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Abstract:	A 'broad-spectrum' anti-vomiting effect of neurokinin1 receptor antagonists (NK1RA), shown in preclinical animal studies, has been supported by a more limited range of clinical studies in different indications. However, this review suggests that compared with vomiting, the self-reported sensation of nausea is less affected or possibly unaffected by NK1 receptor antagonism, a common finding for 'anti-emetics'. The stimulus-independent effects of NK1RAs against vomiting are explicable by actions within the central pattern generator (CPG; ventral brainstem) and the nucleus tractus solitarius (NTS; dorsal brainstem), with additional effects on vagal afferent activity for certain stimuli (e.g., highly emetogenic chemotherapy). The CPG and NTS neurones are multifunctional so the notable lack of obvious effects of NK1RAs on other reflexes mediated by the same neurones suggests that their anti-vomiting action is dependent on the activation state of the pathway leading to vomiting. Nausea requires activation of cerebral pathways by projection of information from the NTS. Although NK1 receptors are present in cerebral nuclei implicated in nausea, and imaging studies show very high receptor occupancy at clinically used doses, the variable or limited ability of NK1RAs to inhibit nausea emphasises (a) our inadequate understanding of the mechanisms of nausea and (b) that classification of a drug as an "anti-emetic" gives a false impression of efficacy against nausea versus vomiting. We discuss the potential mechanisms for the differential efficacy of NK1RA and the implications for future development of drugs which can effectively treat nausea, an area of unmet clinical need.

An assessment of the effects of neurokinin$_1$ receptor antagonism against nausea and vomiting: Relative efficacy, sites of action and lessons for future drug development.

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Abbreviations:

AP: Area postrema

AVP: Arginine vasopressin

CB_1: Cannabinoid$_1$ receptor

CCK: Cholecystokinin

CI: Confidence Interval

CINV: chemotherapy-induced nausea and vomiting

CPG: central pattern generator for vomiting

CUNV: Chronic Unexplained Nausea and Vomiting

D_2: dopamine$_2$ receptor

EC: Enterochromaffin cell

EEC: Enteroendocrine cell

GABA: Gamma amino butyric acid

$GABA_B$: Gamma amino butyric acid B receptor

GCSI: Gastroparesis Clinical Symptom Index

GDF15: Growth differentiation factor 15

GLP-1: Glucagon like peptide 1

5-HT: 5-Hydroxytryptamine

5-HT_{1A}: 5-Hydroxytryptamine$_{1A}$ receptor

5-HT_3: 5-Hydroxytryptamine$_3$ receptor

HEC: Highly emetogenic chemotherapy

H_1: Histamine$_1$ receptor

ICC: interstitial cells of Cajal

i.v.: Intravenous

MSSS: motion sickness severity scale

mACh: Muscarinic acetylcholine receptor

mNTS: medial nucleus tractus solitarius

MRI: Magnetic resonance imaging

NA: Nucleus ambiguus

NK_1RA: Neurokinin$_1$ receptor antagonist

NN: no nausea

NSN: no significant nausea

NTS: Nucleus tractus solitarius

PET: Positron emission tomography

p.o.: *Per oral*

PONV: post-operative nausea and vomiting

PSC: prodromal sign centre

RGC: Retrograde giant contraction

RR: Risk ratio

SP: Substance P

VRG: Ventral respiratory group

VIMS: Visually-induced motion sickness

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Abstract

A 'broad-spectrum' anti-vomiting effect of neurokinin$_1$ receptor antagonists (NK_1RA), shown in preclinical animal studies, has been supported by a more limited range of clinical studies in different indications. However, this review suggests that compared with vomiting, the self-reported sensation of nausea is less affected or possibly unaffected by NK_1 receptor antagonism, a common finding for 'anti-emetics'.

The stimulus-independent effects of NK_1RAs against vomiting are explicable by actions within the central pattern generator (CPG; ventral brainstem) and the nucleus tractus solitarius (NTS; dorsal brainstem), with additional effects on vagal afferent activity for certain stimuli (e.g., highly emetogenic chemotherapy). The CPG and NTS neurones are multifunctional so the notable lack of obvious effects of NK_1RAs on other reflexes mediated by the same neurones suggests that their anti-vomiting action is dependent on the activation state of the pathway leading to vomiting.

Nausea requires activation of cerebral pathways by projection of information from the NTS. Although NK_1 receptors are present in cerebral nuclei implicated in nausea, and imaging studies show very high receptor occupancy at clinically used doses, the variable or limited ability of NK_1RAs to inhibit nausea emphasises (a) our inadequate understanding of the

mechanisms of nausea and (b) that classification of a drug as an "anti-emetic" gives a false impression of efficacy against nausea *versus* vomiting.

We discuss the potential mechanisms for the differential efficacy of NK_1RA and the implications for future development of drugs which can effectively treat nausea, an area of unmet clinical need.

1. Introduction

Drugs treating nausea and vomiting as disease symptoms or as adverse effects of therapy are usually classified as 'anti-emetics'. However, the term 'emetic' refers to a substance which causes vomiting (or retching). Emesis does not mean nausea. Further, increasing evidence indicates differential efficacy of 'anti-emetic' drugs against nausea *versus* vomiting. Seifert & Alexander (2022) proposed a "rational drug class terminology" based on a drug's pharmacological actions rather than its therapeutic orientation (e.g., anti-emetic). Applying this terminology to nausea and vomiting means that the term 'anti-emetic' must be written in inverted commas to denote the fact that efficacy against nausea and vomiting should not be assumed to be the same (Sanger & Andrews, 2022). Here, we emphasise the importance of differentiating between nausea, a self-reported aversive sensation involving cortical and sub-cortical brain regions (Napadow et al., 2013; Farmer et al.,2015; Ruffle et al., 2019; Varangot-Reille et al., 2023) and the mechanical events of retching and vomiting involving multiple brainstem nuclei (Stern et al., 2011).

The introduction of NK_1 receptor antagonists (NK_1RAs) further improved control of 'chemotherapy-induced nausea and vomiting' (CINV) and 'post-operative nausea and vomiting' (PONV) (Sanger & Andrews, 2018). In addition, a potential expansion of indications

may be appropriate, to include, for example, motion sickness (Polymeropoulos et al., 2020). If confirmed, this would point towards a relatively wide spectrum of 'anti-emetic' activity for the NK_1RAs in humans, as suggested by animal studies (see below). However, originating primarily from studies of CINV including the earliest clinical studies of NK_1RAs (e.g., Navari et al., 1999) there has been a concern that nausea is less well treated than vomiting (Andrews & Sanger, 2014) and this concern persists, as reflected in the comment by Aapro (2018, p.57) that "Perhaps the greatest unmet need in CINV is the lack of complete nausea control". Accordingly, in an attempt to understand the nausea *versus* vomiting question in relation to NK_1RAs, from both clinical and basic science perspectives, we identified five key questions:

1. Has the broad spectrum of activity of NK_1RAs suggested by animal studies of vomiting translated to humans?
2. Where do NK_1RAs act to inhibit vomiting?
3. To what extent do NK_1RAs inhibit nausea as compared to vomiting?
4. If NK_1RAs have a differential effect against nausea compared to vomiting, what is the explanation?
5. What are the implications of the answers to the above questions in terms of patient satisfaction and for future development of drugs to treat nausea?

Different emetic stimuli signal to the brain via different routes. This is why it is first necessary to determine if the broad-spectrum ability of NK_1RAs to prevent vomiting in animals translates to humans in a similar manner; such a profile directs the discussion on potential mechanism of action against vomiting and nausea. Accordingly, we begin by briefly describing the NK_1RA studies in animals and then review the effects of NK_1RAs against vomiting and

nausea in different clinical indications (see below for selection criteria), identifying differences in efficacy between these different indications.

2. Animal studies: Spectrum of NK_1RA effects against vomiting and nausea-like behaviours

In this section we consider only data from species with a vomiting reflex (ferret dog, cat, House musk shrew [*Suncus murinus*] and Least shrew [*Cryptotis parva*]). To simplify comparisons between species and between the effects of drugs on vomiting and nausea, we have not considered 'nausea-like' behaviour data from rodents, which cannot vomit (Sanger et al., 2011; Horn et al., 2013).

2.1. Vomiting. Studies in multiple animal species (**Table 1**) have demonstrated 'broad spectrum' effects of NK_1RAs, markedly reducing/blocking retching and/or vomiting induced by diverse stimuli acting via three key inputs to the brainstem (**Figure 1**) (Stern et al., 2011; Sanger & Andrews, 2018 for references).

2.2. 'Nausea-like behaviours.' Administration to animals of substances inducing nausea and vomiting in humans evoke behavioural changes (often referred to as 'nausea-like'), but their significance and relevance to the human sensation of nausea is contentious (Stern et al., 2011, Chapter 11; Andrews & Sanger, 2014). In summary, and in contrast to the clear effects of NK_1RA on vomiting, effects on 'nausea-like behaviours' are absent or inconsistent (**Supplementary Table 1**). Given this lack of clarity and since the relevance of these behaviours to the human experience is unknown, they will not be considered further (Stern et al., 2011, Chapter 11; Andrews & Sanger, 2014, for detailed discussion).

3. Human studies: Spectrum of NK_1RA effects against vomiting and nausea.

It is important to determine if the broad-spectrum ability of NK_1RAs to prevent vomiting in animals translates to the vomiting and nausea of humans. Accordingly, we searched either

the name of individual antagonists and/or the therapeutic area (e.g., motion sickness, CINV, PONV, gastroparesis, and cyclical vomiting syndrome). For CINV and PONV where there has been more extensive investigation of NK_1RAs 'anti-emetic' efficacy we initially reviewed systematic reviews/meta-analyses and then analysed data in selected original papers. As our focus was on the relative efficacy of NK_1RAs against nausea and vomiting we included papers where data on *both* vomiting and nausea was presented and in particular where adequate information was provided in the methods about how each was quantified, with data presented in a form allowing comparison. We note that few studies have given an NK_1RA *alone*, 'N' values can be small (e.g., in PONV the N value for 7 studies of aprepitant included in a meta-analysis ranged from 30-55; Cavaye et al., 2021) and some studies are uncontrolled. Nausea is often a secondary outcome with methodological variations in its assessment complicating inter-study comparisons (see below).

Sections 3.1 to 3.6 describe the results of studies investigating the effects of NK_1RAs against different emetic challenges. Section 3.7 then provides an overview of the spectrum of efficacy against nausea and vomiting.

3.1. Motion sickness (MS). Studies in humans are limited as ethical considerations usually dictate that vomiting endpoints cannot be used in laboratory-based studies inducing motion sickness in healthy human volunteers. Two laboratory-based studies employed the well proven method of highly provocative whole-body rotational motion with head movements to induce motion sickness (so-called "Cross-coupled motion"). These studies showed no significant efficacy of an NK_1RA (GR205171 [vofopitant]; L758,298) using the degree of motion exposure tolerated before onset of nausea as the endpoint; this suggests no efficacy against nausea (Reid et al., 1998; Reid et al., 2000). A study of healthy human volunteers using

inescapable motion at sea investigated the NK_1RA tradipitant (VLY-686/ LY686017) (Polymeropoulos et al., 2020) and unlike laboratory-based trials, it was possible to measure both vomiting and nausea. Tradipitant was significantly effective (placebo comparator) in protecting against vomiting, but less effective against nausea, using the motion sickness severity scale (MSSS) as an index (**Figure 2**). Only for selected data obtained during rough seas did the NK_1RA provide any protection against nausea compared to vomiting in this sub-group (**Figure 2**). By contrast, well proven muscarinic acetylcholine (ACh) receptor antagonists such as scopolamine (hyoscine), provided protection against both nausea (Golding et al., 1997; 2018) and vomiting (Golding et al., 2017). More detailed studies are now required, investigating for example, the effects of NK_1RA on the physiological changes accompanying motion sickness such as the reduced gastric antral contractile activity (Faas et al., 2001), a pathway of potential relevance to understanding the effects of NK_1RAs in gastrointestinal conditions associated with nausea, such as gastroparesis (see below).

From these very limited data, we tentatively conclude that NK_1RAs are effective against *vomiting* induced by abnormal motion but are less effective against *nausea*.

3.2 Chemotherapy-induced nausea and vomiting. We focus on NK_1RA use in the acute and delayed phases of highly emetogenic chemotherapy (HEC) discussing their effects against vomiting before effects against nausea.

