rimonobant (Parker and Mechoulam, 2003). Pre-treatment of rats with the fatty acid amide hydrolase (FAAH) inhibitor URB597, which prevents the breakdown of anandamide (an endogenous cannabinoid), prior to lithium chloride-saccharin pairing, attenuated the conditioned gaping response (Cross-Mellor et al., 2007).

The site of action of CB_1 agonists that account for their anti-nausea properties is unknown. Conflicting evidence exists regarding whether the location of target receptors is peripheral or central. Administration of the peripherally restricted CB_1 antagonist, AM6545, failed to induce conditioned taste avoidance or conditioned gaping in rats (Cluny et al., 2010), suggesting a central site of action of CB_1 receptors in the development of conditioned gaping. However, systemic administration of the CB_1 antagonist AM251 increased conditioned gaping in rats, whereas central administration into the lateral and fourth ventricles did not potentiate conditioned gaping. This suggests that nausea is mediated by peripheral CB_1 receptors, or central CB_1 receptors located at a site other than the ventricles (Limebeer et al., 2010). No data are available on cannabinoid receptors and nausea in companion animals.

Conclusions

The mechanisms controlling the genesis and processing of the sensation of nausea are complex and poorly understood. Brain areas involved in nausea perception are diverse, fitting with nausea as a complex perceptual experience. Currently available antiemetic therapies are effective in both preventing and treating emesis, but nausea is still a problem. Novel therapies that are more efficacious for the treatment and prevention of nausea would have clinical value. Current behavioural measures of nausea are sub-optimal and identification of a valid objective marker of nausea in the dog could provide a useful tool for both research and clinical practice. Such an objective marker would be of great value in the veterinary practice to identify circumstances where nausea is problematic, and to increase the veterinarian's awareness of nausea in the veterinary patient population. An objective marker would also have application in research to aid assessment of the efficacy of new anti-emetic compounds in preventing nausea, or to assess the nausiogenic liability of novel chemical entities as an adverse effect. Nausea is a neglected and potentially important area of companion animal medicine, primarily because the subjective nature of nausea makes it challenging to detect clinically, therefore evaluation of the response and choice of appropriate treatment is difficult.

Conflict of interest statement

The authors have received financial support from Zoetis Ltd, which produces Cerenia (maropitant citrate), an anti-emetic for use in dogs and cats. Professor Jonathan Elliott has acted a paid consultant to Pfizer Animal Health now Zoetis Ltd in relation to maropitant and other drugs. Karine Savary-Bataille is currently employed by Zoetis Ltd. Other than mentioned above none of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

Acknowledgements

Financial support was provided by the Biotechnology and Biosciences Research Council (BBSRC), Ref. BB/153237X/1, and Zoetis Ltd. The important input of the European Gastroenterology Council (formerly the European Emesis Council: P. Devauchelle, C. Elwood, V. Freiche, A. German, M. Gualtieri, E. Hall, E.D. Hertog, R. Neiger, D. Peeters and X. Roura) in both the content of this manuscript and in its review is gratefully acknowledged.

References

Aapro, M.S., Alberts, D.S., 1981. High-dose dexamethasone for prevention of cis-platin-induced vomiting. Cancer Chemotherapy and Pharmacology 7, 11–14.
Alphin, R.S., Proakis, A.G., Leonard, C.A., Smith, W.L., Dannenburg, W.N., Kinnier, W.J., Johnson, D.N., Sancilio, L.F., Ward, J.W., 1986. Antagonism of cisplatin-induced emesis by metoclopramide and dazopride through enhancement of gastric motility. Digestive Diseases and Sciences 31, 524–529.
André, P.E., Caprioli, R.M., 1995. In vivo metabolism of substance P in rat striatum utilizing microdialysis/liquid chromatography/micro-electrospray mass spectrometry. Journal of Mass Spectrometry 30, 817–824.
