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Measuring the nausea-to-emesis continuum in non-human animals: Refocusing on gastrointestinal vagal signaling

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Abstract

Nausea and vomiting are ubiquitous as drug side effects and symptoms of disease; however, the systems that determine these responses are arguably designed for protection against food poisoning occurring at the level of the gastrointestinal (GI) tract. This basic biological pathway using GI vagal afferent communication to the brain is not well understood. Part of this lack of insight appears to be related to current experimental approaches, such as the use of experimental drugs, including systemic chemotherapy and brain penetrant agents, which activate parts of the nausea and vomiting system in potentially unnatural ways. Directly related to this issue is our ability to understand the link between nausea and vomiting, which are sometimes argued to be completely separate processes, with nausea as an unmeasurable response in animal models. An argument is made that nausea and emesis are the efferent limbs of a unified sensory input from the GI tract that is likely to be impossible to understand without more specific animal electrophysiological experimentation of vagal afferent signaling. The current paper provides a review on the use of animal models and approaches to define the biological systems for nausea and emesis and presents a potentially testable theory on how these systems work in combination.

Keywords

nausea; emesis; vomiting; vagus; animal model

Introduction

Nausea and vomiting greatly reduce nutritional balance, appetite, quality of life, and adherence to therapy in patients with gastrointestinal (GI) disorders (Chia and Egan 2008; Murakami et al. 2008; Cherian and Parkman 2012). Antiemetic drugs are often potent for controlling emesis, but largely ineffective for treating nausea (Sanger and Andrews 2006). The design of effective anti-nausea drugs depends on a better understanding of the neuronal and behavioral relationships between the biology of nausea and emesis. To date, many

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studies in this research domain are difficult to interpret because of the use of non-specific emetic stimuli that activate multiple levels of the gut-brain axis (e.g., chemotherapy), as well as using animals, such as rats and mice, which lack an emetic reflex (Horn 2013).

A recent conference at the University of Pittsburgh, Biology and Control of Nausea and Vomiting 2013 (October 3 and 4), highlighted diverse views on the use of non-human animal models to study physiological substrates of nausea and vomiting. Researchers at this meeting, and elsewhere in the literature, either supported the use of or advocated for replacing or reducing animal experimentation in nausea and emesis research. This review presents the view that animal research studies on the biology of nausea and emesis are essential to understand the mechanisms of these systems; the focus here is to provide a brief overview of the use of animal models and methods in this research domain. I will then end this report by presenting a testable theory, based on the potential for gastrointestinal (GI) vagal afferent fibers to provide a unifying input for both nausea and vomiting, with the essential idea that nausea and vomiting operate on a continuum.

What is the human experience of nausea and vomiting?

Humans report nausea as a highly negative perception that involves a feeling of gastric discomfort and an urge to vomit (Stern et al. 2011). Nausea can be described as a specialized warning system, not unlike pain, that derives from signals from the epigastric region; however, people report this symptom separately from abdominal pain (e.g., Hammer and Vogelsang 2007). Nausea does not appear to be a unitary percept; there are differing descriptions of this experience between people and, consequently, survey tools are sometimes focused on capturing its multi-dimensionality (e.g., somatic, GI, and emotional components, Muth et al. 1996; Gianaros et al. 2001). Disgust and the avoidance of food intake are closely associated with nausea (Bjorklund and Hursti 2004), and the feeling of nausea almost always proceeds activation of the emetic reflex. Indeed, most cases of nausea could be defined as an awareness of low intensity emetic activation that fails to reach sufficient intensity to activate the reflex; this suggests that nausea and vomiting fall on a continuum of activation of the emetic system, with low intensity emetic stimulation triggering nausea. Based on experimental psychology, nausea might be more appropriately described as a perception because it is assigned meaning and shaped by experience as opposed to the simple awareness of sensation (Coren et al. 2004).

Nausea is provoked by an extraordinary range of stimuli and conditions, including medical treatments such as cancer chemotherapy, radiotherapy, opioid analgesics, and general anesthetics (Meyer 1999; Kreis 2006; Urba 2007; Chia and Egan 2008; Hesketh 2008). Nausea is also common in chronic diseases; GI disease, late-stage cancer, and AIDS (Glare et al. 2004; Norval 2004; Murakami et al. 2008). Many of these treatments and diseases are believed to provoke nausea by affecting sensory signals arising from the GI tract. Due to the complexity of these various nausea-provoking situations, it is often difficult to determine the precise mechanisms that underlie the instigation and/or maintenance of the resulting nausea, thereby limiting our ability to develop targeted and effective therapies.

In contrast to nausea, vomiting (emesis) can be assessed objectively, independent of reports from the subject. An emetic episode is often composed of several retches leading up to a final vomit (fluid expulsion). Retches are considered to be preparatory events to position the contents in the gastric compartment for efficient vomiting (Andrews et al. 1990b). Although emesis can be directly observed and even recorded continuously via video and detected with computer vision algorithms in animal experiments (Huang et al. 2010), it is sometimes based on non-objective self-reports of daily experience in clinical research studies.

Can we measure nausea in non-human animals?

