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Signals for nausea and emesis: Implications for models of upper gastrointestinal diseases

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Abstract

Nausea and vomiting are amongst the most common symptoms encountered in medicine as either symptoms of diseases or side effects of treatments. In a more biological setting they are also important components of an organism's defences against ingested toxins. Identification of treatments for nausea and vomiting and reduction of emetic liability of new therapies has largely relied on the use of animal models, and although such models have proven invaluable in identification of the anti-emetic effects of both 5-hydroxytryptamine3 and neurokinin1 receptor antagonists selection of appropriate models is still a matter of debate. The present paper focuses on a number of controversial issues and gaps in our knowledge in the study of the physiology of nausea and vomiting including: The choice of species for the study of emesis and the underlying behavioural (e.g. neophobia), anatomical (e.g. elongated, narrow abdominal oesophagus with reduced ability to shorten) and physiological (e.g. brainstem circuitry) mechanisms that explain the lack of a vomiting reflex in certain species (e.g. rats); The choice of response to measure (emesis[retching and vomiting], conditioned flavour avoidance or aversion, ingestion of clay[pica], plasma hormone levels[e.g. vasopressin], gastric dysrhythmias) and the relationship of these responses to those observed in humans and especially to the sensation of nausea; The stimulus coding of nausea and emesis by abdominal visceral afferents and especially the vagus—how do the afferents encode information for normal postprandial sensations, nausea and finally vomiting?; Understanding the central processing of signals for nausea and vomiting is particularly problematic in the light of observations that vomiting is more readily amenable to pharmacological treatment than is nausea, despite the assumption that nausea represents "low" intensity activation of pathways that can evoke vomiting when stimulated more intensely.

Keywords

Nausea; Vomiting; Vagus; Pica; Flavour aversion; Conditioned taste aversion Contents

1. Introduction

Nausea and vomiting are amongst the most common symptoms encountered in medicine. They occur separately and together in a diverse range of diseases, following anaesthesia and surgery, and are side effects of both current drug treatments and novel therapies in development where there may be dose limiting toxicities (for review, see Rudd and Andrews, 2005). Nausea and vomiting are also components of the body's defensive response to toxins accidentally ingested with food. Understanding the pathways by which the sensation of nausea is generated and reflex vomiting is evoked is essential to identifying novel pharmacological approaches to the

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development of antiemetics and also for gaining insights into the underlying defect in disorders where nausea and vomiting are cardinal features, such as cyclic vomiting syndrome where patients may have a median peak intensity of 6 vomits an hour at the height of an attack (Li and Fleisher, 1999). The investigation of pathways and their pharmacology relies to a large extent upon the use of appropriate animal models and this paper will focus on some of the issues related to the selection of models for the investigation of nausea and vomiting and also on the limitations of using species without an emetic reflex (e.g. rats) to study malaise originating in the upper gut.

In addition, research into nausea and vomiting provides important insights into information processing in the autonomic nervous system. For example, the abdominal vagal afferent fibres can evoke both responses, the nucleus tractus solitarius (NTS) plays a major role in integrating the emetic response and is a target for anti-emetic agents, and the autonomic efferents mediate many of the physiological changes that accompany both nausea (e.g., cutaneous vasoconstriction and sweating) and vomiting (e.g., proximal stomach relaxation, retrograde giant contraction of the small intestine). Furthermore, because some motor components (e.g. inhibition of the crural diaphragm) of the emetic reflex occur in other reflexes, such as belching, and diseases, for example gastro-oesophageal reflux disease, the study of emesis may provide fortuitous insights into the pathophysiology and treatment of other disorders. In this context it is important to note that several “agonist” antiemetics are also effective in gastroesophageal reflux disease or models (e.g., the opioid receptor agonist morphine; cannabinoid CB1 receptor agonists, GABA B receptor agonists (Penagini and Bianchi, 1997; Holloway, 2001; Tonini et al., 2004).

2. Choice of species in nausea and emesis research

Vertebrates (fish, amphibia, reptiles, birds and mammals) have significant species differences in the mechanisms and especially the mechanics of vomiting that make it difficult to make more than general comparisons between animals. Even amongst the mammals it may be difficult to extrapolate findings from laboratory animal studies to explain nausea and vomiting in humans, especially as we begin to understand more of the species differences between neurotransmitter receptors and the way that they interact with synthetic ligands (e.g., neurokinin NK1 receptors; Andrews and Rudd, 2004). Emesis (retching and vomiting), which can be overtly measured in some laboratory animals, is much easier to study and interpret than behaviours that have been associated with the subjective experience of nausea. However, even with research on vomiting there are important species differences.

2.1. The vomiting reflex is lacking in some species

In general, the vomiting reflex is arguably not essential for survival; but it is advantageous for ridding the body of ingested toxins and may prove particularly useful for a species in a specific niche. Several mammalian species commonly used in laboratory research, including the rat, mouse, hamster, guinea pig, and rabbit, appear not to have a vomiting reflex. Although a large number of toxicosis studies have been conducted in the rat, a relatively limited number of stimuli, including, gastrointestinal irritants, motion, apomorphine, and cytotoxic drugs, have been used to study behaviours associated with malaise. While there is little doubt that overt emesis has not been observed in the laboratory rat, only a few strains (e.g., Wistar) have been studied, and this may be significant because it is known that conditioned flavour avoidances are variably induced in different strains of mice (e.g., Risinger and Brown, 1996; Risinger and Cunningham, 2000; Bielavska et al., 2002). Furthermore, there are isolated reports of “retching” but not vomiting in mice, which if replicated may suggest that they have a degenerate reflex rather than an absent one (e.g., Furukawa and Yamada, 1980). Rats do have a gag reflex triggered by mechanical stimulation of the pharynx (Andrew, 1956) and a gag has features that could be considered similar to a single retch. This observation provides some evidence that the

emetic reflex is degenerate in rodents. Some potentially emetic stimuli have been used in mice, hamsters, and rabbits to induce conditioned flavour avoidance or pica (measures of malaise; see below) and have failed to induce emesis (e.g., Hobbs et al., 1976; Fox, 1977; Santucci et al., 2000; Christian et al., 2001; Santucci et al., 2002; Yamamoto et al., 2002a). However, before stating that all rodents and lagomorphs lack an emetic reflex it may be wise to undertake further formal studies of this phenomenon using a wide range of doses and stimuli. As an alternative to emesis, the rat and other non-vomiting species probably use rapidly learned aversions to avoid toxicosis (see below). This is supported by the "nibbling" type of food intake in these species and some indications that they are neophobic (avoiding novel foods or tasting a small amount and returning later to ingest more if illness does not occur) (Mitchell, 1976). Both behaviours would serve to limit the consumption of a potentially poisonous meal. Furthermore, the rat and mouse possess more hepatic genes involved in detoxification than the human, and therefore the emetic reflex might provide less advantage in these species (Gibbs et al., 2004). The Rodentia are a very successful Order adapting to a variety of habitats and they account for >40% of all mammalian species (Dawkins, 2004), which provides support for the comment that the vomiting reflex is not essential for survival.