Andrews, P.L., Horn, C.C., 2006. Signals for nausea and emesis: Implications for models of upper gastrointestinal diseases. Autonomic Neuroscience 125, 100–115.
Andrews, P.L., Rapeport, W.G., Sanger, G.J., 1988. Neuropharmacology of emesis induced by anti-cancer therapy. Trends in Pharmacological Sciences 9, 334–341.
Andrews, P.L., Davis, C.J., Bingham, S., Davidson, H.I., Hawthorn, J., Maskell, L., 1990. The abdominal visceral innervation and the emetic reflex: Pathways, pharmacology, and plasticity. Canadian Journal of Physiology and Pharmacology 68, 325–345.
Beleslin, D.B., Strbac, M., 1987. Noradrenaline-induced emesis. Alpha-2 adrenoceptor mediation in the area postrema. Neuropharmacology 26, 1157–1165.
Chelen, W.E., Kabrisky, M., Rogers, S.K., 1993. Spectral analysis of the electroencephalographic response to motion sickness. Aviation, Space, and Environmental Medicine 64, 24–29.
Chen, J.D., Qian, L., Ouyang, H., Yin, J., 2003. Gastric electrical stimulation with short pulses reduces vomiting but not dysrhythmias in dogs. Gastroenterology 124, 401–409.
Cluny, N.L., Vemuri, V.K., Chambers, A.P., Limebeer, C.L., Bedard, H., Wood, J.T., Lutz, B., Zimmer, A., Parker, L.A., Makriyannis, A., et al., 2010. A novel peripherally restricted cannabinoid receptor antagonist, AM6545, reduces food intake and body weight, but does not cause malaise, in rodents. British Journal of Pharmacology 161, 629–642.
Coil, J.D., Hankins, W.G., Jenden, D.J., Garcia, J., 1978. The attenuation of a specific cue-to-consequence association by antiemetic agents. Psychopharmacology 56, 21–25.
Conder, G.A., Sedlacek, H.S., Boucher, J.F., Clemence, R.G., 2008. Efficacy and safety of maropitant, a selective neurokinin 1 receptor antagonist, in two randomized clinical trials for prevention of vomiting due to motion sickness in dogs. Journal of Veterinary Pharmacology and Therapeutics 31, 528–532.
Cross-Mellor, S.K., Ossenkopp, K.P., Piomelli, D., Parker, L.A., 2007. Effects of the FAAH inhibitor, URB597, and anandamide on lithium-induced taste reactivity responses: A measure of nausea in the rat. Psychopharmacology 190, 135–143.
Cubeddu, L.X., Hoffman, I.S., Fuenmayor, N.T., Finn, A.L., 1990a. Antagonism of serotonin S3 receptors with ondansetron prevents nausea and emesis induced by cyclophosphamide-containing chemotherapy regimens. Journal of Clinical Oncology 8, 1721–1727.
Cubeddu, L.X., Hoffmann, I.S., Fuenmayor, N.T., Finn, A.L., 1990b. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. New England Journal of Medicine 322, 810–816.
Cubeddu, L.X., Lindley, C.M., Wetsel, W., Carl, P.L., Negro-Vilar, A., 1990c. Role of angiotensin II and vasopressin in cisplatin-induced emesis. Life Sciences 46, 699–705.
Cubeddu, L.X., Hoffmann, I.S., Fuenmayor, N.T., Malave, J.J., 1992. Changes in serotonin metabolism in cancer patients: Its relationship to nausea and vomiting induced by chemotherapeutic drugs. British Journal of Cancer 66, 198–203.
Cullen, L.K., 1996. Medetomidine sedation in dogs and cats: A review of its pharmacology, antagonism and dose. British Veterinary Journal 152, 519–535.
de la Puente-Redondo, V.A., Tilt, N., Rowan, T.G., Clemence, R.G., 2007. Efficacy of maropitant for treatment and prevention of emesis caused by intravenous infusion of cisplatin in dogs. American Journal of Veterinary Research 68, 48–56.
