Review

Nausea: Current knowledge of mechanisms, measurement and clinical impact

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A B S T R A C T
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.

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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

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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). Prodomal signs of vomiting, such as salivation, cutaneous vasconstriction 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., 2002; 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 temporoparietal 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 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 anxiolytic agents (Coll et al., 1978); however, CTA is also induced when the flavour is paired with non-nausigenic 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 and Parker, 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 Δ9-tetrahydrocannabinol (Δ9-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 nausception could be coined from nausea, the Greek origin of the nausea. By analogy to nociception, nausception 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 nocistimulation (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 nausceptive stimulus. In rodents, this would describe the conditioned gaping behaviour and in other species the proominal 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, nausception 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

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<th>Table 1</th>
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<td>Characteristics of noceptive and posited nauseative responses.</td>
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<tr>
<td>Sensation</td>
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<td>Pain</td>
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<td>Nausea</td>
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a number of chemical emetogens. These emetogens act peripheral-ly 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 (Soderpalma 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 (Minarni 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.

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

<table>
<thead>
<tr>
<th>Stimulus/drug</th>
<th>Representative example</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Purgative emetogen</td>
<td>Apomorphine, syrup of ipecac</td>
<td>(Sedlacek et al., 2008)</td>
</tr>
<tr>
<td>Cytoxic drugs</td>
<td>Cisplatin, doxorubicin, methotrexate, carboplatin</td>
<td>European Emesis Council³ (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)</td>
</tr>
<tr>
<td>Opioids</td>
<td>Morphine, hydromorphone</td>
<td>(Villablanca et al., 1984; Foss et al., 1993; Hay Kraus, 2013)</td>
</tr>
<tr>
<td>Alpha-2 adrenoceptor agonists</td>
<td>Xylazine, medetomidine</td>
<td>(Lusco and Crompton, 1986; Vaba-Vahe, 1989; Hikasa et al., 1992; Cullen, 1996)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Erythromycin and other macrolides, metronidazole, doxycycline</td>
<td>European Emesis Council³</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Ketocnoazole</td>
<td>(Medleau and Chalmers, 1992; Mayer et al., 2008)</td>
</tr>
<tr>
<td>Plant alkaloids</td>
<td>Digoxin, lycorine</td>
<td>European Emesis Council³ (Kretzing et al., 2011a)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>Vasopressin infusion</td>
<td>(Chen et al., 2003; Tatewaki et al., 2005)</td>
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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 100mm line on which a mark is made to denote perceived nausea, where 0mm 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).

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
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-HT₃, 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). Pretreatment of rats with the selective 5-HT₃a 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 (Fredriksen et al., 1994). Alpha₂-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 pretreatment NA excretion is predictive of the intensity of delayed nausea of cancer chemotherapy (Fredriksen 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, (NK₁) receptor and its endogenous ligand the peptide neurotransmitter, substance P, have been identified as mediators of emetic responses. NK₁ 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 NK₁ 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

Table 4

Circumstances associated with nausea in veterinary clinical practice.

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<tr>
<th>Recognised conditions associated with nausea in animals</th>
<th>Recognised association with nausea in humans but lacking evidence in animals</th>
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<tbody>
<tr>
<td>Pancreatitis (European Emesis Council)</td>
<td>Pregnancy (Lacasse et al., 2008)</td>
</tr>
<tr>
<td>Uraemia (Krawiec, 1996)</td>
<td>Diabetes-associated nausea (Koch, 1999)</td>
</tr>
<tr>
<td>Vestibular disease (Rossmeisl, 2010) and motion sickness (Conder et al., 2008)</td>
<td>Post-operative nausea and vomiting (Koivuranta and Laara, 1998)</td>
</tr>
<tr>
<td>Drugs (see Table 2)</td>
<td></td>
</tr>
<tr>
<td>Hormones (vasopressin; Chen et al., 2003)</td>
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</tr>
<tr>
<td>Emetogens (ipecac and apomorphine; Sedlacek et al., 2008)</td>
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necrose scores (Fredrikson et al., 1992). Additionally, serum cortisol concentrations were significantly reduced 1 h following either cisplatin or carboplatin/cyclophosphamide administration (Morrow et al., 2000a, 2002b). 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 prodomal 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; Dowek 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 nauseaogenic, 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 nauseaigenic 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<sub>2</sub> receptor antagonists**

Metoclopramide, a dopamine<sub>2</sub> (D<sub>2</sub>) and weak 5-HT<sub>3</sub> 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<sub>3</sub> receptor antagonists**

As described earlier, 5-HT<sub>3</sub> 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<sub>3</sub> antagonists are commercially available as antiemetics, and all use the suffix ‘tretor’ e.g. ondansetron, 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 (Leeson 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 daf-fold 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<sub>3</sub> 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<sub>1</sub>, 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<sub>1</sub> 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-nauseogenic 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-nauseogenic properties of maropitant further using more objective measures, if these can be developed and validated.

**CB<sub>1</sub>, receptor agonists**

Cannabinoids (CB) are involved in the regulation of nausea. The active ingredient of marijuana, delta-9-tetrahydrocannabinol (Δ<sub>9</sub>-THC), has been found to be efficacious in CINV (Tramer et al., 2001),...
leading to the development of a synthetic Δ²-THC, dronabinol, for anti-emetic therapy. The CB₁ receptor agonist HU-210 prevents the development of lithium chloride-induced conditioned gagging; this effect is reversible when rats are also treated with the cannabinoid (CB₁) antagonist rimonabant (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 gagging response (Cross-Mellor et al., 2007).

The site of action of CB₁ 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 CB₁ antagonist, AM6545, failed to induce conditioned taste avoidance or conditioned gagging in rats (Cluny et al., 2010), suggesting a central site of action of CB₁ receptors in the development of conditioned gagging. However, systemic administration of the CB₁ antagonist AM251 increased conditioned gagging in rats, whereas central administration into the lateral and fourth ventriciles did not potentiate conditioned gagging. This suggests that nausea is mediated by peripheral CB₁ receptors, or central CB₁ receptors located at a site other than the ventriciles (Limebeet 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 antiemetic compounds in preventing nausea, or to assess the nauseogenic 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.

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