Although apparently absent in rodents and lagomorphs,the vomiting reflex is present in representatives of severalmammalian Orders, including Primates (e.g. human, Cynomologousmonkey, marmoset), Carnivora (dog, cat, ferret), Cetartiodactyla (e.g. pig, sperm whale), and Insectivora (e.g., house musk shrew, Suncus murinus), and it is also present throughout the Vertebrates, being demonstrated in prototypical fish, amphibia, reptiles and birds (Andrews et al., 1990, 2000; King, 1990; Sims et al., 2000; Tanihata et al., 2004). A discussion of the vomiting mechanisms in these non-mammalian species is beyond the scope of the current paper.

There are anatomical and neural circuitry differences between vomiting and non-vomiting mammalian species that would make vomiting difficult for non-emetic species even if they attempted to. The abdominal oesophagus is relatively wider and shorter in emetic species (Andrews, 1995). In addition, a comparison of the mouse and Suncus revealed that in the non-vomiting mouse the vagus had little ability to shorten the oesophagus longitudinally and hence educe one of the resistances to the flow of vomitus (Andrews et al., 2003). In general, the diaphragm appears to be more muscular in the emetic species so far studied with a reduced area of central tendon but this is not a universal finding (Andrews, unpublished observations) and the non-emetic roles of the diaphragm (e.g. breathing, coughing, sneezing, belching, hiccupping) make the significanceof this observation difficult to link to emesis. Taken overall these structural characteristics probably provide greater propulsive power and less resistance for expelling vomitus. Furthermore, the brainstem circuitry, e.g., medial medullary reticular neurons that provide input to phrenic motor neurons, that might be important for the production of emesis appear to be absent in the rat compared to the ferret, an emetic species (Dobbins and Feldman, 1994; Yates et al.,1999). It is worth noting that rats, like emetic species, have an area postrema (AP) but it is difficult to assign specific functions to this brain region because lesions of this site ablate vagal sensory neurons that terminate in the AP and often destroys some portion of the adjacent NTS, which receives a large vagal sensory projection from the gut (Norgren and Smith, 1988). The AP appears to be nonessential for the production of vomiting, e.g., motion can produce emesis in the cat and monkey after AP ablation(Fox et al., 1990) and gastric irritants (e.g., copper sulphate)can also induce emesis in the absence of the AP in the dog (Andrews et al., 2001). Other reflex neural circuitry of the brainstem appears to be similar between vomiting and nonvomiting species, e.g., the cardio-respiratory reflexes in rat versus Suncus (Paton et al., 2000; Smith et al., 2001b). It should also be noted that although rats do not vomit to intragastric stimuli that evoke emesis in susceptible species (e.g. ferret) (Andrews et al., 1990), rats do respond to stimuli such as veratridine and high concentrations of KCl and NaCl by markedly delaying gastric emptying (see Fig. 1). A delay in gastric emptying has been

argued to be a component of the defensive response in rodents and in emetic species because this action would delay delivery of any toxin into the small intestine where it may produce more damage, especially if absorbed (Davis et al., 1986).

Among those animals that have a vomiting reflex there are several important issues that affect the interpretation of research findings across species. (1) There is no consistent profile across species for the rank order of sensitivity to different emetic stimuli. Although data are relatively limited in some species it is clear that the sensitivity profile to emetic stimuli is species dependent. For example, amongst species sensitive to apomorphine the rank order of emetic sensitivity is dog>human>ferret >cat (note: the cat requires doses in the mg/kg range in comparison to other species where the dose is Ag/kg), with Suncus and monkey being unresponsive. For the chemotherapeutic agent cisplatin the rank order is monkey>human>dog>ferret>cat>Suncus; and for total body X-radiation ferret > dog > human = monkey > cat (Andrews et al., 1990). Furthermore, the dog is sensitive to swinging-type motion whereas the cat is resistant (Noble, 1945) and it is argued that dogs appear to have approximately the same sensitivity to motion sickness as man (Money, 1970). Even amongst monkeys there are reports of sensitivity differences between squirrel and rhesus monkeys (Corcoran et al., 1990). (2) Not all emetic species are sensitive to all stimuli that cause vomiting. This is illustrated by Suncus, which unlike most vomiting species does not show emesis to morphine and apomorphine treatments (Selve et al., 1994). Apomorphine-induced emesis, although present in humans, is reported to be absent in the monkey (Brizzee et al., 1955) but present in another primate, the marmoset (Costall et al., 1987). (3) In some cases the function of emesis is different.

In most animals vomiting is a protective function that serves to expel toxins from the gastrointestinal tract prior to absorption, but in some species it is also used to rid the gut of indigestible material, such as bones from the guts of birds, hairballs from crocodiles and indigestible squid beaks in sharks (Darolova, 1991; Andrews et al., 2000), whilst vomiting is used as means of defence when Petrels are threatened. In addition, some species regurgitate partially digested food from the stomach to feed the young and relatives (e.g. wild dogs; Van Lawick-Goodall and Van Lawick-Goodall, 1970). Emesis might also serve as an anticipatory response generated by cognitive, visual, or flavour stimuli, and several categories of stimuli produce incidental activation of the emetic reflex, including chemotherapy, stress, intracranial pressure, and motion. Other behaviours also appear to be very similar to emesis. Although rumination and regurgitation are functionally different from vomiting and lack the propulsive power of emesis, the neural systems engaged in these different behaviours might be similar, e.g., in sheep (Carr et al., 1983).