Davidson, E.D., Hersh, T., Brinner, R.A., Barnett, S.M., Boyle, L.P., 1979. The effects of metoclopramide on postoperative ileus. A randomized double-blind study. Annals of Surgery 190, 27–30.
Diemunsch, P., Gan, T.J., Philip, B.K., Girao, M.J., Eberhart, L., Irwin, M.G., Pueyo, J., Chelly, J.E., Carides, A.D., Reiss, T., et al., 2007. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: A randomized, double-blind phase III trial in patients undergoing open abdominal surgery. British Journal of Anaesthesia 99, 202–211.
Doweck, I., Gordon, C.R., Shlitner, A., Spitzer, O., Gonen, A., Binah, O., Melamed, Y., Shupak, A., 1997. Alterations in R-R variability associated with experimental motion sickness. Journal of the Autonomic Nervous System 67, 31–37.
Elwood, C., Devauchelle, P., Elliott, J., Freiche, V., German, A.J., Gualtieri, M., Hall, E., den Hertog, E., Neiger, R., Peeters, D., et al., 2010. Emesis in dogs: A review. Journal of Small Animal Practice 51, 4–22.
Fan, R.J., Shyu, B.C., Hsiao, S., 1995. Analysis of nocifensive behavior induced in rats by CO2 laser pulse stimulation. Physiology and Behaviour 57, 1131–1137.
Foss, J.F., Bass, A.S., Goldberg, L.I., 1993. Dose-related antagonism of the emetic effect of morphine by methylnaltrexone in dogs. Journal of Clinical Pharmacology 33, 747–751.

Fredrikson, M., Hursti, T., Furst, C.J., Steineck, G., Borjeson, S., Wikblom, M., Peterson, C., 1992. Nausea in cancer chemotherapy is inversely related to urinary cortisol excretion. British Journal of Cancer 65, 779–780.
Fredrikson, M., Hursti, T.J., Steineck, G., Furst, C.J., Borjesson, S., Peterson, C., 1994. Delayed chemotherapy-induced nausea is augmented by high levels of endogenous noradrenaline. British Journal of Cancer 70, 642–645.
Gralla, R.J., Itri, L.M., Pisko, S.E., Squillante, A.E., Kelsen, D.P., Braun, D.W., Jr., Bordin, L.A., Braun, T.J., Young, C.W., 1981. Antiemetic efficacy of high-dose metoclopramide: Randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. New England Journal of Medicine 305, 905–909.
Hahn, K.A., McEntee, M.F., Daniel, G.B., Legendre, A.M., Nolan, M.L., 1997. Hematologic and systemic toxicoses associated with carboplatin administration in cats. American Journal of Veterinary Research 58, 677–679.
Hay Kraus, B.L., 2013. Efficacy of maropitant in preventing vomiting in dogs premedicated with hydromorphone. Veterinary Anaesthesia and Analgesia 40, 28–34.
Hickman, M.A., Cox, S.R., Mahabir, S., Miskell, C., Lin, J., Bunger, A., McCall, R.B., 2008. Safety, pharmacokinetics and use of the novel NK-1 receptor antagonist maropitant (Cerenia) for the prevention of emesis and motion sickness in cats. Journal of Veterinary Pharmacology and Therapeutics 31, 220–229.
Hikasa, Y., Ogasawara, S., Takase, K., 1992. Alpha adrenoceptor subtypes involved in the emetic action in dogs. Journal of Pharmacology and Experimental Therapeutics 261, 746–754.
Holmes, A.M., Rudd, J.A., Tattersall, F.D., Aziz, Q., Andrews, P.L., 2009. Opportunities for the replacement of animals in the study of nausea and vomiting. British Journal of Pharmacology 157, 865–880.
Horn, C.C., 2008. Why is the neurobiology of nausea and vomiting so important? Appetite 50, 430–434.