A study of CINV in seven patients given CP-122,721 *alone* showed that in the acute phase (first 24h) of HEC five patients had ≤2 episodes *v.* 7 episodes of "emesis" in an historic control group and in the delayed phase, 6 had no emesis (Kris et al., 1997). A larger study with L-758, 298 (the prodrug for the NK_1RA, aprepitant [L-754,030]) showed that 37% of patients (n=30) had no vomiting or retching in the acute phase, compared with 52% of patients in an ondansetron

(5-HT_3RA) group (n=23; not significantly different) (Cocquyt et al., 2001). However, confining analysis to the first 8h following cisplatin showed 37% of patients had no vomiting or retching in the NK_1RA group compared to 83% in the 5-HT_3RA group (*P*=0.001) but in the delayed phase 72% of patients were without vomiting or retching in the NK_1RA group *vs* 30% in the ondansetron group (*P*=0.005) (Cocquyt et al., 2001). This study suggests a shift in the relative involvement of 5-hydroxytryptamine$_3$ (5-HT_3) and NK_1 receptors driving retching and vomiting between the acute and delayed phases following cisplatin, a finding confirmed by detailed time course analysis of the efficacy of aprepitant, L-758, 298, ondansetron and granisetron in treatment of CINV (Hesketh et al., 2003).

Recent meta-analyses demonstrate additional protection against vomiting when NK_1RAs are given with a 5-HT_3RA and dexamethasone during both acute and delayed phases in HEC (~15-20% more complete protection), with a greater effect in the delayed phase (Jordan et al., 2016; Yokoe et al., 2019; Qiu et al., 2020).

Overall, and despite an ability of NK_1RAs to further reduce the incidence of vomiting during the acute phase when combined with a 5-HT_3RA and dexamethasone, the incidence of nausea is not further reduced during this phase. For example, an initial study with L-754,030 showed a clear additional effect on vomiting in the acute phase following cisplatin when added to a 5-HT_3RA/dexamethasone regimen (Kris et al., 1997), but no difference in the median nausea score. An analysis of the Phase III studies of NK_1RAs added to a 5-HT_3RA and dexamethasone regime in HEC, found no consistent evidence for an improvement in the incidence of "*no significant nausea*" (NSN) or "*no nausea*" (NN) in the acute phase (Bošnjak et al., 2017). For example, the percentage of patients experiencing "*no nausea*" in the NK_1RA arm *v.* placebo in the acute phase was 53.6% *v.* 52% (Roila et al., 2014), 65% *v.* 66% (Schwartzberg et al.,

2015), 68% *vs* 61% (Study 2, Rapoport et al., 2015; statistically significant) and 73% *vs* 68% (Study 1, Rapoport et al., 2015). A pooled analysis of studies with rolapitant showed a small but statistically significant increase in the percentage of patients reporting NN (respectively, 64% and 70%) in the acute phase of HEC (Bošnjak et al., 2017). Saito et al., (2013) found a tendency for the incidence of NSN to increase (90.2% *v.* 84.9%) when using intravenous fosaprepitant (150mg+granisetron/dexamethasone) in patients receiving high-dose cisplatin, although the difference was not statistically significant and the NN incidence was unchanged (67.6% *vs.* 67.5%) compared to placebo.

Some, but not all, studies reported that during the delayed phase the addition of an NK_1RA significantly increased the percentage of patients reporting NN or NSN. In the initial study with L-754,030 (±placebo+ granisetron/dexamethasone; Navari et al., 1999) the median nausea score was reduced on a 100mm VAS (higher score indicating more severe nausea) from 19mm to 1mm on day 2 and over days 2-5 from 10mm to 1mm. Similarly, others reported that the percentage of patients experiencing NN in the NK_1RA arm *vs* placebo in the delayed phase increased significantly: 52.7% *v.* 39.9% (Poli-Bigelli et al.,2003), 53% *v.* 42% (Study 1, Rapoport et al., 2015) and 58% *v.* 47% (Study 2, Rapoport et al., 2015). However, some showed no statistically significant change in NN (e.g., 43.9% *vs* 49.1%, Roila et al., 2014; 71.4% *v.* 73%, Roila et al., 2015; 48% *v.* 45%, Schwartzberg et al., 2015). A pooled analysis of studies using rolapitant showed a significant 12% increase in the NN percentage (44% *v*. 56%) in the delayed phase (Bošnjak et al., 2017).

A recent meta-analysis investigated the addition of aprepitant to a 5-HT_3RA/dexamethasone regimen in patients (only 258 in the final analysis) receiving HEC treatments for lung cancer (He et al., 2021). While the overall complete response rate (no vomiting/no rescue

medication) was significantly better when aprepitant was given, the NN rate was not statistically significantly different (although significant in two of the studies included in the analysis; Dupuis et al., 2020; Yokoe et al., 2019).

In summary, there is insufficient data to compare different NK_1RAs, but it is possible to draw general conclusions about their efficacy in HEC:

i) NK_1RAs further reduce the incidence of vomiting during the acute phase when combined with a 5-HT_3RA and dexamethasone, but the effect is more marked in the delayed phase of HEC.

ii) When added to a 5-HT_3RA/dexamethasone regime, any ability of NK_1RAs to further reduce the incidence of nausea appears inconsistent and in one meta-analysis the NN rate was not statistically significant.

3.3. Post-operative nausea and vomiting.

Table 2 summarises the effects of NK_1RAs in PONV using the outcome from studies reporting nausea and vomiting separately to illustrate the efficacy differences. Overall, several NK_1RAs show efficacy against post-operative *vomiting* in a proportion of patients but the block is not complete in all patients and, the efficacy against *nausea* is inconsistent (e.g., small changes in incidence, inconsistent change in intensity, **Table 2**) and lower than against vomiting. A Cochrane meta-analysis examined the efficacy of diverse pharmacological agents in treating *vomiting* in the first 24h (Weibel et al., 2020) and concluded that *single* NK_1RAs were as effective as other *drug combinations.* The analysis did not compare efficacy against nausea.

Assessment of the overall efficacy of NK_1RAs against PONV is complicated by the variety of types or surgery (e.g., open abdomen, laparoscopic) and anaesthesia/analgesia protocols. A further issue is that in studies where a range of doses has been investigated the relationship

between NK_1RA dose and efficacy against either nausea or vomiting is not always clear (e.g., casopitant, Singla et al., 2010; rolapitant, Gan et al., 2011; vestepitant, Kranke et al., 2015).

3.4. Cyclical vomiting syndrome. An open-label uncontrolled trial of aprepitant in a paediatric population refractory to conventional treatment showed reduction in the number of cyclic vomiting episodes/year and number of vomits/h (Cristofori et al., 2014). Although nausea is a feature of CVS it was not assessed in this study.

3.5. Paediatric patients with life-limiting conditions.

A case series showed aprepitant (2.0-2.5mg/kg, i.v.) was effective in complete resolution of nausea (parental reports of impact on mobility and feeding used as proxy efficacy markers) in paediatric patients receiving palliative care, with different diagnoses and unresponsive to at least two drugs classified as 'anti-emetics' (e.g., cyclizine, ondansetron, metoclopramide, levomepromazine; Patel et al., 2021). Additionally, aprepitant increased the ability to tolerate feeds as might be expected from the proposal that food refusal in children could be used as a surrogate marker for nausea (Richards & Andrews, 2004), although NK_1RA-induced changes in gastric accommodation (Jacob et al., 2017) offers an alternative explanation.

3.6. Gastric distension induced sensations and gastroparesis.

In healthy human volunteers a single dose of aprepitant (80 or 125mg) had no effect on gastric compliance or sensitivity to distension (Ang et al., 2013). Also, in healthy volunteers, aprepitant (125mg p.o. day 1 + 80mg p.o. days 2-5) did not affect gastric emptying of liquids or solids, intestinal or colonic transit (Madsen & Fuglsang, 2008). Using the same repeat dosing schedule but following a 'dyspeptogenic' meal, Jacob et al. (2017) confirmed no change in gastric emptying with aprepitant but found a modest increase in fasting (~10%), postprandial (~9%) and gastric accommodation (~5%) volumes, and a tendency to increase

maximal tolerated volume (~25%). Interestingly, the aggregate symptoms, nausea, and pain scores (but not bloating or fullness) increased significantly following the 'dyspeptogenic' meal in the aprepitant group compared to placebo (median 36 *v.* 4).

A four-week placebo-controlled study of aprepitant (125mg/day, p.o.) involving 126 patients failed to demonstrate an improvement in the primary outcome measure of nausea (Pasricha et al., 2018), in a population with 57% gastroparesis patients and the remainder with Chronic Unexplained Nausea and Vomiting (CUNV). The study also used the Gastroparesis Clinical Symptom Index (GCSI; Revicki et al., 2004) to assess symptom severity as a secondary outcome and this showed significant reductions in overall symptom score (1.3 *v.* 0.7), vomiting (1.6 *v.* 0.5 [69% decrease]) and nausea (1.8 *v.* 1 [44% decrease]). The number of hours per day when nausea was experienced, was reduced and the proportion of nausea-free days increased (~ twofold).

A placebo-controlled trial of 152 patients with idiopathic or diabetic gastroparesis and moderate-to-severe nausea, investigated tradipitant (85mg orally) twice daily (daily total 170mg) for 4 weeks (Carlin et al., 2020). The trial met the primary outcome measure of a reduction in average daily diary nausea score measured using the GCSI Daily Diary with a difference in score reduction between placebo and tradipitant of ~10%. Nausea severity appeared to begin decreasing by week 2 and this was statistically significant by week 3. Additionally, tradipitant increased secondary outcomes of nausea free days (~14%>placebo) and nausea response rate (~21%>placebo). Patients who responded to tradipitant with a reduction in nausea also had improved early satiety, excessive fullness, bloating and upper abdominal pain, compared to placebo. Two case reports involving single patients with

gastroparesis report stoppage of previously intractable nausea (Fahler et al., 2012) or vomiting (Chong & Dhatariya, 2009) on administration of aprepitant.

A recent systematic review and network meta-analysis of drugs used to treat gastroparesis showed that NK_1RAs were efficacious (RR=0.69) using global symptom score. When individual symptoms were assessed tradipitant was more effective than placebo in treating nausea (tradipitant RR=0.77; 95% CI 0.65-0.91) (Ingrosso et al., 2023). By contrast, a recent phase III trial of tradipitant in gastroparesis showed no difference from placebo in the intensity of nausea over a 12 week period (Vanda, 2022).

3.7. Overview of clinical efficacy against nausea *versus* vomiting.

Summarising sections 3.1 to 3.6, NK_1RAs can block vomiting induced by HEC (± $5HT_3$RA and dexamethasone) and PONV, and with much more limited evidence perhaps also the vomiting associated with CVS and motion-induced vomiting. NK_1RAs do not block vomiting in all patients/subjects exposed to a given stimulus and for CINV the efficacy may depend on the phase (potentially, delayed>acute). When nausea is assessed, several studies report no significant benefit although there is some evidence that even if not completely blocking nausea NK_1RAs may reduce its intensity (e.g., see PONV data, **Table 2**). Overall, however, the NK_1RAs are less efficacious or have more variable efficacy against nausea than vomiting over the same range of stimuli but more quantitative data are needed.

We now attempt to explain this differential effect by a detailed analysis of the sites at which NK_1RAs could act to affect vomiting (section 4) and nausea (section 5).

4. Potential site(s) of action of NK_1RA against retching and vomiting (Figure 3).

The sites at which NK_1RA block retching and vomiting have been investigated in animals (primarily dog and ferret). The findings of these studies are included here because the afferent, integrative and motor pathways responsible for vomiting are comparable between animals (e.g., dog, ferret; Onishi et al., 2007) and humans (Stern et al., 2011). For each potential site of action, we will consider whether it could account for a 'broad spectrum' effect against vomiting or whether it can only explain an action against vomiting induced by a specific stimulus or pathway. This analysis also provides an essential background for understanding the differential effects against nausea.