2.2. What do conditioned flavour avoidance (CFA) and clay ingestion (pica) measure?

In species that do not possess a vomiting reflex, such as the rat, it is common to measure a conditioned flavour avoidance (CFA) or clay ingestion (pica; consumption of non-nutritive substances) as an index of malaise. It is tempting to be anthropomorphic and conclude that these measures reflect “nausea,” but we have no way of knowing whether this is true with reference to the human experience of nausea. We know that CFA and pica are associated with sickness and malaise, and appear to be additional strategies by which animals deal with toxicosis. Furthermore, unlike emesis, we lack an adequate understanding of the physiology of nausea and have little basis for comparing the behaviours of CFA and pica with reports of nausea in humans. However, investigations of the neural systems that produce CFA and pica might shed some light on the physiology of human nausea because these systems appear to have related neural circuitry and pharmacology, e.g., antiemetic drugs inhibit CFA and pica (e.g., Limebeer and Parker, 2000; Saeki et al., 2001; Rudd et al., 2002). Table 1 shows a list of species and stimuli that have been using to study emesis, CFA, and pica.

2.2.1. Conditioned flavour avoidance (CFA)—Many species show CFA or learned flavour aversion to foods or flavours associated with toxicosis, including humans (Mattes et al., 1991; Mattes, 1994). CFA is used extensively to study malaise in laboratory animals, particularly the rat. In many cases this effect is simply called a conditioned “taste” aversion or “CTA.” However, there are two problems with this terminology. First, the modality of the conditioned stimulus is not always known, particularly with learned responses to complex foods. The conditioned stimulus could be any one of the three components of flavour, which include gustation, olfaction, or chemaesthesia (touch, temperature, or irritation sensitivity, subserved by trigeminal innervation of the oral cavity), or a combination of these. Therefore the phenomenon is more properly referred to as a conditioned “flavour” avoidance or aversion in a general sense, particularly when the modality of the flavour component for the conditioned stimulus has not been determined.

The second problem is the distinction between conditioned flavour avoidance and aversion. Typically in testing this phenomenon in laboratory animals, a novel flavour is paired with injection of a suspected toxin. When animals are later tested they avoid consumption of a flavoured solution that was associated with toxicosis, demonstrating a CFA. In contrast, a conditioned flavour “aversion” must be tested by measuring consumption of a flavoured fluid that is directly infused through a cannula implanted in the oral cavity (Parker, 1995). This methodological difference can critically affect the interpretation of results because even drugs with rewarding properties, such as amphetamines and cocaine, produce CFA, but do not generate learned flavour aversions in the rat (Parker, 1995); however, there may be important species differences here because some emetic species show amphetamine-induced CFA, e.g., cat and ferret, but Suncus does not (Rabin and Hunt, 1992). Consequently, CFA may not always represent malaise in the rat. For example, an antiemetic drug, a 5-HT3 (5-hydroxytryptamine; serotonin) receptor antagonist, had no effect on CFA but did attenuate learned flavour aversions (tested with intra-oral infusions) produced by intra-peritoneal injections of lithium chloride (LiCl, a gastrointestinal irritant) (Rudd et al., 1998; Limebeer and Parker, 2000). Nearly all of the references cited in the present review refer to results with bottle consumption measures, and are therefore tests of CFA and may not represent learned flavour aversions.

It is likely that learned flavour aversion is an indicator of malaise or nausea, and this type of learning might serve to predict foods that should be avoided. A similar learning process may occur in cancer patients because they often show learned avoidance to foods, or even environmental stimuli, associated with chemotherapy (Mattes et al., 1991; Mattes, 1994; Matteson et al., 2002). In laboratory animals learned flavour aversion produced by emetogenic treatments, including cytotoxic chemotherapy agents, can be blocked by anti-emetic medications. Ondansetron, a 5-HT3 receptor antagonist, and delta-9-tetrahydrocannabinol, a cannabinoid receptor agonist, which inhibit nausea and vomiting in humans (e.g., Cassidy et al., 1988; Massidda and Ionta, 1996), suppress learned flavour aversions in rats produced by intra-peritoneal injections of LiCl or cyclophosphamide, a chemotherapy agent (Limebeer and Parker, 1999, 2000).

The relation between CFA or learned flavour aversion and malaise might be directly assessed by using emetogenic stimuli to produce CFA in emetic species. To date, there are no reports showing conditioned flavour aversion, using intra-oral infusion testing, in an emetic species. However, several studies show toxicosis-induced CFA in emetic species, including human, cat, dog, monkey, Suncus, and ferret (e.g., Jackson and Smith, 1978; Vavilova and Kassil, 1984; Rabin et al., 1986b; Fox et al., 1990; Rabin and Hunt, 1992; Smith et al., 2001a). These studies suggest a complex relation between a toxin’s emetogenic potential and its potency to produce a CFA. For example, although radiation and LiCl produce vomiting in the ferret, LiCl treatment, but not radiation, induced a CFA (Rabin and Hunt, 1992). Further studies using

conditioned flavour aversion testing, with intra-oral infusion testing, might clarify the relation between emesis, learned flavour aversion, and CFA.

It is difficult to assess the physiology for the generation of malaise using CFA or learned flavour aversion testing because many pharmacological and lesion treatments to the brain affect neural processes, such as learning and memory, that are not specifically involved in the systems for toxin detection. Additionally, it is very difficult to assess the properties of the toxin detection system using CFA testing because the conditioning protocol involves a delay in testing that is not conducive to a detailed temporal analysis of malaise. For example, it is clear from research on emesis that an analysis of the acute and delayed phases of toxin detection is critical, but this type of investigation is not possible using CFA or learned flavour aversion testing (Hesketh et al., 2003). Although CFA and learned flavour aversion appear to measure the malaise producing potential of a stimulus, this is probably not always true. For example, intra-cerebroventricular infusions of neuropeptide Y produce robust increases in food intake in the rat, but also generate learned flavour aversions (Sipols et al., 1992), which suggests that the hunger stimulus can also produce conditioned flavour aversion.