Nausea, as a self-reported perception in humans, cannot be directly measured in animal models. Nausea-like measures using animal models have been extensively reviewed (Andrews and Horn 2006; Stern et al. 2011; Andrews and Sanger 2013; Horn 2013); here, I will briefly discuss these assays. Animal studies of nausea either focus on behavior or biological indicators. Behavioral metrics include conditioned taste avoidance (CTA), pica, and general measures of behavior. CTA is sometimes distinguished from conditioned taste aversion because a true taste aversion is believed to be associated with a disgust reaction when fluid is infused into the oral cavity (Parker 2003). CTA is generally believed to reflect a conditioned nausea response in humans and preclinical models (Schwartz et al. 1996; Scalera 2002; Parker 2006). Counter-intuitively, rats – but not musk shrews – form a CTA to chemicals with rewarding properties, like morphine and amphetamine (Parker 2006). Pica is the ingestion of a non-nutritive substance, like kaolin clay. Rats and mice ingest kaolin clay in response to injection of toxins (Takeda et al. 1993; Yamamoto et al. 2002); a response that is inhibited by antiemetic drugs (Saeki et al. 2001; Malik et al. 2007). Clay ingestion could be an adaptive response to toxicosis, because silicate clays can bind to toxins in the GI tract, and therefore, limit absorption (Phillips et al. 1995; Phillips 1999). Lastly, changes in ongoing behavioral activity have been used as measure of nausea. Humans report postural change, lying down, and avoidance of eating when experiencing nausea (Stern et al. 2011). In general, animal species with an emetic reflex show postural change and reduced movement and eating (e.g., reduced eating, rearing, and rotation in musk shrews, and reduced eating and increased curling up and lying flat in ferrets) (Bermudez et al. 1988; Watson et al. 1995; Horn et al. 2011; Stern et al. 2011). Reports from my laboratory have explored the possibility of analyzing these patterns of behavior using temporal pattern analysis (Horn et al. 2011; Horn et al. 2013c), a statistical approach to grouping the timing of behavioral events (Magnusson 2000).

Other metrics of nausea-like responses in animal models are the physiological correlates of nausea in humans (Stern et al. 2011). Salivation (Furukawa et al. 1998), gastric dysrhythmia (Percie du Sert et al. 2009a; Percie du Sert et al. 2010), and systemic vasopressin release (Billig et al. 2001) have also been reported in humans experiencing nausea (Koch 1997; Stern et al. 2011), but these parameters can be difficult to measure and require invasive procedures in animal studies (Lau et al. 2005; Percie du Sert et al. 2009a; Percie du Sert et al. 2010).

On one level, the use of the word “nausea” is an approximation of a human perception, which is not only difficult to measure in animals but also a challenge to accurately record in

humans. Indeed, the word traces its roots to a connection with seasickness (i.e., nautical), which appears to not apply to most of its current usage, for example, chemotherapy-induced nausea. Should we simply discard the word nausea? If we do, we can simply redefine nausea as the "detection of emetic system activation." In this manner, it would be easier to define this response in animal experiments. For example, it appears unequivocal that animals are detecting an emetic stimulus in conditioning experiments, even when not vomiting, based on studies of CTA. Low intensity activation of the emetic system (i.e., below the threshold for triggering the reflex) might also be related to the idea of "illness behavior" or "visceral malaise" (Kent et al. 1992).

Can emesis be used as a marker of nausea? It would seem that emesis has at least as much validity as other nausea-like measures used in animal studies. Indeed, in the domain of pain research, nociceptive reflexes in non-human animal models are used as measures of pain sensitivity (Gregory et al. 2013). It is reasonable to consider analogies with the field of pain research as we proceed to develop the field of nausea and vomiting research (see review Horn 2014). The possibility exists to refine measures of emesis to achieve greater sensitivity. In a recent paper from my laboratory, we tried to accomplish this in musk shrews by assessing measures of emesis duration (the time from the first to the last emetic episode) and rate of responding; but the latency to the first emetic response was the most notable success (Horn et al. 2013c). It is often difficult to decide how to analyze behavioral latency data because they often lack a normal distribution with censored values (non-responders); therefore, parametric statistical tests are not an appropriate choice. We chose to use the an approach similar to survival analysis on emesis latency data (Horn et al. 2013c), which can be analyzed by Cox regression and does not require assumptions about the nature of sampling distributions (Jahn-Eimermacher et al. 2011). A follow-up report showed that this type of analysis could be more sensitive than parametric statistics (i.e., total number of emetic episodes) when comparing groups (Horn et al. 2014). Using one of our datasets from a prior study (Horn et al. 2014), Figure 1 illustrates an example of this approach to the analysis of emetic latency. These data show that a high dose of copper sulfate ($CuSO_4$; 120 mg/kg) administered intragastrically to musk shrews produced a statistically significant effect on latency to emesis but not on the total number of emetic responses following vagotomy; the effects of lower doses of $CuSO_4$ on the total number of emetic episodes are more dependent on an intact abdominal vagus (Horn et al. 2014).

Should we take a step back from the outputs of nausea and emesis?