4.1.1. Vestibular system. The vestibular system is essential for induction of nausea and vomiting caused by abnormal body motion. From an evolutionary perspective the vestibular system is considered a component of the mechanisms protecting the body against ingested toxins (see Treisman 1977, Money & Cheung, 1983, Oman, 2012; Lackner, 2014). Although sensitivity to motion sickness is a predictive factor for both CINV and PONV (Gan, 2006; Warr, 2014) there is no evidence that the vestibular system (including vestibular nuclei) is directly implicated in the induction of either. During motion sickness, the motor pathways for vomiting are activated via projections of the vestibular nuclei to the medial and caudal nucleus tractus solitarius (NTS) (studies in the cat; Yates et al., 1994; Sugiyama et al., 2011). There is no evidence that NK_1RAs affect transmission in the pathway between the vestibular system, the vestibular nuclei and the NTS, to block induction of vomiting. This contrasts with the actions on this pathway of H_1 and mACh (M_3/ M_5) receptor antagonists, used to treat motion sickness (Soto & Vega, 2010; Golding & Stott, 1997; Golding et al., 2018). An action of

NK_1RAs within the NTS or at a site(s) deeper in the brainstem is therefore the most likely site for effects against motion-induced vomiting.

4.1.2. Area postrema (AP). The AP projects to neurones in the medial NTS (mNTS) which can be activated by emetic stimuli applied to the AP (e.g., apomorphine, L-glutamate) and by vagal afferent stimulation (dog studies; Koga & Fukuda, 1992). However, the evidence that NK_1 receptors occur within the AP is weak, and their functional relevance uncertain. For example, low levels of [^{3}H]-substance P binding displaced by CP-99,994 (0.1nm-100nM) were found in the ferret AP, as compared to the NTS (particularly subnucleus gelatinosus) (Watson et al., 1995). Ariumi et al. (2000) reported dense ^{3}H-substance P binding in the AP and NTS of ferret but displacement by an NK_1RA was not studied. Comparable evidence is available for *Suncus murinus* and rat (Maubach et al., 1997; Andrews & Rudd, 2004). Iontophoretic application of substance P (SP) activated ~50% of AP neurones tested (dog; Carpenter et al., 1988), but although assumed to play a role during vomiting induced by intravenously-administered SP (dog; Carpenter et al., 1984), the receptor type activated by the applied concentration of SP and the link between activation and vomiting was not identified. In the ferret, application of SP to the AP can evoke vomiting (Andrews & Rudd, 2004) but microinjection studies (Gardner et al., 1994) suggest that this response was probably due to SP penetration to the subjacent NTS as the blood-brain barrier between these two areas may have some permeability. A similar explanation of leak into the NTS may account for the block in morphine (s.c.) and reduction in copper sulphate (intragastric) induced vomiting in the ferret by administration of CP-99,994 or HSP-117 into the AP (Ariumi et al. 2000).

It is a possibility that NK_1 receptors in the AP could be activated if SP (or other tachykinins) are released from gut enteroendocrine cells (EEC; Rezzani et al., 2022) to enter the blood

circulation in addition to acting more locally. However, the evidence for this possibility in response to emetic stimuli is weak. Thus, in patients undergoing chemotherapy, the elevation of serum concentrations of SP during the delayed phase of vomiting was inconsistent (Higa et al., 2006, 2012; Matsumoto et al., 1999; Park et al., 2020; Takahashi et al., 2011) although this is the phase during which NK_1RA are most effective (see above).

Another possibility is that SP could arise from neurones intrinsic to the AP following direct activation by endogenous or exogenous emetic substances or by abdominal vagal afferents projecting to the AP. However, SP-like immunoreactivity (SP-Li) was absent in the AP of a human infant (Rikard-Bell et al., 1990), consistent with the absence of SP-Li cell bodies in the AP of adult cat, rat (Newton et al., 1985) and ferret (Boissonade et al., 1996). Previously, extraction studies in humans found some SP in the AP (Zettler & Schlosser, 1955; Cooper et al., 1981) and radioligand binding showed a "moderate" uptake of an NK_1RA by the human AP (Hietala et al., 2005). Sparse SP-Li nerve fibres have been found in the AP (cat, rat) but their origin is most likely from either vagal nerve afferents terminating there or from the NTS (Newton et al., 1985); this is consistent with the finding of high-densities of SP immunoreactive fibres in lateral borders of the AP in the ferret (Boissonade et al., 1996). However, in the least shrew SP-Li fibres and puncta were present at a "moderate" level in the AP (Ray & Darmani, 2007).

Finally, it is worth noting that the concept of the AP as a site at which systemic agents act to induce nausea and vomiting was originally derived from studies showing abolition of vomiting induced by apomorphine (a dopamine D_2 receptor agonist), following surgical ablation of the AP including in humans (Lindstom & Brizzee,1962; Borison & Wang, 1953). Similarly, other exogenously administered agents (e.g., morphine, loperamide, cisplatin) can induce emesis

via the AP (Borison, 1989; Bhandari et al., 1992; Percie du Sert et al., 2009). However, there is only limited evidence that systemic endogenous agents which can induce vomiting (e.g., adrenaline, cholecystokinin [CCK], GDF15, vasopressin), act via the AP, with alternative sites of action suggested (Borison,1989; Borner et al., 2020; Makwana et al., 2022). The above discussion suggests that SP, acting via NK_1 receptors in the AP should be added to the list of systemic endogenous emetic agents.

4.1.3. Abdominal vagal afferents.

There are two sites at which vagal afferent activation by emetic stimuli could be affected by an NK_1RA; they are not mutually exclusive (**Figure 3**).

4.1.3.1. **The peripheral transduction mechanism.** A potential ability of SP from enterochromaffin cells (ECs) to induce vomiting by acting on vagal afferents was hypothesised >30 years ago (Andrews et al., 1988; for details see Andrews & Rudd, 2004). Potentially, such a mechanism would be similar to that for 5-HT, which is released from ECs in response to chemotherapeutic agents (e.g., cisplatin) and other emetic stimuli (e.g., rotavirus), causing vomiting by stimulating and sensitizing abdominal vagal afferent terminals via 5-HT_3 receptor activation (Andrews & Rudd, 2015; Sanger and Andrews, 2018; for reviews). In rats, treatment with methotrexate or cisplatin increased the number of SP-containing ECs within the intestine, 24h after administration (Machida et al., 2017; Obara et al., 2018) but studies have not yet looked for local release of SP from ECs in response to anti-cancer chemotherapeutic agents or other emetic stimuli. By analogy with 5-HT (see above), any release of SP might be expected to activate vagal nerve terminals. Recently, SP (1µM)-induced depolarisation of human isolated vagus was shown to be blocked by aprepitant (Smith et al., 2021). However, the authors used a concentration (10µM) at least 10000x the human NK_1 receptor binding

IC_{50}, at or above the concentrations examined for selectivity of action (Tattersall et al., 2000), and now understood to also activate the mechanosensitive two-pore domain potassium channel, TRAAK (encoded by the *KCNK4* gene) (McCoull et al., 2022). Interestingly, recordings from abdominal vagal afferents of ferrets show an interaction between 5-HT and SP (Minami et al., 2001) and 'cross talk' has been demonstrated between NK_1 and $5\text{-}HT_3$ receptors in relation to the 'anti-emetic' effect of palonosetron (Rojas et al., 2014).

4.1.3.2. Vagal afferent to NTS transmission. Abdominal vagal afferents terminate in the mNTS (Fukuda & Koga, 1992). There is evidence that SP is a transmitter from vagal afferents to NTS neurones (cat, Baude et al., 1989; dog, Shiroshita et al., 1997) and for activation of NTS neurones by iontophoretically applied SP (ferret, Saito et al., 1998; rat, Maubach & Jones, 1997). However, any action of NK_1RA on vagal to NTS transmission must be selective for afferents involved in induction of vomiting as NK_1RAs do not block the gag reflex, the cardiac or respiratory components of the von Bezold-Jarisch reflex or apnoea induced by cervical vagal afferent stimulation (Watson et al., 1995; Fukuda et al., 1999). Additionally, while systemic administration of the NK_1RA, CP-99,994 in the anaesthetised ferret blocked licking, swallowing and retching induced by electrical stimulation of the abdominal vagal afferents, the accompanying rise in blood pressure was unaffected (Watson et al., 1995). This makes it unlikely that vagal to NTS transmission *per se* is blocked and suggests that the block is either within the NTS integrative pathways which initiate vomiting or on the output side of the system in the 'central pattern generator' (CPG) for vomiting located in the reticular formation dorsomedial to the retrofacial nucleus (Bötzinger complex) in the region of the NA (compact region) and the associated 'prodromal sign centre' (PSC in the semi-compact area of the nucleus ambiguus (Fukuda & Koga, 1991, 1992; Fukuda et al., 2003). Further support for a specific activity on some but not all vagal functions comes from studies in the decerebrate

dog where the NK_1RA, GR-205171 (i.v.) blocked fictive retching, the accompanying antral contractile response (most likely the extension of the Retrograde Giant Contraction (RGC) that originates in the small intestine and immediately precedes the onset of retching mediated by vagal efferents; see Lang et al., 1986; Lang, 1990), and reduced the hypersalivation (mediated by PSC) evoked by vagal afferent stimulation, but not the accompanying vagal efferent mediated relaxation of the proximal stomach (Furukawa et al., 1998).

It is self-evident that blockade of vagal afferent activation at a peripheral site or vagal afferent transmission to the mNTS would only contribute to the anti-vomiting effects of NK_1RAs when the primary stimulus activates the vagus (e.g., acute phase of CINV, possibly gastroparesis; Sanger & Andrews, 2023). Therefore, a vagal site of action would not account for block of stimuli acting only either via the AP or the vestibular system so additional site(s) of action need to be considered.

4.1.4. Brainstem integrative mechanism and the drive to the visceral and somatic motor outputs. The selective effects of NK_1RA on reflex responses to vagal afferent stimulation (as above) show that actions of NK_1RA within the brain stem integrative pathways (i.e. NTS, CPG, ventral respiratory group [VRG]) are selective to neurones involved in the 'vomiting motor programme' occurring as a result of reconfiguration of the pattern of activity in the multifunctional respiratory neurones (Grélot & Bianchi, 1997; Grélot & Miller, 1997) (c.f. cough, yawn, sneeze). These same sets of neurones can also be driven to evoke vomiting by stimuli acting on the vestibular system and the AP (**Figure 4**). Thus, the effects of NK_1RAs on the brainstem pathways are 'state dependent' and this can explain the selectivity of effects against vomiting; when the brainstem is involved in baseline respiration and some respiratory

reflexes there is little dependence on SP as a transmitter but when the pathway reconfigures and is highly active as occurs for vomiting then it becomes critically dependent on SP.

Overall, there is evidence for either the presence of SP positive neurones and/or NK_1 receptors in the key brainstem sites implicated in vomiting.

4.1.4.1. Nucleus tractus solitarius. SP-like immunoreactive neurones are present in the human NTS, particularly subnucleus gelatinosus (mNTS) and this is consistent with studies in both the cat and ferret (Leslie, 1985; Boissonade et al., 1996). A human brain PET study using a fluorine-18 labelled NK_1RA reported 'moderate' uptake in the NTS, the nucleus ambiguus and "other nuclei of the vagus" (not specified) (Hietala et al., 2005).

A site of action within the NTS is supported by studies showing microinjection of CP-99,994 in the "region of the NTS" inhibited, but did not completely block, cisplatin-induced acute retching and vomiting in the ferret (Gardner et al., 1994; Tattersall et al., 1996). An important point is that the NK_1RA was injected after retching/vomiting began showing that the antagonist was blocking a pathway driven by ongoing NK_1 receptor activation. The peptide NK_1RA, GR-82334 was infective against cisplatin-induced retching/vomiting when given intravenously but was effective (77% reduction) when given into the NTS (Gardner et al., 1994). Rupniak et al (1997) correlated anti-emetic activity against cisplatin in the ferret with central penetration using a range of NK_1RAs with differing brain penetration. These studies argued strongly that central penetration (at least to the NTS) is required for the acute anti-emetic effect of an NK_1RA. Further support for an action of NK_1RA in the NTS comes from inhibition of SP (1µM)-induced discharge in NTS slices by the NK_1RA HSP-117 (10µM), without affecting baseline spontaneous neuronal discharge (ferret, Saito et al., 1998).