Horn, C.C., Ciucci, M., Chaudhury, A., 2007. Brain Fos expression during 48 h after cisplatin treatment: Neural pathways for acute and delayed visceral sickness. Autonomic Neuroscience 132, 44–51.
Hornby, P.J., 2001. Central neurocircuitry associated with emesis. American Journal of Medicine 111 (Suppl. 8A), 106S–112S.
Hu, S., Grant, W.F., Stern, R.M., Koch, K.L., 1991. Motion sickness severity and physiological correlates during repeated exposures to a rotating optokinetic drum. Aviation, Space, and Environmental Medicine 62, 308–314.
Japundzic-Zigon, N., Samardzic, R., Beleslin, D.B., 1997. Clonidine-induced emesis: A multitransmitter pathway concept. Pharmacological Research 35, 287–297.
Jenns, K., 1994. Importance of nausea. Cancer Nursing 17, 488–493.
Kenward, H., Pelligand, L., Elliott, J., 2014. Assessment of low-dose cisplatin as a model of nausea and emesis in beagle dogs, potential for repeated administration. Experimental Brain Research 1–13.
Kim, M.S., Chey, W.D., Owyang, C., Hasler, W.L., 1997. Role of plasma vasopressin as a mediator of nausea and gastric slow wave dysrhythmias in motion sickness. American Journal of Physiology 272, G853–G862.
Koch, K.L., 1995. Approach to the patient with nausea and vomiting. In: Textbook of Gastroenterology, Second Ed. JB Lippincott, Philadelphia.
Koch, K.L., 1999. Diabetic gastropathy: Gastric neuromuscular dysfunction in diabetes mellitus: A review of symptoms, pathophysiology, and treatment. Digestive Diseases and Sciences 44, 1061–1075.
Koivuranta, M., Laara, E., 1998. A survey of postoperative nausea and vomiting. Anaesthesia 53, 413–414.
Kowalski, A., Rapps, N., Enck, P., 2006. Functional cortical imaging of nausea and vomiting: A possible approach. Autonomic Neuroscience 129, 28–35.
Krawiec, D.R., 1996. Managing gastrointestinal complications of uremia. Veterinary Clinics of North America: Small Animal Practice 26, 1287–1292.
Kretzing, S., Abraham, G., Seiwert, B., Ungemach, F.R., Krugel, U., Regenthal, R., 2011a. Dose-dependent emetic effects of the Amaryllidaceous alkaloid lycorine in beagle dogs. Toxicon 57, 117–124.
Kretzing, S., Abraham, G., Seiwert, B., Ungemach, F.R., Krugel, U., Teichert, J., Regenthal, R., 2011b. In vivo assessment of antiemetic drugs and mechanism of lycorine-induced nausea and emesis. Archives of Toxicology 85, 1565–1573.
Kristal, O., Lana, S.E., Ogilvie, G.K., Rand, W.M., Cotter, S.M., Moore, A.S., 2001. Single agent chemotherapy with doxorubicin for feline lymphoma: A retrospective study of 19 cases (1994–1997). Journal of Veterinary Internal Medicine 15, 125–130.
Kvale, G., Hugdahl, K., Asbjornsen, A., Rosengren, B., Lote, K., Nordby, H., 1991. Anticipatory nausea and vomiting in cancer patients. Journal of Consulting and Clinical Psychology 59, 894–898.
Lacasse, A., Rey, E., Ferreira, E., Morin, C., Berard, A., 2008. Nausea and vomiting of pregnancy: What about quality of life? BJOG: An International Journal of Obstetrics and Gynaecology 115, 1484–1493.
Le Bars, D., Gozariu, M., Cadden, S.W., 2001. Animal models of nociception. Pharmacological Reviews 53, 597–652.
Leeser, J., Lip, H., 1991. Prevention of postoperative nausea and vomiting using ondansetron, a new, selective, 5-HT3 receptor antagonist. Anesthesia and Analgesia 72, 751–755.