An exclusive focus on only measuring the responses of nausea and vomiting (and modeling such effects in animals) will potentially provide little insight into the sensory processes that lead to these events. Figure 2 shows the division of this system into potential nausea and vomiting efferent pathways. Indeed, a general property of neurosensory systems is divergence within the CNS, which also appears to occur with the system of nausea and vomiting. Focusing on downstream effects (nausea and vomiting) can potentially lead to a more complex problem. Figure 3 shows the critical divergence point of these systems in the nucleus of the solitary tract (NTS) and area postrema (AP), ultimately producing respective efferent pathways for nausea and emesis. Primary afferent signaling to the hindbrain by vagal input (Fig. 3) involves several neurotransmitters, including glutamate, substance P,

and serotonin. Here, I only show neurotransmitters that participate in the first stage of this GI vagal input for nausea and vomiting; the reader is refered to several pharmacological reviews of the nausea and vomiting for indepth coverage (Sanger and Andrews 2006; Andrews and Sanger 2013; Horn et al. 2013b). The AP is often called the “chemoreceptor trigger zone” for emesis; a brain region that is outside the blood-brain barrier and potentially capable of detecting circulating toxins. It is a matter of faith that this functional role applies since it is very difficult to unambiguously confirm its function. Notably, the AP also receives vagal afferent input and lesions to this area affect these signals and potentially damage the adjacent NTS (Andrews et al. 1990a).

An example of the quagmire that can exist when focusing only on downstream effects can be drawn from research on the controls of food intake. In this regard, there are many variables and systems that are associated with producing feeding behavior but primarily these are guided by the sensing of metabolic events (e.g., Friedman 1997), and it is these signaling processes that determine the downstream effects on food intake and energy metabolism. Similarly, nausea and vomiting are the efferent responses and we have only scratched the surface as to what the sensory coding and transduction are for these outputs. It is reasonable to assume that some range of nausea and vomiting in people is produced by GI vagal sensory stimulation, and decoding (and inhibiting) this input might be a more tractable problem than trying to determine the CNS targets for the control of nausea and vomiting. If recent history provides predictive value, identifying and targeting higher brain functions is a huge challenge.

What is the role of gastrointestinal vagal afferent fibers in nausea and vomiting?

Although activation of GI vagal afferent input arguably makes a significant contribution to nausea and emesis, a mechanistic understanding of this GI-to-brain neural pathway is lacking; two common research problems present barriers. First, rodents have significant functional differences compared to humans and other animals, limiting their translational value to studies of nausea and vomiting. Rodents lack a emetic reflex due to a potentially absent hindbrain circuit (Horn et al. 2013a); this removes the opportunity to compare the systems of nausea and emesis in these species. Indeed, without an emesis endpoint in the continuum of stimulation it is less clear that nausea has been generated by a specific stimulus. Second, the use of chemical agents in preclinical studies that act on multiple sites along the GI-to-forebrain axis makes it difficult to determine the contribution of vagal signaling on nausea and emesis. Chemotherapeutic agents have been used extensively to define the biology of nausea and vomiting, but they exert combined actions on vagal signaling and directly on the brain (Andrews et al. 1990a; Percie du Sert et al. 2009b). Oddly, cytotoxic chemotherapy agents, such as cisplatin, produce an acute phase of emesis (up to 24 h) and a delayed phase (the next several days) of emesis in humans (e.g., Hesketh et al. 2003) and animal models (Sam et al. 2001; Sam et al. 2003; Huang et al. 2011). Although the role of an intact vagus seems supported in the acute phase of cisplatin-induced emesis (Hawthorn et al. 1988; Sam et al. 2003), the impact of the vagal ablation on the delayed reponse is generally not supported in few studies that have attempted this testing

(Percie du Sert et al. 2009b). It should also be recognized that the vagotomy procedure leads to plasticity of neural responses (e.g., enhanced sensitivity of abdominal spinal afferents) and it is possible that the vagus does indeed play a role in chemotherapy-induced delayed emesis in the nerve intact animal (Andrews et al. 1990a; Hillsley and Grundy 1999).

Provocative or illusionary motion can also produce nausea and emesis. There is no generally accepted explanation for the adaptive role for these responses, which seem to be ill-designed for protection against ingested toxins. Motion-induced emesis also does not appear to require an intact abdominal vagus (e.g., Horn et al. 2014), but as noted above it is difficult to rule out plasticity following nerve ablation. Illusionary motion-induced nausea is associated with gastric dysrthmia in humans and animals (Stern et al. 2011), and vagotomy can disrupt motion-induced CTA in rats (Fox and McKenna 1988). A review in the current special edition by Bill Yates and his colleagues focuses on the potential for integration of vestibular and emetic GI signals to produce nausea and vomiting (Yates et al. 2014).