4.1.4.2. Dorsal motor vagal nucleus. NK_1 receptors are present in the dorsal motor vagal nucleus (DMVN; ferret, Watson et al., 1995), the site of origin of vagal efferents supplying the upper digestive tract and regulating the proximal gastric relaxation and RGC prior to the onset of retching and vomiting (Lang, 1990). In the rat, neurones in the DMVN responsive to gastric distension±24h post-cisplatin had their baseline activity altered by CP-99,994 (5µM) (Sun et al., 2017) but the results should be interpreted with caution as the efferent projection (e.g., the stomach) of the neurones was not identified (e.g., using antidromic collision, Andrews et al., 1980) and the effects of CP-99,994 were not controlled for by using its less potent 2R, 3R enantiomer, CP-100,263 (Watson et al., 1995). Although these studies show that the DMVN is a potential target for NK_1RA it should be noted that preventing the gastric relaxation and RGC will not block retching and vomiting as they can occur even in the absence of the stomach (Magendie, 1813) and when the RGC is blocked by atropine (Lang et al., 1986). An action of NK_1RA on the DMVN is therefore unlikely to explain their anti-vomiting action.

4.1.4.3. Ventral brainstem. Neurophysiological studies of fictive emesis in the dog implicate nuclei in the ventral brainstem (Fukuda & Koga, 1991, 1992; Fukuda et al., 2003; Onishi et al., 2007). When administered systemically, the NK_1RA, GR-205171 reduces vagal afferent activation (via the mNTS) of the CPG for vomiting and/or in the pathway linking the NTS to the CPG via the PSC (Fukuda & Koga, 1991, 1992); immunohistochemistry has demonstrated the presence of NK_1 receptors in both regions of the dog ventral brainstem (Fukuda et al., 2003). The CPG connects with the VRG, the location of the neurones driving the phrenic and abdominal motor neurones involved in normal respiration as well as retching and vomiting (**Figure 4**).

Total block of transmission at either the NTS or CPG is probably not required to stop induction of vomiting; a *reduction* in transmission at either site is likely to be sufficient as triggering vomiting requires a higher frequency stimulus which also lasts for an extended time (e.g., ~20s of vagal afferent stimulation is required in dog [Koga & Fukuda, 1992] and ferret [Andrews et al., 1990]), presumably to prevent inappropriate triggering. It is particularly notable that NK_1RAs prevent the 'wind-up' of CPG neurones induced by vagal afferent stimulation and blunts the rise in firing frequency when continuous vagal afferent stimulation is used, preventing the CPG reaching a threshold for induction of the oscillatory activity required for retching and vomiting (Fukuda et al., 1999, 2003) (**Figure 5**).

4.1.5. Overview of site(s) of action against vomiting

The clinically used NK_1RAs are brain penetrant so when given systemically they can act at both the central and peripheral neuronal sites involved in retching and vomiting:

i) For vomiting induced by abnormal motion, the brainstem integrative pathways (NTS, CPG) are the most likely site of action.

ii) For stimuli involving abdominal vagal afferents it is possible that NK_1RA can a) block effects of any SP released from EEC cells onto NK_1 receptors on the peripheral afferent nerve terminals (Minami et al., 2001); b) reduce tachykininergic transmission between vagal afferents and the NTS (Fukuda et al., 2003; Andrews & Rudd, 2004); c) modulate the brainstem integrative pathways (NTS, CPG) sufficiently to disrupt the signals encoding induction of vomiting (Fukuda et al., 1999, 2003; Fukuda & Koga, 1991, 1992; Watson et al., 1995) . At present, the evidence for (b) and (c) is stronger.

iii) For stimuli acting on the AP via the circulation (or cerebrospinal fluid) including exogenous emetics and endogenous substances released for example from the digestive tract because of damage/inflammation (e.g., during the delayed phase of CINV and chronic phases of infection) (Sanger & Andrews, 2018; Andrews et al., 2021, 2023 for references), the brainstem integrative mechanisms (NTS, CPG) are the most likely sites at which vomiting is affected as there is little evidence for an action within the AP itself.

The NTS and CPG sites of action of NK_1RA are common to all stimuli inducing vomiting. However, for stimuli where abdominal vagal afferent activation occurs two additional sites of action are implicated which, if operational, would block vagal afferent input and thereby make it unnecessary for NK_1RA to act within the NTS and CPG. However, although the NK_1RA are highly effective against vomiting in a number of clinical settings, NK_1 receptors are not the only receptors involved in all of the pathways and this may explain why they may not always be fully effective in all patients. For example, SP is likely to co-transmit with a non-peptide (e.g., glutamate) with the former likely to be released by a higher frequency or different pattern of nerve firing (Svensson et al., 2019). Further, glutamate has been implicated in abdominal vagal afferent to mNTS transmission as NBQX blocked vagal afferent-induced retching in dog and ferret and the resulting mNTS activation in the dog (Furukawa et al., 2001; Onishi et al., 2007). Nevertheless peptides, as co-transmitters, are known to be involved in network reconfiguration with release determined by both neuronal firing pattern and time (Cropper et al., 2018). Variations in the predominant transmitters in the nausea and vomiting pathways, possibly as a response to disease, especially if chronic (e.g., in chronic visceral pain NK_1 receptor availability is downregulated; Jarcho et al., 2013), may also contribute to NK_1RAs spectrum of clinical efficacy.

5. The potential site(s) of NK_1RA action against nausea

'Anti-emetics' must not be assumed to equally affect both nausea and vomiting (Sanger & Andrews, 2022). Accordingly, we discuss the relative effects of NK_1RA against nausea and vomiting by considering specific questions about the pathways involved; this also informs directions for development of novel drugs (section 6). Direct experimental data is not available to answer all the questions raised, so some answers are speculative and hypothetical but experimentally testable.

5.1. What information reaches the mNTS from the abdominal vagal afferents in the presence of NK_1RAs?

This question is relevant to both CINV and gastroparesis where abdominal vagal afferents are implicated in genesis of nausea and vomiting (Sanger and Andrews, 2018, 2023). Regardless of whether NK_1RAs reduce vagal afferent firing by acting peripherally (e.g., Minami et al., 2001) or centrally (e.g., Fukuda et al., 2003), the degree of activation, and the pattern, frequency and duration of abdominal vagal afferent activity required for induction of nausea as compared to vomiting is unknown. It is, nevertheless, a reasonable assumption that nausea requires less intense activation of afferent pathways than vomiting (see Horn 2014 for discussion in relation to the vagus). The effects of NK_1RAs on vagal afferent activity evoked by a wide range of stimulus intensities, ± substances which may sensitise the afferents (e.g., 5-HT, prostaglandins), need to be investigated directly to answer the above question. The development of vagal afferent recording techniques in humans may eventually allow direct testing of this hypothesis (Ottaviani et al., 2020).

5.2. Do differential effects of NK_1RAs on the NTS account for the differential effects against nausea and vomiting?

NK_1RA modulation of the vagal afferent drive to the mNTS and/or transmission within the NTS (vagal, AP and vestibular inputs) could contribute to a *reduction* in nausea *intensity* by decreasing the drive from the NTS to supra-medullary structures implicated in the sensation of nausea. However, the evidence for such an action is poor, as discussed below.

5.3. Are NK_1 receptors in the mid-brain and cerebral hemispheres involved in potential anti-nausea effects of NK_1RA?

In contrast to vomiting, the brain pathways responsible for nausea are not well defined. The majority of brain imaging studies are in subjects reporting nausea induced by illusory-self motion (vection; visually-induced motion sickness, VIMS), with only single studies using 'real' motion or a pharmacological challenge (see Varangot-Reille et al., 2023) making it difficult to assess whether the findings have general applicability. Cortical and sub-cortical areas consistently showing an increase in activity in healthy volunteers reporting nausea include the frontal lobe (e.g., anterior cingulate cortex), occipital lobe (e.g., posterior cingulate cortex), temporal lobe (e.g., amygdala, part of the 'limbic cortex') and basal ganglia (e.g., putamen) (Varangot-Reille et al., 2023).

NK_1RA binding in the human brain using PET shows NK_1 receptors in several brain areas implicated in nausea. For example, aprepitant has receptor occupancy of 50% in the caudate and 90% in the putamen (basal ganglia) at plasma concentrations of ~$2x10^{-9}$ M and ~$2x\ 10^{-8}$ M respectively (Bergstrom et al., 2004). Based on the striatal occupancy levels, the authors concluded that the recommended 'anti-emetic' aprepitant regime of 125mg on day 1 and 80mg on the subsequent two days in CINV would result in an occupancy of >90% (Bergstrom et al.,2004). Hietala et al., (2005) using the same radioligand confirmed the highest uptake in the caudate and putamen and levels ~50% in regions of the occipital lobe (e.g., posterior

cingulate cortex), temporal lobe (e.g., amygdala [forms the 'limbic cortex' with the hippocampus]) and frontal lobe (anterior cingulate cortex) all of which have been implicated in nausea in brain imaging studies (Varangot-Reille et al., 2023).

Pharmacological MRI studies provide additional unexpected insights. Using fosaprepitant (pro-drug of aprepitant) the NK_1 receptor distribution profile identified in the above PET studies was confirmed but in addition identified *activation* of brain areas (e.g., cerebellum, red nucleus) where there were thought to not be any NK_1 receptors, an effect attributed to "downstream pharmacodynamic effects" (Borsook et al., 2012, Fig. 2; Upadhyay et al., 2011). Such effects demonstrate that in identifying brain sites of drug action we should not only consider regions which have their activity inhibited; activation of a pathway which itself is inhibitory on the function under consideration should not be overlooked. Brain imaging studies in nausea have identified areas with both *increased* and *decreased* activity (Farmer et al., 2015).

Although we focus on areas directly implicated in nausea, as nausea involves heightened anxiety, the potential anxiolytic effects of NK_1RA (Hoppe et al., 2018) could indirectly contribute to reducing nausea scores especially in chronic conditions (e.g., gastroparesis).

Overall, NK_1RAs do not appear to have a consistent ability to reduce nausea induced by multiple stimuli despite high levels of NK_1RA binding in many of the relevant brain areas. Therefore, it is reasonable to conclude that NK_1 receptors do not have a major role in transmission in the 'higher' brain regions currently implicated in nausea. We note that NK_1RA efficacy in depression (e.g., Keller et al., 2006; Ratti et al., 2013), panic disorder (Fujimura et al., 2009), pain (Boorsook et al., 2012) and anxiety (Hoppe et al., 2018) are also variable and less than might be anticipated from NK_1 receptor distribution.

5.4. Do NK_1 RA reduce vasopressin secretion?

Relatively high plasma concentrations of arginine vasopressin (AVP) are associated with nausea induced by stimuli activating the vestibular system, AP and abdominal vagal afferents (Makwana et al., 2022). A causal link between AVP and nausea is not proven, but a credible possibility in at least some clinical scenarios involves the actions of low concentrations of AVP on gastric pacemaker activity (the interstitial cells of Cajal; ICC), synergising with actions of other nauseagenic stimuli to disrupt motility and hence, initiate vagal afferent discharge; the demonstration of synergy between two different nauseagenic stimuli (adrenaline + AVP) was used to argue that antagonism of one alone (e.g., the effects of vasopressin) might reduce but not prevent the symptom of nausea (Makwana et al., 2022). In dogs, following cisplatin administration, the NK_1RA maropitant was without significant effect on the peak [AVP] or the area under the curve whereas both were significantly reduced by ondansetron (Kenward et al., 2017). In human patients treated with cisplatin the acute rise in [AVP] was blocked by ondansetron (Barreca et al., 1996) as in the dog, but as far as we are aware similar patient studies have not been performed with an NK_1RA.

5.5. Do NK_1RA have a role in treating nausea by gastric motility modulation?

The presence of SP in the digestive tract in nerve terminals and EEC (Sanger, 2004) and of NK_1 receptors on smooth muscle cells and Interstitial cells of Cajal (ICCs) (Lavin et al., 1998; Faussone-Pellegrini, 2006; Cheng et al., 2007; Liu & Rudd, 2023) makes the digestive tract a potential target for NK_1RA. However, an ability of NK_1RAs to affect nausea by a direct effect on gastric motility is unlikely. Thus, in healthy volunteers there is little evidence for an effect of NK_1RA on digestive tract motility (assessed by gastric emptying or compliance, or small and large bowel propulsion) (Madsen & Fuglsang 2008; Ang et al., 2013; Jacob et al., 2017; Khanna

et al., 2022). Interestingly, after a dyspeptogenic meal, aprepitant (125 mg on day 1, then 80 mg on days 2–5) increased fasting, postprandial, and accommodation gastric volume but increased aggregate symptoms, nausea, and pain scores after ingestion of the maximum tolerated volume; the authors suggested that differences between these studies may be dependent on what is measured and on the application of acute- or longer-term dosing with aprepitant (Jacob et al., 2017) but activation of TRAAK channels (see above) should also be considered.