2.2.2. Kaolin ingestion (pica)—Another way to test for malaise is to measure the consumption of non-nutritive substances following a toxic treatment. Ingestion of dirt or clay, also called pica, in response to toxicosis is a common phenomenon in animals and is also observed in humans (Reid, 1992; Root-Bernstein and Root-Bernstein, 2000; Engel, 2002; Kushner et al., 2004). Rats injected with toxins or subjected to motion consume non-nutritive clay (kaolin) that they would normally not ingest (Mitchell et al., 1977a; Takeda et al., 1993; Santucci et al., 2000; Saeki et al., 2001; Yamamoto et al., 2002a). The presence of pica in mice is controversial with some studies reporting it (Santucci et al., 2000, 2002; Yamamoto et al., 2002a) whilst others do not (Liu et al., 2005). The consumption of clay induced by toxicosis might represent an adaptive response to bind or dilute a toxin in the gastrointestinal tract and reduce its adverse effects on the organism. Clay is particularly effective for binding and diluting toxic chemicals (e.g., Phillips et al., 1995; Sarr et al., 1995; Phillips, 1999), and pica seems to be a specific response in rats because they select clay rather than pebbles or soil when poisoned (Mitchell et al., 1976). However, pica can also be related to nutritional needs; mineral deficiencies in humans and other animals can promote ingestion of clay and other materials that are rich in minerals (e.g., Reynolds et al., 1968; Smith and Halsted, 1970; Roselle, 1970).

Evidence indicates that the positive relation between level of toxicosis and pica is not always maintained at higher doses of a toxin. For example, a high dose of cisplatin, 6 mg/kg, in the rat failed to generate the delayed phase of kaolin consumption, 48–72 h after injection, that was characteristic of a lower dose, 3 mg/kg; and the high dose was associated with successive reductions in food intake and body weight over the 3 days after cisplatin treatment (Rudd et al., 2002). This effect appears to be counterintuitive but high doses of toxins might make animals unable to eat kaolin. However, this phenomenon needs to be investigated using stimuli other than cisplatin as it induces marked gastric stasis and the reduction in kaolin intake may be secondary to this effect.

There are compelling relations between pica, CFA and emesis. Like CFA, pica can be a learned response. Treatment with LiCl or cyclophosphamide produce CFA to a saccharin flavoured solution in the rat and subsequent access to this flavour will stimulate kaolin intake (Mitchell et al., 1977b). Furthermore, there appears to be a close association between the neuropharmacology of toxicosisinduced pica and emesis. Like emesis in cancer patients receiving chemotherapy (Tsukada et al., 2001; Hesketh et al., 2003; de Wit et al., 2004), cisplatin-induced pica in the rat can be characterized into acute and delayed phases that are most sensitive to 5-HT3 and NK1 receptor antagonists, respectively (Saeki et al., 2001; Rudd

et al., 2002). However, the relation between emesis and pica is not always so clear. Diphenidol, an anti-emetic drug in humans, is a potent inhibitor of apomorphine-induced pica in the rat (Takeda et al., 1995), but does not affect emesis induced by apomorphine in the dog or ferret (Nakayama et al., 2004). To directly relate pica to emesis it is important to test both phenomena in the same species. Two studies using Suncus have addressed this issue and show that although emesis was induced by treatment with copper sulphate, nicotine, and cisplatin, none of these agents stimulated pica (Yamamoto et al., 2004; Liu et al., 2005).

2.3. Neurohypophyseal hormonal secretions and gastric dysrhythmias as measures of nausea?

Toxins and treatments that produce nausea and vomiting can potentially inhibit behavioural systems that generate CFA and pica, which might lead to an underestimation of the level of malaise. One way to avoid this problem is to measure a correlate of malaise that does not depend on animal behaviour. Blood levels of the neurohypophyseal hormones, vasopressin (ADH) and oxytocin, and gastric dysrhythmia are two physiological parameters that are proposed to be correlates of malaise in animal models and reports of nausea in humans.

Although vasopressin is normally secreted in response to reduced hydration, vasopressin is elevated in well hydrated humans who experience nausea, e.g., nausea produced by gastric distension with a water load can elevate vasopressin levels (Rowe et al., 1979). Many treatments that produce nausea and vomiting, such as apomorphine, chemotherapy, motion, and cholecystokinin, also increase plasma vasopressin to varying extents including to levels exceeding maximal levels for anti-diuresis (Rowe et al., 1979; Fisher et al., 1982; Grant et al., 1986; Feldman et al., 1988; Miaskiewicz et al., 1989; Edwards et al., 1989; Koch et al., 1990b). Plasma vasopressin levels appear to increase slightly before or at the onset of nausea (Miaskiewicz et al., 1989; Koch et al., 1990b). Administration of vasopressin at supraphysiological doses produced nausea in humans, but when vasopressin was infused to match the plasma level during nausea induced by motion nausea was not reported (Kim et al., 1997). Additionally, apomorphine induces nausea in patients with idiopathic diabetes insipidus despite the absence of an increase in plasma vasopressin (Nussey et al., 1988). Although this does not exclude a role for vasopressin in the genesis of nausea in intact individuals, it is a clear that a rise in plasma vasopressin is not essential for the production of nausea under all circumstances and taken together with the studies of vasopressin infusion and plasma levels could indicate that vasopressin requires an additional factor(s) to be present for the induction of nausea when it is released at a lower concentration. This appears to be particularly likely in the case of the circular vection model of motion sickness (Kim et al., 1997).

Animal models also show an increase in neurohypophyseal hormonal secretions after treatments that produce emesis or malaise. Doses of apomorphine and cholecystokinin (CCK) that induce emesis in the ferret also elevate plasma vasopressin (Hawthorn et al., 1988; Billig et al., 2001), and vasopressin is elevated by electrical stimulation of abdominal vagal afferent fibres (Hawthorn et al., 1988). Importantly, it is plasma oxytocin levels, much more than vasopressin, that is elevated following malaise producing treatments in the rat, e.g., LiCl and CCK treatments (Flanagan et al., 1988; Huang et al., 2000). In contrast emetigenic doses of apomorphine and CCK did not produce an increase in plasma oxytocin levels in the ferret (Hawthorn et al., 1988; Billig et al., 2001). These differences in toxicosis induced neurohypophyseal secretions between species needs to be further studied in other emetic and non-emetic species. In the rat, elevated oxytocin has been implicated in the mechanisms by which they cope with stress induced by non-noxious sensory stimuli, whereas noxious stimuli in the rat are associated with corticotrophin releasing factor (CRF) and vasopressin secretion (Uvnas-Moberg, 1998).