The research limitations noted above (i.e., lack of emetic reflex in rodents and non-specific stimuli) can be overcome by using animal models with an emetic reflex, like the musk shrew (*Suncus murinus*), and testing specific GI stimuli. In humans and preclinical models with an emetic reflex, application of gastric stretch or toxins to the gastric lumen produce nausea and emesis (Blackshaw et al. 1987; Ladabaum et al. 1998; Araya et al. 2001; Olivares et al. 2001; Hu et al. 2007; Uchino et al. 2008). Preclinical research using intragastric $CuSO_4$ (a mucosal irritant) has provided significant insights into this GI pathway: 1) $CuSO_4$ stimulates release of 5-HT from enteroendocrine cells in ferrets; 2) intragastric $CuSO_4$ increases vagal afferent activity in ferrets; 3) abdominal vagotomy markedly inhibits intragastric $CuSO_4$-induced emesis in dogs, ferrets, and musk shrews; and, 4) systemic antagonism of 5-HT_4 receptors blocks $CuSO_4$-induced emesis in dogs, ferrets, and musk shrews (Bhandari and Andrews 1991; Makale and King 1992; Fukui et al. 1994; Endo et al. 1995; Reynolds et al. 1995; Hu et al. 2007). In contrast, 5-HT_3 antagonists fail to inhibit intragastric $CuSO_4$-induced emesis in ferrets, dogs, and musk shrews (Bhandari and Andrews 1991; Yoshida et al. 1992; Ito et al. 1995). Although 5-HT_3 signaling has been a dominant target in the biology of nausea and emesis, antagonists of this receptor can produce effects by action at central sites (Marazziti et al. 2001); and, potentially at presynaptic sites on vagal afferents in the hindbrain (Fig. 3). The role of the 5-HT_4 receptor in nausea and vomiting represents an under-developed potential therapeutic target (Sanger 2009; Mawe and Hoffman 2013). One hypothesized mechanism for $CuSO_4$-induced nausea and emesis signaling by vagal afferents is shown in Figure 4. This model also shows the ubiquitous 5-HT_3 receptors on vagal afferent fibers. 5-HT_4 and 5-HT_3 receptors do not necessarily require locations on separate populations of vagal afferent fibers for differential signaling to the hindbrain; there is evidence that 5-HT_4 and 5-HT_3 receptors mediate distinct slow and fast phases of depolarization, respectively (Bley et al. 1994).

How can we understand the emetic and nauseogenic signaling by gastrointestinal vagal afferent fibers?

To more accurately assess vagal afferent communication it will be necessary to record multiple single fiber responses in each experimental animal. Some work using the

chemotherapy agent cisplatin and recording primary vagal and spinal single-unit afferent responses has been conducted (Hillsley and Grundy 1999; Horn et al. 2004), but these investigations were limited to a few fibers in the rat, a non-vomiting species. Vagal afferent fibers are heterogeneous and sampling a population of single-fiber responses is an important goal. We must also move beyond traditional one fiber per experiment methodology, and bring forth computational approaches to decoding vagal information (Horn 2009). Analysis of spike trains and the pattern of responses should be implemented.

A small animal model is beneficial because these studies of neurophysiological signaling will likely require a significant number of animals that may be cost prohibitive in the larger models (ferrets, cats, and dogs). The musk shrew appears to be a good candidate. I have had success with *in vivo* and *in vitro* preparations using this animal (Fig. 5 and 6); and, another research group has also reported nerve recordings *in vitro* using the musk shrew stomach (Javid et al. 2013). Figures 5 and 6 illustrate a multi-electrode technique to make a high throughput recording that was previously developed for recording vagal afferents in the rat (Horn and Friedman 2003; Horn and Friedman 2004; Horn et al. 2004; Horn 2009). Both approaches lead to robust recordings of single-unit vagal afferent responses; however, each has advantages and disadvantages. For the *in vivo* preparation (Fig. 5), the brainstem is included and emetic responses are readily measured, but this preparation uses urethane anesthesia and it is unclear what effects this has on the coding of sensory signals. Conversely, the *in vitro* preparation (Fig. 6) does not have the effects of anesthesia but it lacks an emetic response. The *in vitro* approach is often applied in the field of nociception research to mechanistically determine spinal afferent coding (e.g., Feng et al. 2013); and, this could be a major direction of nausea and emeis research, as more information is acquired from the *in vivo* preparation. Importantly, these preparations have the requisite “hardware” of vagal afferents and other cells types that will allow a detailed analysis of sensory function related to emetic and nauseogenic stimulation.

All representative experiments shown in the figures were approved by the University of Pittsburgh Institutional Animal Care and Use Committee, and animals were housed in an Association for Assessment and Accreditation of Laboratory Animal Care international-accredited animal care facility.

Summary

It is clearly too soon to discard the use of animal experimentation to determine the mechanistic underpinnings of nausea and emesis; much of this work cannot be conducted in human studies. Very limited physiological research on the gut-brain axis can occur in human research, and there are limited ethical ways to use electrophysiology to decode emetic signals from the human vagus. We are also appropriately hampered by limits on the types and intensities of stimuli that can be used in these studies; for example, the use of emetogenic chemicals outside the context of patient care is mostly forbidden. Furthermore, it is common that human studies require many more subjects than animal experiments for statistical power; and, indeed, the variability of humans (e.g., genetics, personal history) often precludes the study of effects that are obscured by baseline subject variability, even with a large pool of human subjects. The disadvantages to using animal models are that they

cannot communicate directly their internal states, such as nausea, and secondly, they are not humans; and, therefore, physiological processes from other mammals might not translate to humans. I think the first disadvantage is not as large as it might seem since human and patient reports are not always factual, and it is sometimes unclear what they are reporting since opinions can differ on what constitutes “nausea” between people. The second aspect leads to an open question; is mammalian physiology with regard to emetic (and nausea-like) signaling similar across species? I believe that the answer is generally yes, specifically at the level of sensory inputs. Conversely, where there is likely less commonality in these systems between species is in what occurs further along the neuro-axis through the process of interpretation of sensory signals by higher levels of the CNS.