Dysrhythmic gastric electrical activity has been associated with nausea in disorders including gastroparesis, CUNV, functional dyspepsia, gastro-oesophageal reflux disease, all linked with loss of ICCs (Koch 2014; O'Grady et al., 2021). Thus, any ability of NK_1RAs to affect ICC functions (see above) could, in theory, have an influence on *induction* of nausea although an effect on vagal afferent signalling or the NTS seems more likely based on current knowledge.

6. Concluding comments.

Irrespective of the stimulus, the effects of NK_1RA against *vomiting* are explicable by a central action on the NTS and CPG in the brain stem with potential additional peripheral effects on vagal afferent activity when activated by an emetic stimulus (e.g., HEC, some ingested toxins). NK_1RAs are not always 100% effective against vomiting in humans (c.f., pre-clinical studies, **Table 1**) implicating other transmitter/receptor systems and explaining why optimal *anti-vomiting* therapy may require drug combinations (e.g., netupitant + palonosetron + dexamethasone) in treating complex situations such as HEC. An additional role for other neurotransmitters/co-transmitters (e.g., glutamate) has not yet been fully explored.

A reduction in the projection of information from the NTS to the higher brain regions by suppression of NTS pathways and the drive from the abdominal vagal afferents is likely to

contribute to any reduction of nausea by NK_1RAs, no matter how sub-optimal the current evidence suggests. It could be argued that the distribution of NK_1 receptors in cortical and subcortical structures implicated in nausea may predict efficacy against nausea, but it is also possible these receptors are coupled to non-nauseagenic pathways, such as those involved in fear and/ or anxiety (which nonetheless may contribute to the overall sensation of nausea).

Mechanistically, vomiting is well understood and studies with NK_1RAs show that targeting the NTS/CPG in the brainstem is a valid approach and adverse effects on the respiratory, cardiovascular and digestive systems all regulated from the brainstem appear to be avoided. The apparent specificity of NK_1RA blockade of vomiting likely reflects the functional reconfiguration of the neural network to coordinate retching/vomiting where tachykininergic signalling becomes critical (state dependence; see Doi & Ramirez 2010 for a study of NK_1 receptors and state dependent functions of pre-Bötzinger complex respiratory neurones). The NTS and CPG need investigating in emetic species using neurophysiological studies similar to those in rodents showing complex interaction between NK_1 receptor activation, glutamate and GABA release (Bailey et al., 2004) to understand how NK_1RAs are 'functionally specific' for vomiting.

Nausea remains a challenge as there are major gaps in knowledge of the cerebral pathways involved and hence in identifying potential receptor targets to identify 'broad spectrum' anti-nausea drugs. As the insular cortex is the "highest" cortical region consistently activated in subjects reporting nausea (Varangot-Reille et al., 2023) this would be a logical place to target a drug to block nausea although the associated physiological changes (e.g., regional cold sweating, AVP secretion) may not be blocked as they involve 'lower' brain regions. An alternative approach is to selectively suppress transmission of 'nauseagenic' signals from the

NTS to the mid-brain with consideration being given to the parabrachial nucleus as a potential target. Whilst this might be achieved by a combination of receptor antagonists the use of agonists (e.g., $GABA_B$, CB_1, 5-HT_{1A}, ghrelin, opioid) may provide a more fruitful approach as this makes fewer assumptions about the nature of the nauseagenic stimulus (Sanger & Andrews, 2006). A gastric inhibitory polypeptide-1 receptor agonist has been shown to block the acute vomiting induced by the chemotherapeutic agent cisplatin in the ferret (Borner et al., 2023), further extending the list of receptor agonists with 'anti-emetic' potential. The electroceutical approaches to treatment of gastrointestinal symptoms, including nausea (Horn et al., 2019; Ramadi et al., 2020), may provide a route by which this system may be controlled but further study is needed to determine the pathways and cell types involved. A final approach is to target the abdominal vagal afferents at a peripheral site but this would only be applicable when a peripheral release of SP has been demonstrated and when the original signal originates from disordered upper digestive tract function (e.g., gastroparesis; Sanger & Andrews, 2023). Research into the development of anti-nausea drugs is further hampered by the paucity of human volunteer studies using stimuli other than motion. Studies of 'anti-emetics' have been undertaken in humans using apomorphine, ipecacuanha and morphine as challenges (Proctor et al., 1978; Minton et al., 1993; Soergel et al., 2014) and a wider range of challenges could be identified from the side effect profile of licenced drugs (e.g., GLP-1 receptor agonists). The final issue is quantification of nausea. The assessment tools widely used in clinical trials rely on an accurate classification of nausea by the subject, an assumption that subjects are reporting the same sensation and reliable recollection as data may only be collected daily giving data with a low temporal resolution (see Varangot-Reille et al., 2023, Suppl. files). The heterogeneity of nausea assessment instruments was identified as an issue in a recent US, F.D.A. review of endpoints in CINV and PONV studies which identified

nausea assessment as an "opportunity for continued research and development" (Gabby et al., 2021). A reliable, subject independent method for assessing nausea in real time is needed to ensure an accurate assessment of candidate drug efficacy (Andrews & Sanger, 2014).

We close by dedicating this review to a colleague and friend Wes Miner who died while we were drafting this review. Wes was co-author of the first paper demonstrating the remarkable anti-emetic effect of a 5-HT_3 receptor antagonist (Miner & Sanger, 1986) and spent his career in the pharmaceutical industry. In a note to one of the authors (PLRA) in January 1999 Wes made the following insightful comment of relevance to this review regarding the Navari et al., 1999 paper reporting some of the earliest clinical data on NK_1RA: "*results are very, very good and I think this will just about wrap it up for pharmaceutical company interest in the N+V area for the next 20 years.*" As Wes predicted, there have indeed been no major advances in the development in drugs affecting vomiting and especially nausea in the last 20 plus years and as this review shows the accepted dogma that 'anti-emetics' equally affect nausea and vomiting requires challenging; a view with which we are sure Wes would concur.

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Figure legends

Figure 1. A summary of the major pathways implicated in the motor events of vomiting and the sensation of nausea. The diagram shows the major inputs (vestibular system, abdominal vagal afferents, area postrema) to the nucleus tractus solitarius (NTS) in the brainstem by which both nausea and vomiting are evoked. The mechanical events of vomiting only require activation of brainstem and spinal cord nuclei. Most notable are the dorsal motor vagal nucleus (DMVN) projecting vagal efferents to the digestive tract to induce gastric relaxation and intestinal retrograde giant contraction, and the ventral respiratory group (VRG) of neurones driving the spinal phrenic nerve nucleus (PNN) responsible for contraction of the costal diaphragm which together with the anterior abdominal muscles (not shown) provides the main force compressing the stomach and leading to forceful oral ejection of contents. Nausea requires activation of cerebral structures and is associated with the secretion of high concentrations vasopressin (AVP) from the hypothalamic /pituitary axis

but other hormones are also released (e.g., cortisol). The main sympathetic motor outputs associated with nausea are shown in the right-hand red rectangle and are a consequence of descending pathways from the "visceromotor cortex" activating the pre-sympathetic nuclei (PSN) in the brainstem which in turn drive the pre-ganglionic sympathetic neurones in the spinal cord (ILH). For details and references see text. Adapted and modified from Varangot-Reille et al., 2023.

Figure 2. The effects of the NK_1 receptor antagonist (NK_1RA) tradipant *versus* placebo on motion sickness signs and symptoms, are shown for Vomiting (left diagram) and for Nausea (right diagram). Motion sickness was provoked by motion at sea. Voyages inevitably varied in terms of the weather and roughness of waves, consequently the data are presented in terms of all data (i.e. all voyages combined) and split by lower wave motion 'calm seas' and higher wave motion 'rough seas'. Vomiting is shown as % incidence. Nausea is shown as the mean sickness rating scale, with higher scores indicating more severe nausea. Note the differences in levels of statistical significance for the different comparisons. Data were adapted from Polymeropoulos et al, 2020.

Figure 3. A diagrammatic summary of the central and peripheral sites at which NK_1RA could act to reduce nausea and vomiting. Abbreviations: AP= Area Postrema; CPG= Central pattern Generator for vomiting; DMVN=Dorsal Motor Vagal Nucleus EC=Enterochromaffin cell; EEC=Enteroendocrine Cell; EP=Epithelial cell; HPV= Hepatic Portal Vein; ICC= Interstitial Cells of Cajal; NK_1RA= Neurokinin$_1$ receptor antagonist; NTS= Nucleus Tractus Solitarius; VNN= Vestibular Nerve Nucleus. In the periphery, NK_1 receptors located on the gastric smooth muscle, the enteric neurones and possibly the ICCs could modulate motility contributing to a reduction in nausea when disordered motility is implicated (e.g., gastroparesis). NK_1RA can prevent activation/sensitisation of both muscle

mechanoreceptors and epithelial 'chemoreceptive' vagal afferents driving nausea and vomiting by locally released SP. The latter are particularly implicated in nausea and vomiting induced by anti-cancer chemotherapy, gastric irritant and some infections (e.g., rotavirus). NK_1 receptors are also implicated in inflammation the reduction of which by NK_1RA could also contribute to reducing afferent drive. The sites at which vomiting can be blocked all reside in the brainstem (particularly the NTS and CPG) although it is unclear if the AP is a site of action other than when vomiting is induced by an NK_1 receptor agonist. Induction of nausea requires activation of 'higher' brain regions and although NK_1 receptors are present at multiple sites in the mid-brain and cerebral hemispheres the data implicating them in anti-nausea effects is circumstantial. See text for details and references.

Figure 4 A-D. Diagrammatic representation of a longitudinal section through the brainstem showing the key nuclei and pathways implicated in retching, vomiting and nausea. Abbreviations: AP=area postrema; CPG= Central Pattern Generator responsible for the generation of the oscillatory pattern of activity driving the somato-motor pathways for retching and vomiting in the VRG; DMVN= Dorsal Motor Nucleus of the Vagus, origin of pre-ganglionic efferents to the digestive tract; NTS= Nucleus Tractus Solitarius; VRG= Ventral Respiratory Group of neurones; Ph= Phrenic nerve nucleus in cervical (C3-C-5) spinal cord; Ab= Abdominal muscle motor neurones in ventrolateral thoracic and lumbar spinal cord. See text for further explanation and references.
A: Resting state; B: Low level of activation of pathways inputting to the NTS resulting in activation of NTS and ascending pathways inducing nausea including secretion of anti-diuretic hormone (ADH/AVP) from the posterior pituitary; C= More intense activation of the inputs results in more intense nausea and proximal gastric relaxation, a preparatory action to accommodate refluxed material resulting from the Retrograde Giant Contraction originating in the small intestine when the input is sufficient to exceed the threshold for induction of retching and vomiting when the phrenic and abdominal motor neurones are activated. Note that The CPG and the DMV outputs must be coordinated (dotted arrow) as retching does not begin until the RGC reaches the gastric antrum.

Figure 5. Diagrammatic representation of the neuronal discharge pattern in the medial nucleus tractus solitarius (mNTS) and the Central pattern Generator (located in the compact part of the nucleus ambiguus, cAMB) in response to electrical stimulation of infra-cardia vagal afferents based on neurophysiological studies in the dog reported in Koga & Fukuda, (1992), Fukuda et al., (2003), and Onishi et al., (2007). Vagal afferent stimulation results in a uniform increase in NTS firing frequency which ceases at the end of stimulation. NTS activation results in CPG activation after a lag period and is followed by a progressive increase in frequency which is due to 'wind-up'. The CPG firing frequency reaches at threshold at which the pattern becomes oscillatory with the output driving the ventral respiratory group of neurones (VRG) which in turn drive the phrenic and abdominal motor neurones responsible for the mechanical events of retching a vomiting. The CPG oscillations causing retching are shorter and smaller magnitude than the ultimate burst of activity resulting in vomiting and continue beyond the period of vagal afferent stimulation showing a protracted effect of the initial stimulation.

An assessment of the effects of neurokinin$_1$ receptor antagonism against nausea and vomiting: Relative efficacy, sites of action and lessons for future drug development.