Limebeer, C.L., Parker, L.A., 1999. Delta-9-tetrahydrocannabinol interferes with the establishment and the expression of conditioned rejection reactions produced by cyclophosphamide: A rat model of nausea. Neuroreport 10, 3769–3772.
Limebeer, C.L., Parker, L.A., 2000. The antiemetic drug ondansetron interferes with lithium-induced conditioned rejection reactions, but not lithium-induced taste avoidance in rats. Journal of Experimental Psychology. Animal Behavior Processes 26, 371–384.
Limebeer, C.L., Parker, L.A., 2003. The 5-HT1A agonist 8-OH-DPAT dose-dependently interferes with the establishment and the expression of lithium-induced conditioned rejection reactions in rats. Psychopharmacology 166, 120–126.
Limebeer, C.L., Parker, L.A., Fletcher, P.J., 2004. 5, 7-dihydroxytryptamine lesions of the dorsal and median raphe nuclei interfere with lithium-induced conditioned gaping, but not conditioned taste avoidance, in rats. Behavioral Neuroscience 118, 1391.
Limebeer, C.L., Hall, G., Parker, L.A., 2006. Exposure to a lithium-paired context elicits gaping in rats: A model of anticipatory nausea. Physiology and Behavior 88, 398–403.
Limebeer, C.L., Vemuri, V.K., Bedard, H., Lang, S.T., Ossenkopp, K.P., Makriyannis, A., Parker, L.A., 2010. Inverse agonism of cannabinoid CB1 receptors potentiates LiCl-induced nausea in the conditioned gaping model in rats. British Journal of Pharmacology 161, 336–349.
Lucot, J.B., Crampton, G.H., 1986. Xylazine emesis, yohimbine and motion sickness susceptibility in the cat. Journal of Pharmacology and Experimental Therapeutics 237, 450–455.
Mantione, N.L., Otto, C.M., 2005. Characterization of the use of antiemetic agents in dogs with parvoviral enteritis treated at a veterinary teaching hospital: 77 cases (1997–2000). Journal of the American Veterinary Medicine Association 227, 1787–1793.
Mayer, U.K., Glos, K., Schmid, M., Power, H.T., Bettenay, S.V., Mueller, R.S., 2008. Adverse effects of ketoconazole in dogs–A retrospective study. Veterinary Dermatology 19, 199–208.
Medleau, L., Chalmers, S.A., 1992. Ketoconazole for treatment of dermatophytosis in cats. Journal of the American Veterinary Medicine Association 200, 77–78.
Melzack, R., Rosberger, Z., Hollingsworth, M.L., Thirlwell, M., 1985. New approaches to measuring nausea. Canadian Medical Association Journal 133, 755–758, 761.
Miller, A.D., Rowley, H.A., Roberts, T.P., Kucharczyk, J., 1996. Human cortical activity during vestibular- and drug-induced nausea detected using MSI. Annals of the New York Academy of Sciences 781, 670–672.
Minami, M., Endo, T., Yokota, H., Ogawa, T., Nemoto, M., Hamaue, N., Hirafuji, M., Yoshioka, M., Nagahisa, A., Andrews, P.L., 2001. Effects of CP-99, 994, a tachykinin NK(1) receptor antagonist, on abdominal afferent vagal activity in ferrets: Evidence for involvement of NK(1) and 5-HT(3) receptors. European Journal of Pharmacology 428, 215–220.
Minami, M., Endo, T., Hirafuji, M., Hamaue, N., Liu, Y., Hiroshige, T., Nemoto, M., Saito, H., Yoshioka, M., 2003. Pharmacological aspects of anticancer drug-induced emesis with emphasis on serotonin release and vagal nerve activity. Pharmacology and Therapeutics 99, 149–165.
Morrow, G.R., Andrews, P.L., Hickok, J.T., Stern, R., 2000. Vagal changes following cancer chemotherapy: Implications for the development of nausea. Psychophysiology 37, 378–384.