The sensory processes that trigger emesis and nausea-like responses are critically important; GI vagal afferent communication can potentially provide a significant level of insight into the triggering of these events. Although several emesis capable animal models could be used in these studies, musk shrews provide an efficient approach. The musk shrew has a distinct advantage, similar to mice, as a research model; they are a small animal (40 to 80 g) and can be efficiently used in large numbers. There is also a developing database on the molecular genetics of the GI tract in this species, notably ghrelin and motilin (Ishida et al. 2009; Suzuki et al. 2012; Sugino et al. 2014). Here, I have shown *in vivo* and *in vitro* preparations in this species to perform single-unit electrophysiological recordings of GI vagal afferent fibers. Ultimately, by understanding the transduction and coding of vagal sensory information, we will be able to move towards *in vitro* testing of cell types and possibly *in silico* experiments (Holmes et al. 2009; Rojas et al. 2010a; Rojas et al. 2010b; Stern et al. 2011), all of which can lead to the rationale development of new therapies to control nausea and vomiting.

Lastly, I present a testable model of how this system functions in preclinical animals, as shown in Figure 7. The model suggests that intense activation of GI vagal afferents produces immediate responses; for example, the ejection of toxins (emesis) or ingestion of clay to dilute the effects of toxins on the organism (pica; as observed in rodent studies) (Phillips et al. 1995; Andrews and Horn 2006). Low intensity activation of this pathway is predicted to support a CTA (Garcia et al. 1974), a longer term strategy to prevent the ingestion of toxins in the future. This simple model is indeed testable with a combination of electrophysiological and behavioral methods.

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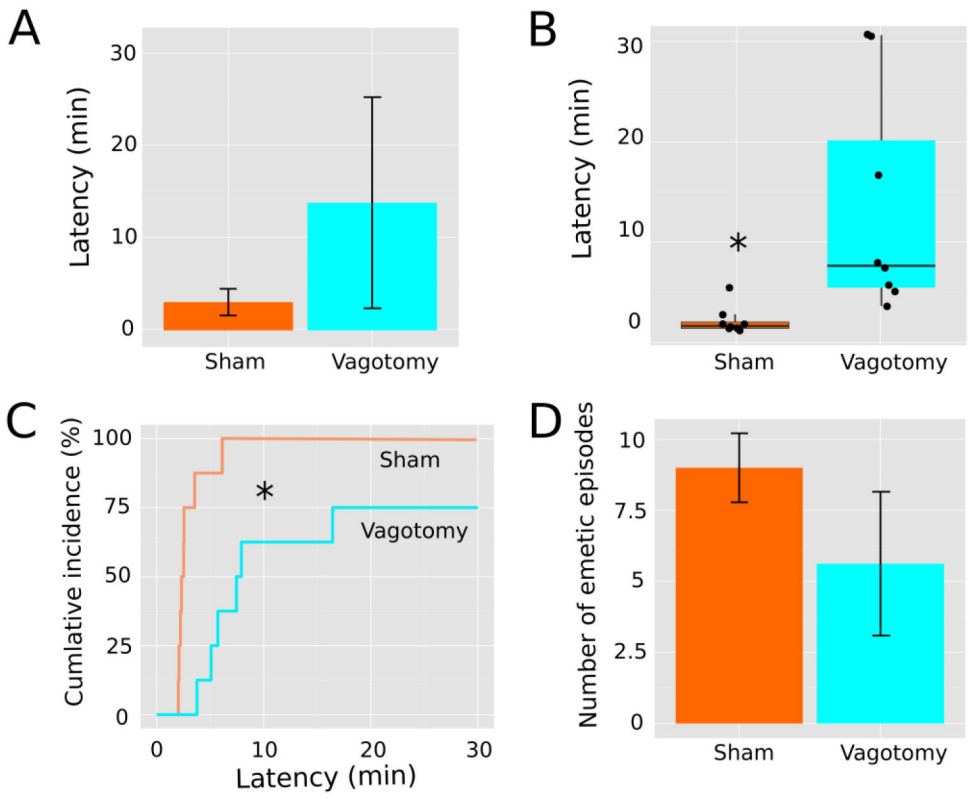

Fig. 1.