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Key words: Anti-cancer chemotherapy, gastroparesis, motion sickness, nausea, neurokinin$_1$, substance P, tradipitant, vomiting.

Abbreviations:

AP: Area postrema

AVP: Arginine vasopressin

CB_1: Cannabinoid$_1$ receptor

CCK: Cholecystokinin

CI: Confidence Interval

CINV: chemotherapy-induced nausea and vomiting

CPG: central pattern generator for vomiting

CUNV: Chronic Unexplained Nausea and Vomiting

D_2: dopamine$_2$ receptor

EC: Enterochromaffin cell

EEC: Enteroendocrine cell

GABA: Gamma amino butyric acid

$GABA_B$: Gamma amino butyric acid B receptor

GCSI: Gastroparesis Clinical Symptom Index

GDF15: Growth differentiation factor 15

GLP-1: Glucagon like peptide 1

5-HT: 5-Hydroxytryptamine

5-HT_{1A}: 5-Hydroxytryptamine$_{1A}$ receptor

5-HT_3: 5-Hydroxytryptamine$_3$ receptor

HEC: Highly emetogenic chemotherapy

H_1: Histamine$_1$ receptor

ICC: interstitial cells of Cajal

i.v.: Intravenous

MSSS: motion sickness severity scale

mACh: Muscarinic acetylcholine receptor

mNTS: medial nucleus tractus solitarius

MRI: Magnetic resonance imaging

NA: Nucleus ambiguus

NK_1RA: Neurokinin$_1$ receptor antagonist

NN: no nausea

NSN: no significant nausea

NTS: Nucleus tractus solitarius

PET: Positron emission tomography

p.o.: *Per oral*

PONV: post-operative nausea and vomiting

PSC: prodromal sign centre

RGC: Retrograde giant contraction

RR: Risk ratio

SP: Substance P

VRG: Ventral respiratory group

VIMS: Visually-induced motion sickness

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Abstract

A 'broad-spectrum' anti-vomiting effect of neurokinin$_1$ receptor antagonists (NK_1RA), shown in preclinical animal studies, has been supported by a more limited range of clinical studies in different indications. However, this review suggests that compared with vomiting, the self-reported sensation of nausea is less affected or possibly unaffected by ~~the different~~ NK_1receptor antagonism~~RAs~~, a common finding for 'anti-emetics'.

The stimulus-independent effects of NK_1RAs against vomiting are explicable by actions within the central pattern generator (CPG; ventral brainstem) and the nucleus tractus solitarius (NTS; dorsal brainstem), with additional effects on vagal afferent activity for certain stimuli (e.g., highly emetogenic chemotherapy). The CPG and NTS neurones are multifunctional so the notable lack of obvious effects of NK_1RAs on other reflexes mediated by the same neurones suggests that their anti-vomiting action is dependent on the activation state of the pathway leading to vomiting.

Nausea requires activation of cerebral pathways by projection of information from the NTS. Although NK_1 receptors are present in cerebral nuclei implicated in nausea, and imaging studies show very high receptor occupancy at clinically used doses, the variable or limited ability of NK_1RAs to inhibit nausea emphasises (a) our inadequate understanding of the

mechanisms of nausea and (b) that classification of a drug as an "anti-emetic" gives a false impression of efficacy against nausea *versus* vomiting.

We discuss the potential mechanisms for the differential efficacy of NK_1RA and the implications for future development of drugs which can effectively treat nausea, an area of unmet clinical need.

1. Introduction

Drugs treating nausea and vomiting as disease symptoms or as adverse effects of therapy are usually classified as 'anti-emetics'. However, ~~,~~ the term 'emetic' refers to a substance which causes vomiting (or retching). Emesis does not mean nausea. Further, increasing evidence indicates ~~with little recognition of~~ differential efficacy of 'anti-emetic' drugs against nausea *versus* vomiting. Seifert & Alexander (2022) proposed a "rational drug class terminology" based on a drug's pharmacological actions rather than its therapeutic orientation (e.g., anti-emetic). Applying this terminology to nausea and vomiting means that ~~In view of this~~the term~~,~~ 'anti-emetic' ~~is used~~ must be written in inverted commas to denote the fact that efficacy against nausea and vomiting should not be assumed to be~~are probably not~~ the same (Sanger & Andrews, 2022). Here, ~~and throughout~~ we emphasise the ~~Here we also avoid using 'anti-emetic' and re-state the argument (Sanger & Andrews, 2022) that it is~~ importance of~~t not to blur the clinical distinction~~ differentiating between nausea, a self-reported aversive sensation involving cortical and sub-cortical brain regions (Napadow et al., 2013; Farmer et al.,2015; Ruffle et al., 2019; Varangot-Reille et al., 2023) and the mechanical events of retching and vomiting involving multiple brainstem nuclei (Stern et al., 2011).

The introduction of NK_1 receptor antagonists (NK_1RAs) further improved control of 'chemotherapy-induced nausea and vomiting' (CINV) and 'post-operative nausea and vomiting' (PONV) (Sanger & Andrews, 2018). In addition, a potential expansion of indications may be appropriate, to include, for example, motion sickness (Polymeropoulos et al., 2020). If confirmed, this would point towards a relatively wide spectrum of 'anti-emetic' activity for the NK_1RAs in humans, as suggested by animal studies (see below). However, oOriginating primarily from studies of CINV including the earliest clinical studies of NK_1RAs (e.g., Navari et al., 1999) there has been a concern that nausea is less well treated than vomiting (Andrews & Sanger, 2014) and this concern persists, as reflected in the comment by Aapro (2018, p.57) that "Perhaps the greatest unmet need in CINV is the lack of complete nausea control". Accordingly, in anTo attempt to understandresolve the nausea *versues* vomiting question in relation to NK_1 RAs, from both aclinical and basic sciencemechanistic perspectives, we identified five5 key questions:

1. Has the broad spectrum of activity of NK_1RAs suggested by animal studies of vomiting translated to humans?
1.2. and Wwhere do NK_1RAs act to inhibit vomiting?
2.3. To what extent do NK_1RAs inhibit nausea as compared to vomiting?
3.4. If NK_1RAs have a differential effect against nausea compared to vomiting, what is the explanation?
4.5. What are the implications of the answers to the above questions in terms of patient satisfaction and for future development of drugs to treat nausea?

Different emetic stimuli signal to the brain via different routes. This is why it is first necessary to determine if the broad-spectrum ability of NK_1RAs to prevent vomiting in animals

translates to humans in a similar manner; such a profile directs the discussion on potential mechanism of action against vomiting and nausea. Accordingly, ~~To answer these questions w~~We begin by briefly describing the NK_1RA studies in animals and then review ~~(see below for selection criteria)~~the effects of NK_1RAs against vomiting and nausea in different clinical indications (see below for selection criteria), ~~and~~ identifying ~~any~~ differences in efficacy between these ~~clinical~~ different indications.

2. Animal studies: Spectrum of NK_1RA effects against vomiting and ~~'~~nausea-like behaviours~~'~~

~~In this section only data from species with a vomiting reflex (i.e. not rodents) are included to~~ In this section we consider ~~illustrate the 'anti-emetic' effects of NK_1RAs against diverse stimuli in a range of animal species~~only data from species with a vomiting reflex (ferret dog, cat, House musk shrew [*Suncus murinus*] and Least shrew [*Cryptotis parva*]). To simplify comparisons between species and between the effects of drugs on vomiting and nausea, we have not considered 'nausea-like' behaviour data from rodents, which cannot vomit (Sanger et al., 2011; Horn et al., 2013).

2.1. Vomiting. Studies in multiple animal species (**Table 1**) have demonstrated 'broad spectrum' effects of NK_1RAs, markedly reducing/blocking retching and/or vomiting induced by diverse stimuli acting via three key inputs to the brainstem (**Figure 1**)~~: the vestibular system (e.g., abnormal motion); the area postrema (e.g., systemic morphine or apomorphine, and the delayed phase of cisplatin CINV); and abdominal vagal afferents (e.g., acute phase of cisplatin CINV, intragastric copper sulphate, electrical stimulation of abdominal vagal afferents)~~ (Stern et al., 2011; Sanger & Andrews, 2018 for references).

2.2. 'Nausea-like behaviours.'~~.~~ Administration to animals of substances inducing nausea and vomiting in humans evoke behavioural changes (often referred to as 'nausea-like'), but their

significance and relevance to the human sensation of nausea is contentious (Stern et al., 2011, Chapter 11; Andrews & Sanger, 2014).

~~In reviewing the effects of NK_1RAs on 'nausea-like behaviours' we only include data obtained using species capable of vomiting (ferret dog, cat, House musk shrew [*Suncus murinus*] and Least shrew [*Cryptotis parva*]) (**Supplementary Table 1**). This enables direct comparison, where possible, with effects on vomiting. Rodents (e.g., rats, mice) are unable to vomit and, compared with species able to vomit, exhibit anatomical and functional differences including: brain stem neuroanatomy (Horn et al., 2013); digestive tract anatomy/physiology (Sanger et al., 2011); subtype composition of the 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor (a ligand-gated ion channel; Holbrook et al., 2009); binding affinity of different NK_1RAs (Beresford et al., 1991; Andrews & Rudd , 2004).~~ In summary, and in contrast to the clear effects of NK_1RA on vomiting, ~~any~~ effects on 'nausea-like behaviours' are absent or inconsistent (**Supplementary Table 1**). Given this lack of clarity and since the relevance of these behaviours to the human experience is unknown, they will not be considered further (Stern et al., 2011, Chapter 11; Andrews & Sanger, 2014, for detailed discussion).

3. Human studies: Spectrum of NK_1RA effects against vomiting and nausea.

It is important to determine if the broad-spectrum ability of NK_1RAs to prevent vomiting in animals translates to the vomiting and nausea of humans. Accordingly, we searched either the name of individual antagonists and/or the therapeutic area (e.g., motion sickness, CINV, PONV, gastroparesis, and cyclical vomiting syndrome). For CINV and PONV where there has been more extensive investigation of NK_1–RAs 'anti-emetic' efficacy we initially reviewed systematic reviews/meta-analyses and then analysed data in selected original papers. As our focus was on the relative efficacy of NK_1-RAs against nausea and vomiting we included papers

where data on *both* vomiting and nausea was presented and in particular where adequate information was provided in the methods about how each was quantified, with data presented in a form allowing comparison. ~~Here the aim is not to identify optimal treatment regimens but to assess the relative efficacies of NK_1RAs against nausea and vomiting.~~ ~~However,~~ Wwe ~~should~~ note that few studies have given an NK_1RA *alone*, 'N' values can be small (e.g., in PONV the N value for 7 studies of aprepitant included in a meta-analysis ranged from 30-55; Cavaye et al., 2021) and some studies are uncontrolled. NAdditionally, nausea ~~is not always measured and~~ is often a secondary outcome with methodological variations in its assessment complicating inter-study comparisons (see below).

Sections 3.1 to 3.6 describe~~s~~ the results of studies investigating the effects of NK_1-RAs against different emetic challenges. Section 3.7 then provides an overview of the spectrum of efficacy against nausea and vomiting.

3.1. Motion sickness (MS). Studies in humans are limited as ethical considerations usually dictate that vomiting endpoints cannot be used in laboratory--based studies inducing motion sickness in healthy human volunteers ~~studies~~. Two laboratory-based studies employed the well proven method of highly provocative whole-body rotational motion with head movements to induce motion sickness (so-called "Cross-coupled motion"). These studies showed no significant efficacy of an NK_1RA (GR205171 [vofopitant]; L758,298) using the degree of motion exposure tolerated before onset of nausea as the endpoint; this suggests no efficacy against nausea (Reid et al., 1998; Reid et al., 2000). A study of healthy human volunteers using inescapable motion at sea investigated the NK_1RA tradipitant (VLY-686/ LY686017) (Polymeropoulos et al., 2020) and unlike laboratory-based trials, it was possible to measure both vomiting and nausea. Tradipitant was significantly effective (placebo

comparator) in protecting against vomiting, but less effective against nausea, using the motion sickness severity scale (MSSS) as an index (**Figure 2**). Only for selected data obtained during rough seas did the NK_1RA provide any protection against nausea ~~protection~~ compared to ~~, albeit at a much lower statistical significance than the equivalent~~ vomiting ~~protection for~~ in this sub-group (**Figure 2**). By contrast, well proven muscarinic acetylcholine (ACh) receptor antagonists such as scopolamine (hyoscine), provided protection against both nausea (Golding et al., 1997; 2018) and vomiting (Golding et al., 2017). More detailed studies ~~with tradipitant~~ are now required, investigating for example, the effects of NK_1RA on the physiological changes accompanying motion sickness such as the reduced gastric antral contractile activity (Faas et al., 2001), a pathway of potential relevance to understanding the effects of NK_1RAs in gastrointestinal conditions associated with nausea, such as gastroparesis (see below).