Despite a focus on vasopressin secretion as a correlate of nausea (and oxytocin as a correlate of malaise in the rat) other hormones are increased in subjects with nausea induced by apomorphine, ipecac, and motion, including adrenaline, cortisol, growth hormone, prolactin, adrenocorticotrophic hormone, and pancreatic polypeptide (Eversmann et al., 1978; Feldman et al., 1988; Nussey et al., 1988; Page et al., 1990; Xu et al., 1993). It remains to be determined whether any of these hormones are related to the genesis for the sensation of nausea in contrast to being indicators of the generally "stressful" nature of malaise. It would be helpful to have a plasma "endocrine profile" monitoring a wide range of signalling molecules with multiple emetic challenges under carefully controlled conditions to identify consistent directional changes associated with nausea (cf. gene microarray approach).

A second important correlate of nausea is gastric dysrhythmia, which is an abnormal frequency of the myoelectric activity of the stomach. Motion or intravenous infusion of vasopressin elicited gastric dysrhythmia in humans, and the dysrhythmia was recording prior to reported nausea (Stern et al., 1987; Koch et al., 1990a; Caras et al., 1997). Gastric dysrhythmia is closely correlated with reported nausea in a variety of conditions that produce nausea, including surgery, pregnancy and chemotherapy (Pezzolla et al., 1991; Riezzo et al., 1992; DiBaise et al., 2001). Few studies have been conducted on gastric dysrhythmia in animal models of malaise. Gastric dysrhythmia precedes vomiting in the dog induced by electrical stimulation of the vagus (Ueno and Chen, 2004), and intravenous infusion of vasopressin produces gastric dysrhythmia in the dog (Xu et al., 2005).

It is unknown whether gastric dysrhythmia, or neurohypophyseal hormonal release, has any causative role in the genesis of nausea or malaise produced by a broad range of stimuli. Furthermore, although the acute association between gastric dysrhythmia, or neurohypophyseal secretions, and nausea is well established more research needs to focus on whether these physiological parameters are involved in delayed or chronic nausea and malaise. Reports indicate that gastric dysrhythmia is associated with unexplained chronic nausea and vomiting (You et al., 1981; Abell et al., 1988).

3. The role of pain in nausea and vomiting

The perceptions of visceral pain and nausea are largely distinct. Visceral pain is a poorly localized phenomenon that can be very intense. In contrast, nausea is an unsettling feeling or sensation of queasiness in the stomach. Although these phenomena appear to be separate, nausea is often associated with pain, and conversely pain can produce nausea and vomiting. For example, postoperative pain and nausea occur together, and when pain is reduced, nausea is also inhibited (Andersen and Krohg, 1976). It is also not clear to what extent CFA (or learned flavour aversion) or pica in laboratory animals measures responses to pain, generalized stress, or a state of visceral malaise that might relate to the human perception of nausea.

It is possible that nausea and visceral pain share some neural pathways or that one might modulate the other. The spinal nerves that innervate the gut play an important role in producing visceral pain, and when these pathways are electrically stimulated humans report pain (White, 1943), whereas electrical stimulation of the vagal afferent fibres in humans can induce nausea (Lewis, 1942). Assuming that gut viscerosensory pathways are a necessary component for the genesis of nausea, spinal pathways might be involved in the production of nausea because nausea can persist in humans even after sub-diaphragmatic vagotomy (Troncon et al., 1995). In contrast, the integrity of the vagal pathways is necessary for the production of emesis by stimuli acting on the gut (Andrews et al., 1990). An alternative explanation for the persistence of nausea in patients with sub-diaphragmatic vagotomy is that stimulation of cardiac vagal afferent fibres contributes to nausea in these patients. Evidence suggests that stimulation of cardiac vagal afferent fibres can evoke vomiting and nausea (Abrahamsson and Thoren,

1973). Additionally, the nausea in vagotomized patients could have an endocrine origin (possibly via an action on the area postrema) as nausea is associated with an increase in the plasma levels of a number of hormones including adrenaline (see above). It is also clear that pain can enhance nausea, e.g., migraine headache or facial pain increases nausea (Drummond and Granston, 2004, 2005).

4. Neural circuitry for nausea

Much is known about the neural system responsible for emesis. Input systems that activate the vomiting reflex include cerebral, vestibular, area postrema (also known as the chemoreceptor trigger zone, although this name should not be taken to mean that all systemic agents inducing emesis act here), cardiac, and gastrointestinal vagal afferent fibres. These input systems activate a distributed brainstem system, known collectively as the “vomiting centre.” The somatic and autonomic outputs of this system are well established but the circuitry of the vomiting centre is still a focus of intense research. In contrast to the system for emesis relatively little is known about the neural system responsible for nausea. This lack of information is largely due to the difficulty in establishing an animal model of nausea, as well as technical problems in studying this phenomenon in humans using brain imaging techniques.

Although little is known about the neural system for nausea, this system appears to be anatomically distinct from the neural circuits responsible for emesis. It is clear that the vomiting reflex is contained within the brainstem because even decerebrate animals are capable of vomiting and emesis-like behaviour, e.g., the cat (Miller et al., 1994). It is likely that many of the autonomic responses that occur preand post-emesis are responses of the Fvomiting motor program_ or are responses to the Fstress_ of nausea. In fact many of the autonomic signs of motion sickness can be observed in a decorticate person on an airplane (Borison and MacCarthy, 1983), and are unlikely to contribute to the genesis of nausea. Forebrain areas are required for learning a flavour aversion in rat because decerebrate animals fail to show a conditioned response (Grill and Norgren, 1978). However, although specific ablation of forebrain regions block CFA in the rat it is difficult to determine whether these brain regions are important for the experience of malaise, and perhaps nausea in humans, or are involved in memory and learning processes of CFA (for review see Yamamoto et al., 1994). Currently there are no published reports on the effects of brain or peripheral nerve lesions on pica.