Analysis of latency to the first emetic response. This data set is derived from a prior published report showing the effects of intragastric administration of 120 mg/kg $CuSO_4$, n = 8 sham-operated and n = 8 abdominal vagotomized animals (Horn et al. 2014). A) The mean and standard deviation of emesis latency for each group. Normality tests indicate that both distributions are non-normal (Shapiro-Wilk test, $p < 0.05$). B) Box and whisker plots of the same data showing the median, 1st and 3rd quartiles, and whiskers representing 1.5 times the inter-quartile range. A scatterplot of all latency values is overlayed. A Mann-Whitney U test between groups is statistically significant, * $p = 0.003$. C) Cumulative incidence plots of the same data. Cox regression indicates statistical significance, $p = 0.003$. D) Number of emetic episodes from these two groups plotted as mean ± standard error of the mean. A two-sample t-test or Mann-Whitney U test was not statistically significant ($p > 0.05$).

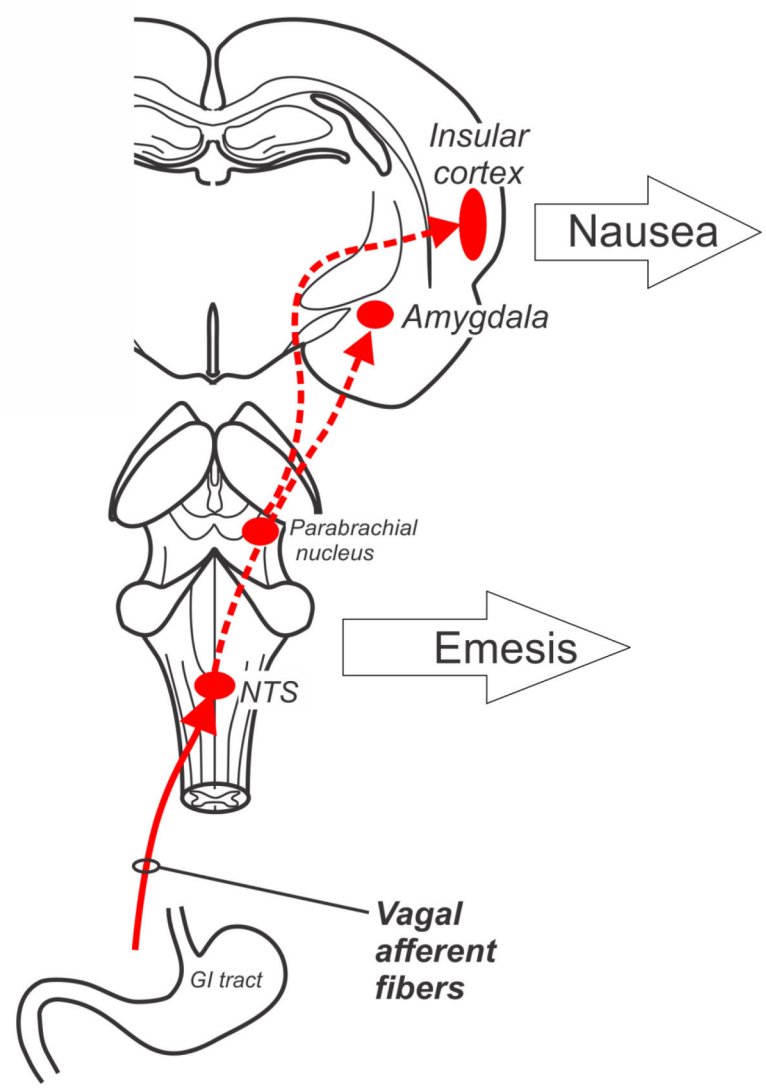

Fig. 2.

Vagal afferent pathway for nausea and emesis. NTS = nucleus of the solitary tract. Brain areas potentially involved in nausea are included, such as the insular cortex and amygdala, but other regions potentially play role (Vandenberghe et al. 2007; Catenoix et al. 2008; Mulak et al. 2008; Wang et al. 2008; Napadow et al. 2012).