Morrow, G.R., Hickok, J.T., Andrews, P.L., Stern, R.M., 2002a. Reduction in serum cortisol after platinum based chemotherapy for cancer: A role for the HPA axis in treatment-related nausea? Psychophysiology 39, 491–495.
Morrow, G.R., Roscoe, J.A., Hickok, J.T., Andrews, P.R., Matteson, S., 2002b. Nausea and emesis: Evidence for a biobehavioral perspective. Supportive Care in Cancer 10, 96–105.
Muth, E.R., Stern, R.M., Thayer, J.F., Koch, K.L., 1996. Assessment of the multiple dimensions of nausea: The Nausea Profile (NP). Journal of Psychosomatic Research 40, 511–520.
Napadow, V., Sheehan, J.D., Kim, J., Lacount, L.T., Park, K., Kaptchuk, T.J., Rosen, B.R., Kuo, B., 2013. The brain circuitry underlying the temporal evolution of nausea in humans. Cerebral Cortex 23, 806–813.
Otto, B., Riepl, R.L., Otto, C., Klose, J., Enck, P., Klosterhalfen, S., 2006. mu-Opiate receptor agonists – A new pharmacological approach to prevent motion sickness? British Journal of Clinical Pharmacology 61, 27–30.
Parker, L.A., 1998. Emetic drugs produce conditioned rejection reactions in the taste reactivity test. Journal of Psychophysiology 12, 3–13.
Parker, L.A., Limebeer, C.L., 2006. Conditioned gaping in rats: A selective measure of nausea. Autonomic Neuroscience 129, 36–41.
Parker, L.A., Mechoulam, R., 2003. Cannabinoid agonists and antagonists modulate lithium-induced conditioned gaping in rats. Integrative Physiology and Behavioral Sciences 38, 133–145.
Parker, L.A., Rock, E., Limebeer, C., 2010. Regulation of nausea and vomiting by cannabinoids. British Journal of Pharmacology.
Poli-Bigelli, S., Rodrigues-Pereira, J., Carides, A.D., Julie Ma, G., Eldridge, K., Hipple, A., Evans, J.K., Horgan, K.J., Lawson, F., 2003. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 97, 3090–3098.
Quimby, J., Lunn, K., 2013. Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: A masked placebo-controlled crossover clinical trial. The Veterinary Journal 197, 651–655.
Rau, S.E., Barber, L.G., Burgess, K.E., 2010. Efficacy of maropitant in the prevention of delayed vomiting associated with administration of doxorubicin to dogs. Journal of Veterinary Internal Medicine 24, 1452–1457.
Ritter, S., McGlone, J.J., Kelley, K.W., 1980. Absence of lithium-induced taste aversion after area postrema lesion. Brain Research 201, 501–506.
Rock, E.M., Benzaquen, J., Limebeer, C.L., Parker, L.A., 2009. Potential of the rat model of conditioned gaping to detect nausea produced by rolipram, a phospho-diesterase-4 (PDE4) inhibitor. Pharmacology, Biochemistry, and Behavior 91, 537–541.
Roila, F., Herrstedt, J., Aapro, M., Gralla, R.J., Einhorn, L.H., Ballatori, E., Bria, E., Clark-Snow, R.A., Espersen, B.T., Feyer, P., et al., 2010. Guideline update for MASCC

and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: Results of the Perugia consensus conference. Annals of Oncology 21 (Suppl. 5), v232–v243.
Rossmeisl, J.H., Jr., 2010. Vestibular disease in dogs and cats. Veterinary Clinics of North America: Small Animal Practice 40, 81–100.
Rowe, J.W., Shelton, R.L., Helderman, J.H., Vestal, R.E., Robertson, G.L., 1979. Influence of the emetic reflex on vasopressin release in man. Kidney International 16, 729–735.