Nausea and emesis also appear to be pharmacologically separable. Despite the introduction of 5-HT3 receptor antagonists (e.g. ondansetron, granisetron) for anti-emetic therapy more than half of patients who receive chemotherapy continue to experience nausea (Herrington et al., 2000; Morrow et al., 2000). Even with the newer, tachykinin NK1 receptor antagonists (e.g., aprepitant) there is less than complete control of the nausea component of chemotherapy (Andrews and Rudd, 2004). Nausea is often considered more troublesome for patients because it can be present continuously in contrast to emesis which usually occurs in discrete episodes. It is usually assumed that nausea is a low level stimulus that if increased would result in emesis. However, counter-intuitively, nausea is more difficult to block pharmacologically than emesis (Morrow et al., 2002b), and nausea and vomiting can be dissociated experimentally by adjusting the stimulus intensity. Nausea and vomiting also occur separately in a number of clinical situations; for example, raised intracranial pressure induces emesis but is said to not be preceded by nausea (Lee and Feldman, 1993) and some cancer patients receiving radio-therapy and pregnant women may experience vomiting without nausea (Tierson et al., 1986; Miralbell et al., 1995). In animal studies LiCl and CCK do not always produce emesis even at high doses when malaise is suggested by behavioural (CFA) or physiological measures (elevated plasma vasopressin or oxytocin) (Rabin and Hunt, 1992; Billig et al., 2001; Smith et al., 2001a).

Collectively, these results indicate that nausea and vomiting are generated by neural systems that are at least partially separate. The brainstem is essential for the integration of the emetic signal and coordination of the motor components of emesis, and the projection of information rostrally from the brainstem to "higher" centres is required for the genesis of the sensation for nausea. Identification of the site at which the nausea and emesis signals diverge in the brainstem is essential for targeting therapeutic interventions likely to influence both nausea and vomiting. Whilst a common pathway for nausea and emesis might apply for stimuli acting via the vagal afferent fibres and the area postrema, it is less clear that nausea requires the same neural routing via the brainstem compared to emesis originating from cerebral or vestibular sites. In this case, nausea originating from cerebral or vestibular sites might directly access the "higher" centres involved in the genesis of nausea without engaging the brainstem circuits responsible for emesis (Rudd and Andrews, 2005). It is worth recalling that Dr. Kyrlov, a colleague of Pavlov's, described studies in the dog showing that nausea, secretion of saliva, vomiting and sleep could all be induced by "the preliminaries of injection" following injection of morphine itself over 5 or 6 days (Pavlov, 1927). In some cases all the symptoms could be induced by "seeing the experimenter", an observation reminiscent of the reports of nausea and vomiting induced in patients when they have encountered the person who administered chemotherapy outside a hospital setting.

4.1. Visceral afferent fibres

Vagal afferent neurons, connecting the gastrointestinal tract to the brain, play a large role in the generation of vomiting (Andrews et al., 1990), and also serve as a pathway for the induction of nausea. In a biological as opposed to a clinical context, the upper gastrointestinal tract vagal afferents are arguably most important post-ingestive system for the induction of nausea (accompanied by reduced food intake, appetite and delayed gastric emptying) and vomiting if the stimulus is sufficiently intense. These peripheral nerve pathways for the initiation of vomiting have been most thoroughly investigated using cancer chemotherapy agents (for review see Rudd and Andrews, 2005). Many chemotherapy agents, such as cisplatin, cause the release of 5-HT from entero-endocrine cells (enterochromaffin) of the gastrointestinal tract that leads to the activation of vagal afferent fibres containing 5-HT3 receptors (Andrews et al., 1988; Minami et al., 1997; Hillsley and Grundy, 1999). 5-HT3 receptor antagonists are very effective blockers of the acute phase of vomiting and partially control the nausea produced by chemotherapy (e.g., Cassidy et al., 1988; Massidda and Ionta, 1996; Morrow et al., 2002b). However, despite the introduction of 5-HT3 receptor antagonists for anti-emetic therapy more than half of patients who receive chemotherapy continue to experience nausea (Herrington et al., 2000; Morrow et al., 2000). Unlike emesis, 5-HT3 receptor antagonists might have their primary effect on nausea through direct action on the brain. These antagonist compounds readily cross the blood brain barrier where they could act on 5-HT3 receptors located throughout the neuroaxis, although present in particularly high levels in the NTS.

Abdominal vagal afferent fibres are not essential for the sensation of nausea because even humans with bilateral abdominal vagotomy experience nausea, which might suggest that spinal pathways play a role in the genesis of nausea by stimuli acting on the gut. There is little information on the role of visceral nerve pathways on animal studies of CFA or pica. Early reports showed that abdominal vagotomy did not affect LiCl-induced CFA (Martin et al., 1978), but did attenuate intra-gastric copper sulphate and motion-induced CFA in the rat (Coil et al., 1978; Fox and McKenna, 1988). There is no information on the effects of vagal lesions on the acquisition of conditioned flavour aversion, using intra-oral infusion testing. Furthermore, as mentioned above, there are no reports on the effects of vagal lesions on toxicosis-induced pica.

4.2. Direct action of stimuli on the brain?

It is also possible that toxins and other treatments act on the brain directly to produce nausea. Activation of the area postrema has been suggested to play a role in CFA produced by copper sulphate and other blood borne toxins (Coil and Norgren, 1981; Borison et al., 1984; Rabin et al., 1985). However, evidence to support this hypothesis has relied on AP ablation experiments, which, as noted above, are difficult to interpret. These studies also did not directly measure learned flavour aversion using the intra-oral infusion method.

Recent research showed that nausea associated with chemotherapy is correlated with a reduction of plasma cortisol levels in cancer patients, which indicates an effect (direct or indirect) on the hypothalamic-pituitary-adrenal axis (Hursti et al., 1993; Morrow et al., 2002a). Studies in rat show elevated plasma cortisol levels with the production of CFA (Smotherman, 1985). Additionally (as mentioned above), there are many potential candidate hormones that might contribute to nausea, including vasopressin, oxytocin, adrenaline, growth hormone, prolactin, adrenocorticotrophic hormone, and pancreatic polypeptide (Eversmann et al., 1978; Feldman et al., 1988; Nussey et al., 1988; Page et al., 1990; Xu et al., 1993). However, the challenge with all the systemic signals for nausea is to understand where and how they gain access to the central nervous system (e.g. via circumventricular organs) and how they then induce the sensation of nausea. It is also possible that some of these systemic agents act either on the gut to disrupt function and it is this which is signalled via the visceral afferents or that they act directly on receptors on the visceral afferent terminals.