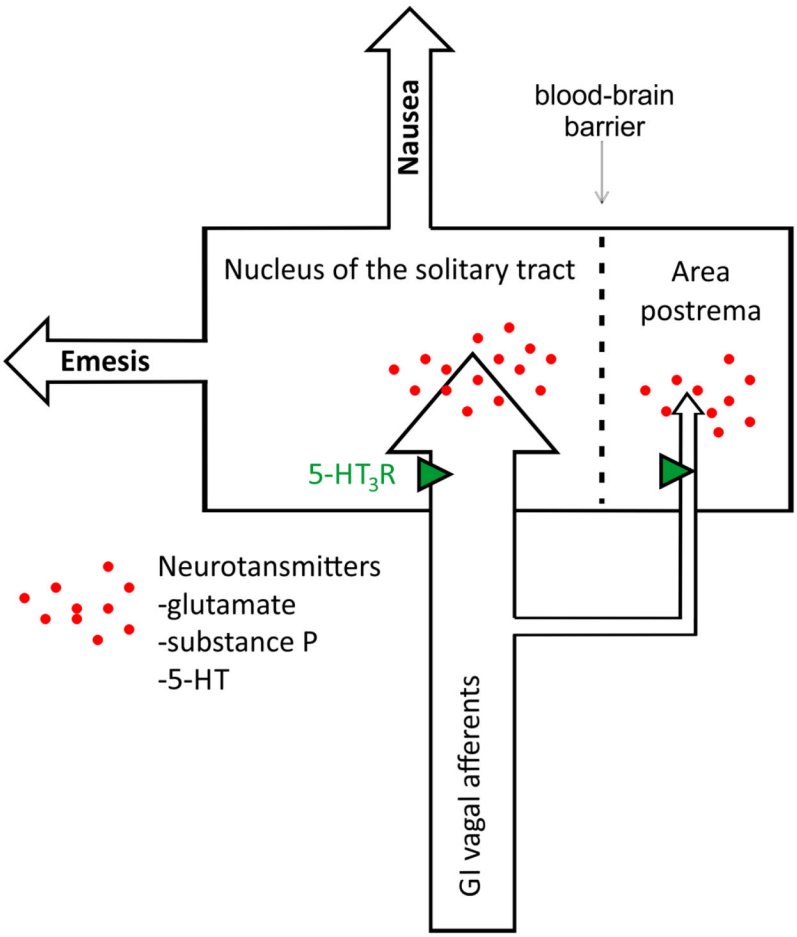

Fig. 3.

Gastrointestinal (GI) vagal afferent projections to the hindbrain and the divergence of the pathways for nausea and vomiting. Neurotransmitters that play a role in signaling from vagal afferents to hindbrain sites are indicated; and, presynaptic 5-HT_3 receptors, located on vagal afferents potentially modulate these GI inputs.

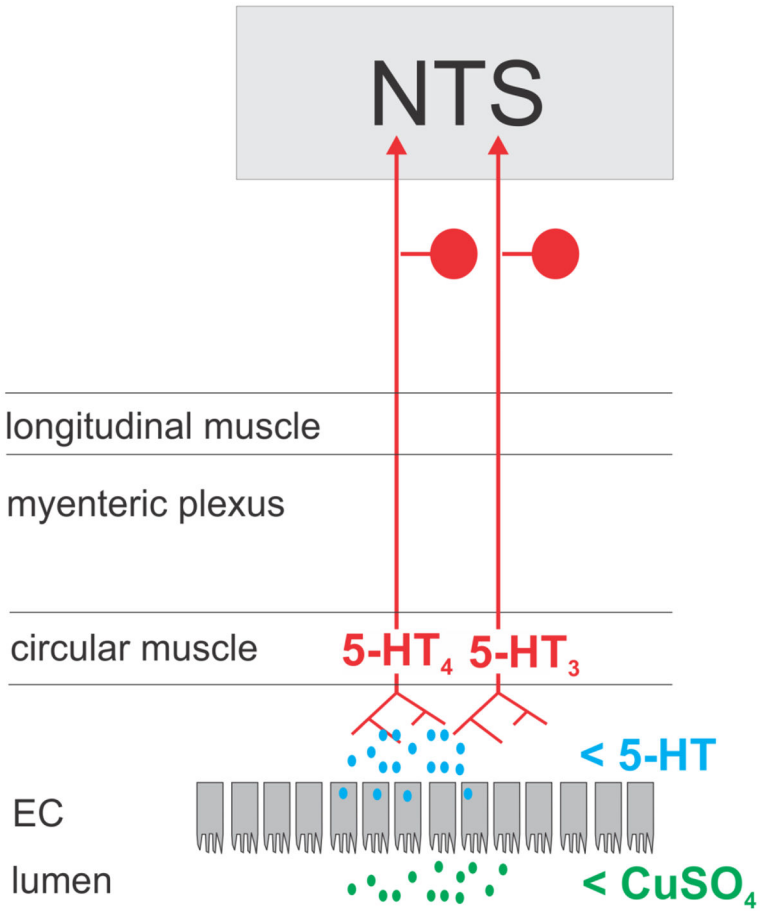

Fig. 4.

Proposed mechanism for $CuSO_4$-induced nausea and emesis signaling in gastrointestinal (GI) vagal afferent fibers. EC = enteroendocrine cells in the mucosal layer of the GI tract.

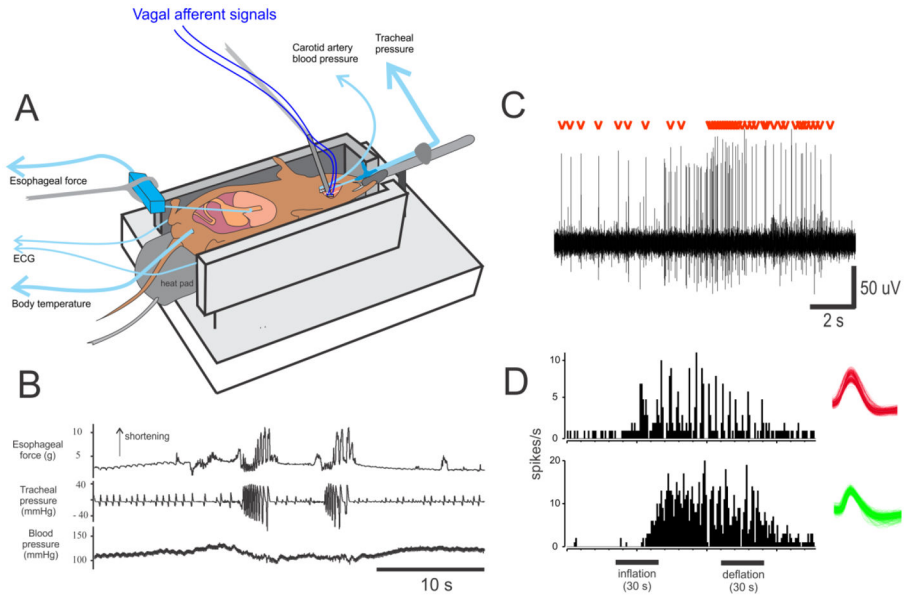

Fig. 5.