From these very limited data, we tentatively conclude that NK_1RAs are effective against *vomiting* induced by abnormal motion but are less effective against *nausea*.

3.2 Chemotherapy-induced nausea and vomiting. We focus on NK_1RA use in the acute and delayed phases of highly emetogenic chemotherapy (HEC) discussing their effects against vomiting before effects against nausea.

A study of CINV in seven patients given CP-122,721 *alone* showed that in the acute phase (first 24h) of HEC five patients had ≤2 episodes ~~*vs*~~*v.* 7 episodes of "emesis" in an historic control group and in the delayed phase, 6 had no emesis (Kris et al., 1997). A larger study with L-758, 298 (the prodrug for the NK_1RA, aprepitant [L-754,030]) showed that 37% of patients (n=30) had no vomiting or retching in the acute phase, compared with 52% of patients in an ondansetron ($5\text{-}HT_3RA$) group (n=23; not significantly different) (Cocquyt et al., 2001).

However, confining analysis to the first 8h following cisplatin showed 37% of patients had no vomiting or retching in the NK_1RA group compared to 83% in the 5-HT_3RA group (*P*=0.001) but in the delayed phase 72% of patients were without vomiting or retching in the NK_1RA group ~~*vs*~~*v.* 30% in the ondansetron group (*P*=0.005) (Cocquyt et al., 2001). This study suggests a shift in the relative involvement of 5-hydroxytryptamine$_3$ (5-HT_3) and NK_1 receptors driving retching and vomiting between the acute and delayed phases following cisplatin, a finding confirmed by detailed time course analysis of the efficacy of aprepitant, L-758, 298, ondansetron and granisetron in treatment of CINV (Hesketh et al., 2003).

Recent meta-analyses demonstrate additional protection against vomiting when NK_1RAs are given with a 5-HT_3RA and dexamethasone during both acute and delayed phases in HEC (~15-20% more complete protection), with a greater effect in the delayed phase (Jordan et al., 2016; Yokoe et al., 2019; Qiu et al., 2020).

Overall, and despite an ability of NK_1RAs to further reduce the incidence of vomiting during the acute phase when combined with a 5-HT_3RA and dexamethasone, the incidence of nausea is not further reduced during this phase. For example, an initial study with L-754,030 showed a clear additional effect on vomiting in the acute phase following cisplatin when added to a 5-HT_3RA/dexamethasone regimen (Kris et al., 1997), but no difference in the median nausea score. An analysis of the Phase III studies of NK_1RAs added to a 5-HT_3RA and dexamethasone regime in HEC, found no consistent evidence for an improvement in the incidence of "*no significant nausea*" (NSN) or "*no nausea*" (NN) in the acute phase (Bošnjak et al., 2017). For example, the percentage of patients experiencing "*no nausea*" in the NK_1RA arm *v.* placebo in the acute phase was 53.6% *v.* 52% (Roila et al., 2014), 65% *v.* 66% (Schwartzberg et al., 2015), 68% *v.* 61% (Study 2, Rapoport et al., 2015; statistically significant) and 73% *v.* 68%

(Study 1, Rapoport et al., 2015). A pooled analysis of studies with rolapitant showed a small but statistically significant increase in the percentage of patients reporting NN (respectively, 64% and 70%) in the acute phase of HEC (Bošnjak et al., 2017). Saito et al., (2013) found a tendency for the incidence of NSN to increase (90.2% *v.* 84.9%) when using intravenous fosaprepitant (150mg+granisetron/dexamethasone) in patients receiving high-dose cisplatin, although the difference was not statistically significant and the NN incidence was unchanged (67.6% *v.* 67.5%) compared to placebo.

Some, but not all, studies reported that during the delayed phase the addition of an NK_1RA significantly increased the percentage of patients reporting NN or NSN. In the initial study with L-754,030 (±placebo+ granisetron/dexamethasone; Navari et al., 1999) the median nausea score was reduced on a 100mm VAS (higher score indicating more severe nausea) from 19mm to 1mm on day 2 and over days 2-5 from 10mm to 1mm. Similarly, others reported that the percentage of patients experiencing NN in the NK_1RA arm ~~*vs*~~*v.* placebo in the delayed phase increased significantly: 52.7% ~~*vs*~~*v.* 39.9% (Poli-Bigelli et al.,2003), 53% ~~*vs*~~*v.* 42% (Study 1, Rapoport et al., 2015) and 58% ~~*vs*~~*v.* 47% (Study 2, Rapoport et al., 2015). However, some showed no statistically significant change in NN (e.g., 43.9% ~~*vs*~~*v* 49.1%, Roila et al., 2014; 71.4% ~~*vs*~~*v.* 73%, Roila et al., 2015; 48% ~~*vs*~~*v.* 45%, Schwartzberg et al., 2015). A pooled analysis of studies using rolapitant showed a significant 12% increase in the NN percentage (44% ~~*vs*~~*v*. 56%) in the delayed phase (Bošnjak et al., 2017).

A recent meta-analysis investigated the addition of aprepitant to a $5\text{-}HT_3RA$/dexamethasone regimen in patients (only 258 in the final analysis) receiving HEC treatments for lung cancer (He et al., 2021). While the overall complete response rate (no vomiting/no rescue medication) was significantly better when aprepitant was given, the NN rate was not

statistically significantly different (although significant in two of the studies included in the analysis; Dupuis et al., 2020; Yokoe et al., 2019).

In summary, there is insufficient data to compare different NK_1RAs, but it is possible to draw general conclusions about their efficacy in HEC:

i) NK_1RAs further reduce the incidence of vomiting during the acute phase when combined with a 5-HT_3RA and dexamethasone, but the effect is more marked in the delayed phase of HEC.

ii) When added to a 5-HT_3RA/dexamethasone regime, any ability of NK_1RAs to further reduce the incidence of nausea appears inconsistent and in one meta-analysis the NN rate was not statistically significant.

3.3. Post-operative nausea and vomiting.

~~In contrast to CINV the mechanisms responsible for PONV are considerably less well understood, contributed to by the lack of a robust animal model (see Gardner & Perrin, 1998; Horn et al., 2012, 2014; Gupta et al., 2017).~~

Table 2 summarises the effects of NK_1RAs in PONV using the outcome from studies reporting nausea and vomiting separately to illustrate the efficacy differences. Overall, several NK_1RAs show efficacy against post-operative *vomiting* in a proportion of patients but the block is not complete in all patients and, the efficacy against *nausea* is inconsistent (e.g., small changes in incidence, inconsistent change in intensity, **Table 2**) and lower than against vomiting. A Cochrane meta-analysis examined the efficacy of diverse pharmacological agents in treating *vomiting* in the first 24h (Weibel et al., 2020) and concluded that *single* NK_1RAs were as effective as other *drug combinations.* The analysis did not compare efficacy against nausea.

Assessment of the overall efficacy of NK_1RAs against PONV is complicated by the variety of types or surgery (e.g., open abdomen, laparoscopic) and anaesthesia/analgesia protocols. A further issue is that in studies where a range of doses has been investigated the relationship between NK_1RA dose and efficacy against either nausea or vomiting is not always clear (e.g., casopitant, Singla et al., 2010; rolapitant, Gan et al., 2011; vestepitant, Kranke et al., 2015).

3.4. Cyclical vomiting syndrome. An open-label uncontrolled trial of aprepitant in a paediatric population refractory to conventional treatment showed reduction in the number of cyclic vomiting episodes/year and number of vomits/h (Cristofori et al., 2014). Although nausea is a feature of CVS it was not assessed in this study.

3.5. Paediatric patients with life-limiting conditions.

A case series showed aprepitant (2.0-2.5mg/kg, i.v.) was effective in complete resolution of nausea (parental reports of impact on mobility and feeding used as proxy efficacy markers) in paediatric patients receiving palliative care, with different diagnoses and unresponsive to at least two drugs classified as 'anti-emetics' (e.g., cyclizine, ondansetron, metoclopramide, levomepromazine; Patel et al., 2021). Additionally, aprepitant increased the ability to tolerate feeds as might be expected from the proposal that food refusal in children could be used as a surrogate marker for nausea (Richards & Andrews, 2004), although NK_1RA-induced changes in gastric accommodation (Jacob et al., 2017) offers an alternative explanation.

3.6. Gastric distension induced sensations and gastroparesis.

In healthy human volunteers a single dose of aprepitant (80 or 125mg) had no effect on gastric compliance or sensitivity to distension (Ang et al., 2013). Also, in healthy volunteers, aprepitant (125mg p.o. day 1 + 80mg p.o. days 2-5) did not affect gastric emptying of liquids or solids, intestinal or colonic transit (Madsen & Fuglsang, 2008). Using the same repeat

dosing schedule but following a 'dyspeptogenic' meal, Jacob et al. (2017) confirmed no change in gastric emptying with aprepitant but found a modest increase in fasting (~10%), postprandial (~9%) and gastric accommodation (~5%) volumes, and a tendency to increase maximal tolerated volume (~25%). Interestingly, the aggregate symptoms, nausea, and pain scores (but not bloating or fullness) increased significantly following the 'dyspeptogenic' meal in the aprepitant group compared to placebo (median 36 ~~*vs*~~ *v.* 4). ~~These seemingly unexpected observations may be consistent with the recent identification of an additional ability of aprepitant to activate the mechanosensitive two-pore domain potassium channel, TRAAK (McCoull et al., 2022), which if expressed by abdominal vagal nerve terminals may also cause some reduction in the ability of aprepitant to reduce nausea and vomiting in other clinical scenarios.~~

A four-week placebo-controlled study of aprepitant (125mg/day, p.o.) involving 126 patients failed to demonstrate an improvement in the primary outcome measure of nausea (Pasricha et al., 2018), in a population with 57% gastroparesis patients and the remainder with Chronic Unexplained Nausea and Vomiting (CUNV). The study also used the Gastroparesis Clinical Symptom Index (GCSI; Revicki et al., 2004) to assess symptom severity as a secondary outcome and this showed significant reductions in overall symptom score (1.3 ~~*vs*~~ *v.* 0.7), vomiting (1.6 ~~*vs*~~ *v.* 0.5 [69% decrease]) and nausea (1.8 ~~*vs*~~ *v.* 1 [44% decrease]). The number of hours per day when nausea was experienced, was reduced and the proportion of nausea-free days increased (~ twofold).

A placebo-controlled trial of 152 patients with idiopathic or diabetic gastroparesis and moderate-to-severe nausea, investigated tradipitant (85mg orally) twice daily (daily total 170mg) for 4 weeks (Carlin et al., 2020). The trial met the primary outcome measure of a

reduction in average daily diary nausea score measured using the GCSI Daily Diary with a difference in score reduction between placebo and tradipitant of ~10%. Nausea severity appeared to begin decreasing by week 2 and this was statistically significant by week 3. Additionally, tradipitant increased secondary outcomes of nausea free days (~14%>placebo) and nausea response rate (~21%>placebo). Patients who responded to tradipitant with a reduction in nausea also had improved early satiety, excessive fullness, bloating and upper abdominal pain, compared to placebo. Two case reports involving single patients with gastroparesis report stoppage of previously intractable nausea (Fahler et al., 2012) or vomiting (Chong & Dhatariya, 2009) on administration of aprepitant.

A recent systematic review and network meta-analysis of drugs used to treat gastroparesis showed that NK_1RAs were efficacious (RR=0.69) using global symptom score. When individual symptoms were assessed tradipitant was more effective than placebo in treating nausea (tradipitant RR=0.77; 95% CI 0.65-0.91) (Ingrosso et al., 2023). By contrast, a recent phase III trial of tradipitant in gastroparesis showed no difference from placebo in the intensity of nausea over a 12 week period (Vanda, 2022).