4.3. The stimulus and coding of signals for nausea and vomiting

Despite the well established role of the abdominal vagal afferents in emesis, and to a much lesser extent nausea, we have no clear understanding of the information code that is conveyed to the brain by the visceral afferent fibres and how this is encoded to signal nausea or induce vomiting. Activation of the vagal afferent fibres by toxins in the gut appears to operate via detection of toxins by enteroendocrine cells that then release 5-HT as a paracrine factor that activates 5-HT3 receptors on vagal afferent fibres. 5-HT seems to be the predominant neurotransmitter in the abdominal vagal system (Uneyama et al., 2002; Horn et al., 2004) although enteroendocrine cells such as the enterochromaffin cells which contain high levels of 5-HT also contain substance P. There is neurophysiological evidence for complex interactions between 5-HT and SP and the activation of vagal afferent fibres via 5-HT3 and NK1 receptors (Minami et al., 2001). Evidence suggests that serotonin signalling is also used for the detection of nutrients, such as carbohydrates (Li et al., 2001; Zhu et al., 2001), which might serve to promote nutrient absorption and processing and modify food intake. It is therefore puzzling how the vagal system can accomplish these multiple functions, including the sensing of toxins, using a sensory system that appears to be highly likely to provide ambiguous information to the brain.

5. Conclusions

It is clear from the current review that investigating the physiology of nausea and vomiting is very challenging, and much of this difficulty stems from limitations that exist when studying animal models. It is not known which species is most predictive of the neuropharmacology of emesis in humans when all types of emetic stimuli are considered, although in the case of chemotherapy-induced emesis the ferret is probably the species used first to test a candidate antiemetic agent. It is particularly difficult to decide what animal model is most appropriate for studying the symptom of nausea. CFA and pica are potential model responses, usually studied in species lacking an emetic reflex, that can be used to address this issue, however, there are likely to be significant overlaps between systems that generate emesis, CFA, and pica (or associated measures of plasma hormones and gastric dysrythmia) with no guarantee that

any of these responses provide insights into the physiology of human nausea. It is therefore important that results from animal experiments concerning nausea be validated in human studies and that the results of such studies are in turn used to refine appropriate models and abandon inappropriate ones. Ideally we should work towards one widely accepted model of nausea and vomiting for pre-clinical testing of candidate therapies whilst simultaneously increasing human studies particularly in the area of nausea.

The current understanding of nausea and vomiting is also limited by other factors that might be independent of species selection. It is not clear how pain and stress are related to nausea and vomiting. There are a large number of autonomic efferent and hormonal responses that accompany vomiting and the experience of nausea but many of these effects appear to be general Fstress_ responses. It also remains an important question as to how the vagal afferent system codes information related to the genesis of nausea and vomiting. These unresolved issues guarantee that the study of nausea and vomiting will remain an active area of research. This is particularly true because an understanding of the physiology and pharmacology of nausea and vomiting is of cardinal importance for developing Fclean_ drugs that target clinically important diseases as many potential therapeutic approaches have nausea and vomiting as dose limiting toxicities and also for developing drugs acting to reduce both nausea and vomiting in a diverse range of clinical settings.

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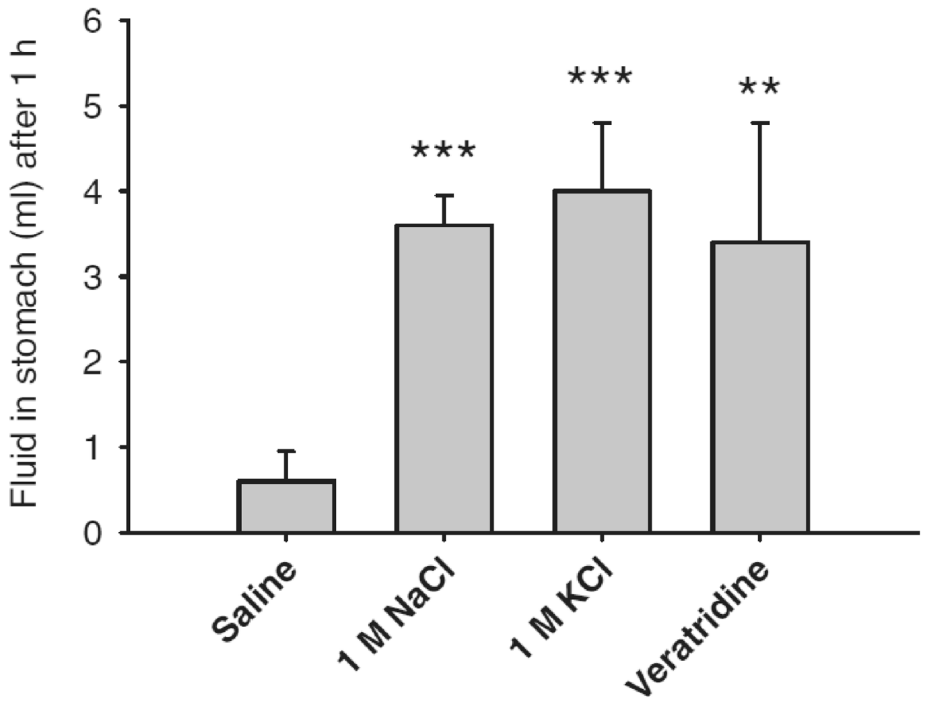

Fig. 1.