In vivo electrophysiology of single afferent fibers in the musk shrews. **A)** An in vivo anesthetized preparation. **B)** Mechanical stimulation of the gastric antrum triggers two emetic episodes (esophageal shortening and closely spaced intratracheal pressure changes; retches). **C)** Activation of GI vagal afferents by gastric distension (1ml balloon). Signal-to-noise ratio of spikes; red marks show the single-unit with the red waveform from section B. **D**) Simultaneous recording of two (of 6) vagal fibers from one shrew that were sensitive to gastric distension. Unit waveforms are shown on the right.

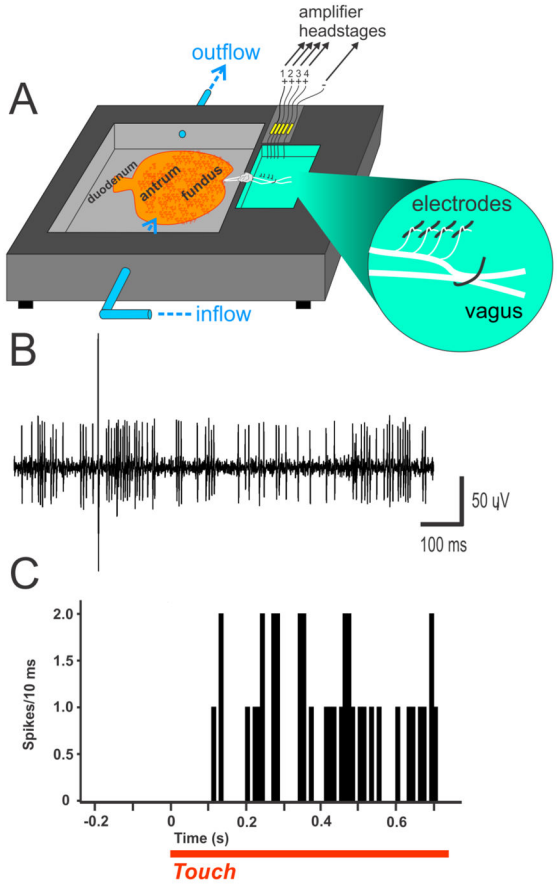

Fig. 6.

In vitro electrophysiology of single afferent fibers in the musk shrew. Mechosensitive vagal afferent activity from the musk shrew stomach. **A)** Recording chamber. **B)** Representive recording showing the signal-to-noise ratio. **(C)** Vagal afferent activity after gentle touch is applied to gastric antrum (spikes/10 ms).

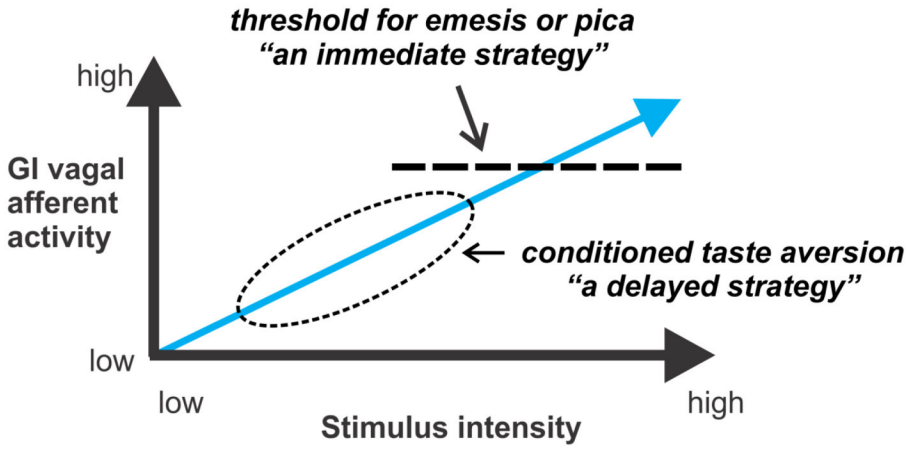

Fig. 7.

Proposed model of emetic stimulation of gastrointestinal (GI) vagal afferent fibers. A threshold is shown for the emetic reflex, for those animals with an emetic reflex (human, cat, dog, ferret, shrew, etc.) and pica in rodents (e.g., rat). This threshold triggers an immediate response to a potential threat (e.g., GI poison). Less immediate dangers (i.e., low concentraions of toxins) can trigger a delayed strategy that supports a conditioned taste aversion, which leads to avoidance of a toxin in the future.