Sanger, G.J., 2004. Neurokinin NK1 and NK3 receptors as targets for drugs to treat gastrointestinal motility disorders and pain. British Journal of Pharmacology 141, 1303–1312.
Sanger, G.J., Andrews, P.L., 2006. Treatment of nausea and vomiting: Gaps in our knowledge. Autonomic Neuroscience 129, 3–16.
Schwartz, M.D., Jacobsen, P.B., Bovbjerg, D.H., 1996. Role of nausea in the development of aversions to a beverage paired with chemotherapy treatment in cancer patients. Physiology and Behavior 59, 659–663.
Sedlacek, H.S., Ramsey, D.S., Boucher, J.F., Eagleson, J.S., Conder, G.A., Clemence, R.G., 2008. Comparative efficacy of maropitant and selected drugs in preventing emesis induced by centrally or peripherally acting emetogens in dogs. Journal of Veterinary Pharmacology and Therapeutics 31, 533–537.
Shelke, A.R., Mustian, K.M., Morrow, G.R., 2004. The pathophysiology of treatment-related nausea and vomiting in cancer patients: Current models. Indian Journal of Physiology and Pharmacology 48, 256–268.
Soderpalm, A.H., Schuster, A., de Wit, H., 2001. Antiemetic efficacy of smoked marijuana: Subjective and behavioral effects on nausea induced by syrup of ipecac. Pharmacology, Biochemistry, and Behavior 69, 343–350.
Stern, R.M., Koch, K.L., Andrews, P.L.R., 2011. Nausea: Mechanisms and Management. Oxford University Press, New York.
Tatewaki, M., Strickland, C., Fukuda, H., Tsuchida, D., Hoshino, E., Pappas, T.N., Takahashi, T., 2005. Effects of acupuncture on vasopressin-induced emesis in conscious dogs. American Journal of Physiology – Regulatory Integrative and Comparative Physiology 288, R401–R408.
Tramer, M.R., Carroll, D., Campbell, F.A., Reynolds, D.J., Moore, R.A., McQuay, H.J., 2001. Cannabinoids for control of chemotherapy induced nausea and vomiting: Quantitative systematic review. British Medical Journal 323, 16–21.
Vaha-Vahe, T., 1989. The clinical efficacy of medetomidine. Acta Veterinaria Scandinavica. Supplementum 85, 151–153.
Villablanca, J.R., Harris, C.M., Burgess, J.W., de Andres, I., 1984. Reassessing morphine effects in cats: I. Specific behavioral responses in intact and unilaterally brain-lesioned animals. Pharmacology, Biochemistry, and Behavior 21, 913–921.
Watson, J.W., Gonsalves, S.F., Fossa, A.A., McLean, S., Seeger, T., Obach, S., Andrews, P.L., 1995. The anti-emetic effects of CP-99,994 in the ferret and the dog: Role of the NK1 receptor. British Journal of Pharmacology 115, 84–94.
Yamakuni, H., Sawai, H., Maeda, Y., Imazumi, K., Sakuma, H., Matsuo, M., Mutoh, S., Seki, J., 2000. Probable involvement of the 5-hydroxytryptamine(4) receptor in methotrexate-induced delayed emesis in dogs. Journal of Pharmacology and Experimental Therapeutics 292, 1002–1007.
Yamamoto, T., Fujimoto, Y., Shimura, T., Sakai, N., 1995. Conditioned taste aversion in rats with excitotoxic brain lesions. Neuroscience Research 22, 31–49.
Yap, K.Y., Low, X.H., Chui, W.K., Chan, A., 2012. Computational prediction of state anxiety in Asian patients with cancer susceptible to chemotherapy-induced nausea and vomiting. Journal of Clinical Psychopharmacology 32, 207–217.
Yu, X., Yang, J., Hou, X., Zhang, K., Qian, W., Chen, J.D., 2009. Cisplatin-induced gastric dysrhythmia and emesis in dogs and possible role of gastric electrical stimulation. Digestive Diseases and Sciences 54, 922–927.