Effect of potentially emetic solutions on gastric emptying in the rat. Five millilitres of each solution was gavaged into the stomachs of rats previously deprived of food overnight (n = 5). ***p <0.0001 versus saline and **p <0.001 versus saline. (Andrews, Payne and Hawthorne, unpublished)

Table 1

Mammalian specias and selected stimuli used to elicit emesis, conditioned flavour avoidance (CFA, and pica[a]

		Emesis	CFA	Pica
Cat	Cytotoxic drugs:	Cisplatin (McCarthy and Borison, 1984), Cyclophosphamide (Fetting et al., 1982)		
	Intragastric irritants:	Copper sulfate (Kayashima and Hyama, 1976)		
	Motion	(Crampton and Daunton, 1983)	(Fox et al., 1990)	
	Apomorphine	(Costello and Borison, 1977)		
	Morphine	(Villablanca et al., 1984)		
	Radiation	(Rabin et al., 1986b)	(Rabin et al., 1986b)	
	Nicotine	(Beleslin et al., 1981)		
	Hormones and neurotransmitters:		Angiotensin II (Rabin et al., 1986a)	
	Other:		Amphetamine (Rabin and Hunt, 1992)	
Dog	Cytotoxic drugs:	Cisplatin (Gylys et al., 1979), Cyclophosphamide (Amber et al., 1990)		
	Intragastric irritants:	Ipecac (Gardner et al., 1996), Copper sulfate (Kayashima and Hayama, 1975)	LiCl (Vavilova and Kassil, 1984)	
	Apomorphine	(Harrison et al., 1972)		
	Morphine	(Lefebvre et al., 1981)		
	Radiation	(Cooper and Mattsson, 1979)		
	Nicotine	(Vig, 1990)		
	Hormones and neurotransmitters:	CCK (Levine et al., 1984), Vasopressin (Wu et al., 1985), Peptide YY (Smith et al., 1989)		
Ferret	Cytotoxic drugs:	Cisplatin, cyclophosphamide (Andrews et al., 1990)		
	Intragastric irritants:	Copper sulfate, ipecac, NaCl, KCl (Andrews et al., 1990)	LiCl (Rabin and Hunt, 1992)	
	Apomorphine	(Andrews et al., 1990)		
	Morphine	(Barnes et al., 1991)		
	Radiation	(Andrews et al., 1990)		
Guinea pig	Intragastric irritants:		LiCl (Braveman, 1974)	

		Emesis	CFA	Pica
Hamster	Cytotoxic drugs:		Cyclophosphamide (Hobbs et al., 1976)	
	Intragastric irritants:		LiCl (Fox, 1977)	
	Apomorphine		(Nowlis et al., 1980)	
	Nicotine		(Etscorn et al., 1986)	
	Other:			2-deoxy-D-glucose (Dibattista, 1988)
Human	Cytotoxic drugs:	Chemotherapy (Rudd and Andrews, 2005)	Chemotherapy (Schwartz et al., 1996)	
	Intragastric irritants:	Ipecac (Jackson and Smith, 1978), Copper sulfate (Liu et al., 2001)	Ipecac (Jackson and Smith, 1978)	
	Motion	(Yates et al., 1998)	(Arwas et al., 1989)	
	Apomorphine	(Schofferman, 1976)		
	Morphine	(Bailey et al., 1993)		
	Radiation	(Cordts et al., 1987)	(Carrell et al., 1986)	
	Hormones and neurotransmitters:	CCK (Miaskiewicz et al., 1989)		
	Other:	Pregnancy (Weigel and Weigel, 1989), Reduced intracranial pressure (Mokri, 2004)	Pregnancy (Bayley et al., 2002)	Pregnancy (Corbett et al., 2003; Lopez et al., 2004), Gastric bypass surgery (Kushner et al., 2004)
Monkey	Cytotoxic drugs:	Cisplatin (Fukui et al., 1993)	Cyclophosphamide (Hikami et al., 1990)	
	Intragastric irritants:	Copper sulfate (Fukui et al., 1993)	LiCl (Bergman and Glowa, 1986)	
	Motion	(Wilpizeski et al., 1987)	(Wilpizeski et al., 1987)	
	Radiation	(Brizzee, 1956)		
	Nicotine	(Spealman, 1983)		
	Hormones and neurotransmitters:	CCK (Perera et al., 1993)		
Mouse	Cytotoxic drugs:			Cisplatin (Yamamoto et al., 2002a)
	Intragastric irritants:		LiCl (Risinger and Cunningham, 2000)	
	Motion		(Kinney et al., 1993)	(Santucci et al., 2002)
	Radiation		(Kimeldorf et al., 1960)	
	Nicotine		(Etscorn, 1980)	
	Other:		Magnetic field (Lockwood et al., 2003)	
Rat	Cytotoxic drugs:		Cisplatin (Rudd et al., 1998), Cyclophosphamide (Ader, 1976)	Cisplatin (Takeda et al., 1993)
	Intragastric irritants:		Ipecac (Rudd et al., 1998), Copper sulfate (Coil et al., 1978), LiCl (Coil et al., 1978)	LiCl, Copper sulfate (Hasegawa et al., 1992)
	Motion		(Hutchison, Jr., 1973)	(Mitchell et al., 1977a)
	Apomorphine		(Krane et al., 1976)	(Hasegawa et al., 1992)
	Morphine			(Aung et al., 2004)

		Emesis	CFA	Pica
	Radiation		(Garcia et al., 1955)	(Yamamoto et al., 2002b)
	Nicotine		(Etscorn et al., 1987)	
	Hormones and neurotransmitters:		NPY (Sipols et al., 1992), CCK (Ervin et al., 1995)	NPY (Woods et al., 1998), CCK (McCutcheon et al., 1992)
	Other:		Fat oxidation inhibitors (Singer et al., 1999), 2-deoxy-D-glucose (Stephan et al., 1999), Magnetic field (Houpt et al., 2003)	2-deoxy-D-glucose (Watson et al., 1987)
House Musk Shrew (*Suncus murinus*)	Cytotoxic drugs:	Cisplatin, cyclophosphamide (Matsuki et al., 1988)		
	Intragastric irritants:	Copper sulfate, ipecac (Ueno et al., 1987), LiCl (Parker et al., 2004)	LiCl (Smith et al., 2001a)	
	Motion	(Ueno et al., 1988)	(Smith et al., 2001a)	
	Radiation	(Torii et al., 1993)		
	Nicotine	(Ueno et al., 1987)	Smith et al., 2001a)	
	Hormones and neurotransmitters:	Vasopressin (Ikegaya and Matsuki, 2002)		

[a]For some stimuli only representative studies or review papers are cited. Only the most common mammalian species used in the study of emesis and malaise are shown. A common set of emetic and nauseogenic stimuli, including cytotoxic drugs, intragastric irritants, etc., are included, but a few less commonly used stimuli are also listed because they demonstrate the broad spectrum of stimuli that can produce emesis, CFA, and pica.