3.7. Overview of clinical efficacy against nausea ~~*v*~~*versus*~~*s*~~ vomiting.

Summarising sections 3.1 to 3.6, NK_1RAs can block vomiting induced by HEC (± $5HT_3$RA and dexamethasone) and PONV, and with much more limited evidence perhaps also the vomiting associated with CVS and motion-induced vomiting. NK_1RAs do not block vomiting in all patients/subjects exposed to a given stimulus and for CINV the efficacy may depend on the phase (potentially, delayed>acute). When nausea is assessed, several studies report no significant benefit although there is some evidence that even if not completely blocking

nausea NK_1RAs may reduce its intensity (e.g., see PONV data, **Table 2**). Overall, however, the NK_1RAs are less efficacious or have more variable efficacy against nausea than vomiting over the same range of stimuli but more quantitative data are needed.

We now attempt to explain this differential effect by a detailed analysis of the sites at which NK_1RAs could act to affect vomiting (section 4) and nausea (section 5).

4. Potential site(s) of action of NK_1RA against retching and vomiting (Figure 3).

The sites at which NK_1RA block retching and vomiting have been investigated in animals (primarily dog and ferret). The findings of these studies are included here because the afferent, integrative and motor pathways responsible for vomiting are comparable between animals (e.g., dog, ferret; Onishi et al., 2007) and humans (Stern et al., 2011). For each potential site of action, we will consider whether it could account for a 'broad spectrum' effect against vomiting or whether it can only explain an action against vomiting induced by a specific stimulus or pathway. This analysis also provides an essential background for understanding the differential effects against nausea.

4.1.1. Vestibular system. The vestibular system is essential for induction of nausea and vomiting caused by abnormal body motion. From an evolutionary perspective the vestibular system is considered ~~as~~ a component of the mechanisms protecting the body against ingested toxins (see Treisman 1977, Money & Cheung, 1983, Oman, 2012; Lackner, 2014). Although sensitivity to motion sickness is a predictive factor for both CINV and PONV (Gan, 2006; Warr, 2014) there is no evidence that the vestibular system (including vestibular nuclei) is directly implicated in the induction of either. During motion sickness, the motor pathways for vomiting are activated via projections of the vestibular nuclei to the medial and caudal

nucleus tractus solitarius (NTS) (studies in the cat; Yates et al., 1994; Sugiyama et al., 2011). There is no evidence that NK_1RAs affect transmission in the pathway between the vestibular system, the vestibular nuclei and the NTS, to block induction of vomiting. This contrasts with the actions on this pathway of H_1 and mACh (M_3/ M_5) receptor antagonists, used to treat motion sickness (Soto & Vega, 2010; Golding & Stott, 1997; Golding et al., 2018). An action of NK_1RAs within the NTS or at a site(s) deeper in the brainstem is therefore the most likely site for effects against motion-induced vomiting.

4.1.2. Area postrema (AP). The AP projects to neurones in the medial NTS (mNTS) which can be activated by emetic stimuli applied to the AP (e.g., apomorphine, L-glutamate) and by vagal afferent stimulation (dog studies; Koga & Fukuda, 1992). However, the evidence that NK_1 receptors occur within the AP is weak, and their functional relevance uncertain. For example, low levels of [^{3}H]-substance P binding displaced by CP-99,994 (0.1nm-100nM) were found in the ferret AP, as compared to the NTS (particularly subnucleus gelatinosus) (Watson et al., 1995). Ariumi et al. (2000) reported dense ^{3}H-substance P binding in the AP and NTS of ferret but displacement by an NK_1RA was not studied. Comparable evidence is available for *Suncus murinus* and rat (Maubach et al., 1997; Andrews & Rudd, 2004). Iontophoretic application of substance P (SP) activated ~50% of AP neurones tested (dog; Carpenter et al., 1988), but although assumed to play a role during vomiting induced by intravenously-administered SP (dog; Carpenter et al., 1984), the receptor type activated by the applied concentration of SP and the link between activation and vomiting was not identified. In the ferret, application of SP to the AP can evoke vomiting (Andrews & Rudd, 2004) but microinjection studies (Gardner et al., 1994) suggest that this response was probably due to SP penetration to the subjacent NTS as the blood-brain barrier between these two areas may have some permeability. A similar explanation of leak into the NTS may account for the block in morphine (s.c.) and

reduction in copper sulphate (intragastric) induced vomiting in the ferret by administration of CP-99,994 or HSP-117 into the AP (Ariumi et al. 2000).

It is a possibility that NK_1 receptors in the AP could be activated if SP (or other tachykinins) are released from gut enteroendocrine cells (EEC; Rezzani et al., 2022) to enter the blood circulation in addition to acting more locally. However, the evidence for this possibility in response to emetic stimuli is weak. Thus, in patients undergoing chemotherapy, the elevation of serum concentrations of SP during the delayed phase of vomiting was inconsistent (Higa et al., 2006, 2012; Matsumoto et al., 1999; Park et al., 2020; Takahashi et al., 2011) although this is the phase during which NK_1RA are most effective (see above).

Another possibility is that SP could arise from neurones intrinsic to the AP following direct activation by endogenous or exogenous emetic substances or by abdominal vagal afferents projecting to the AP. However, SP-like immunoreactivity (SP-Li) was absent in the AP of a human infant (Rikard-Bell et al., 1990), consistent with the absence of SP-Li cell bodies in the AP of adult cat, rat (Newton et al., 1985) and ferret (Boissonade et al., 1996). Previously, extraction studies in humans found some SP in the AP (Zettler & Schlosser, 1955; Cooper et al., 1981) and radioligand binding showed a "moderate" uptake of an NK_1RA by the human AP (Hietala et al., 2005). Sparse SP-Li nerve fibres have been found in the AP (cat, rat) but their origin is most likely from either vagal nerve afferents terminating there or from the NTS (Newton et al., 1985); this is consistent with the finding of high-densities of SP immunoreactive fibres in lateral borders of the AP in the ferret (Boissonade et al., 1996). However, in the least shrew SP-Li fibres and puncta were present at a "moderate" level in the AP (Ray & Darmani, 2007).

Finally, it is worth noting that the concept of the AP as a site at which systemic agents act to induce nausea and vomiting was originally derived from studies showing abolition of vomiting induced by apomorphine (a dopamine D_2 receptor agonist), following surgical ablation of the AP including in humans (Lindstom & Brizzee,1962; Borison & Wang, 1953). Similarly, other exogenously administered agents (e.g., morphine, loperamide, cisplatin) can induce emesis via the AP (Borison, 1989; Bhandari et al., 1992; Percie du Sert et al., 2009). However, there is only limited evidence that systemic endogenous agents which can induce vomiting (e.g., adrenaline, cholecystokinin [CCK], GDF15, vasopressin), act via the AP, with alternative sites of action suggested (Borison,1989; Borner et al., 2020; Makwana et al., 2022). The above discussion suggests that SP, acting via NK_1 receptors in the AP should be added to the~~is~~ list of systemic endogenous emetic agents. ~~.~~

4.1.3. Abdominal vagal afferents.

There are two sites at which vagal afferent activation by emetic stimuli could be affected by an NK_1RA; they are not mutually exclusive (**Figure 3**).

4.1.3.1. **The peripheral transduction mechanism.** A potential ability of SP from enterochromaffin cells (ECs) to induce vomiting by acting on vagal afferents was hypothesised >30 years ago (Andrews et al., 1988; for details see Andrews & Rudd, 2004). Potentially, such a mechanism would be similar to that for 5-HT, which is released from ECs in response to chemotherapeutic agents (e.g., cisplatin) and other emetic stimuli (e.g., rotavirus), causing vomiting by stimulating and sensitizing abdominal vagal afferent terminals via 5-HT_3 receptor activation (Andrews & Rudd, 2015; Sanger and Andrews, 2018; for reviews). In rats, treatment with methotrexate or cisplatin increased the number of SP-containing ECs within the intestine, 24h after administration (Machida et al., 2017; Obara et al., 2018) but studies have

not yet looked for local release of SP from ECs in response to anti-cancer chemotherapeutic agents or other emetic stimuli. By analogy with 5-HT (see above), any release of SP might be expected to activate vagal nerve terminals. Recently, SP (1µM)-induced depolarisation of human isolated vagus was shown to be blocked by aprepitant (Smith et al., 2021). However, the authors used a concentration (10µM) at least 10000x the human NK_1 receptor binding IC_{50}, at or above the concentrations examined for selectivity of action (Tattersall et al., 2000), and now understood to also activate the mechanosensitive two-pore domain potassium channel, TRAAK (encoded by the *KCNK4* gene) (McCoull et al., 2022). Interestingly, recordings from abdominal vagal afferents of ferrets show an interaction between 5-HT and SP (Minami et al., 2001) and 'cross talk' has been demonstrated between NK_1 and $5\text{-}HT_3$ receptors in relation to the 'anti-emetic' effect of palonosetron (Rojas et al., 2014).

4.1.3.2. Vagal afferent to NTS transmission. Abdominal vagal afferents terminate in the mNTS (Fukuda & Koga, 1992). There is evidence that SP is a transmitter from vagal afferents to NTS neurones (cat, Baude et al., 1989; dog, Shiroshita et al., 1997) and for activation of NTS neurones by iontophoretically applied SP (ferret, Saito et al., 1998; rat, Maubach & Jones, 1997). However, any action of NK_1RA on vagal to NTS transmission must be selective for afferents involved in induction of vomiting as NK_1RAs do not block the gag reflex, the cardiac or respiratory components of the von Bezold-Jarisch reflex or apnoea induced by cervical vagal afferent stimulation (Watson et al., 1995; Fukuda et al., 1999). Additionally, while systemic administration of the NK_1RA, CP-99,994 in the anaesthetised ferret blocked licking, swallowing and retching induced by electrical stimulation of the abdominal vagal afferents, the accompanying rise in blood pressure was unaffected (Watson et al., 1995). This makes it unlikely that vagal to NTS transmission *per se* is blocked and suggests that the block is either within the NTS integrative pathways which initiate vomiting or on the output side of the

system in the 'central pattern generator' (CPG) for vomiting located in the reticular formation dorsomedial to the retrofacial nucleus (Bötzinger complex) in the region of the NA (compact region) and the associated 'prodromal sign centre' (PSC in the semi-compact area of the nucleus ambiguus (Fukuda & Koga, 1991, 1992; Fukuda et al., 2003). Further support for a specific activity on some but not all vagal functions comes from studies in the decerebrate dog where the NK_1RA, GR-205171 (i.v.) blocked fictive retching, the accompanying antral contractile response (most likely the extension of the Retrograde Giant Contraction (RGC) that originates in the small intestine and immediately precedes the onset of retching mediated by vagal efferents; see Lang et al., 1986; Lang, 1990), and reduced the hypersalivation (mediated by PSC) evoked by vagal afferent stimulation, but not the accompanying vagal efferent mediated relaxation of the proximal stomach (Furukawa et al., 1998).

It is self-evident that blockade of vagal afferent activation at a peripheral site or vagal afferent transmission to the mNTS would only contribute to the anti-vomiting effects of NK_1RAs when the primary stimulus activates the vagus (e.g., acute phase of CINV, possibly gastroparesis; Sanger & Andrews, 2023). Therefore, a vagal site of action would not account for block of stimuli acting either only via the AP or the vestibular system so additional site(s) of action need to be considered.

4.1.4. Brainstem integrative mechanism and the drive to the visceral and somatic motor outputs. The selective effects of NK_1RA on reflex responses to vagal afferent stimulation (as above) show that actions of NK_1RA within the brain stem integrative pathways (i.e. NTS, CPG, ventral respiratory group [VRG]) are selective to neurones involved in the 'vomiting motor programme' occurring as a result of reconfiguration of the pattern of activity in the multifunctional respiratory neurones (Grélot & Bianchi, 1997; Grélot & Miller, 1997) (c.f.

cough, yawn, sneeze). These same sets of neurones can also be driven to evoke vomiting by stimuli acting on the vestibular system and the AP (**Figure 4**). Thus, the effects of NK_1RAs on the brainstem pathways are 'state dependent' and this can explain the selectivity of effects against vomiting; when the brainstem is involved in baseline respiration and some respiratory reflexes there is little dependence on SP as a transmitter but when the pathway reconfigures and is highly active as occurs for vomiting then it becomes critically dependent on SP.

Overall, t~~T~~here is evidence for either the presence of SP positive neurones and/or NK_1 receptors in the key brainstem sites implicated in vomiting.

4.1.4.1. Nucleus tractus solitarius. SP-like immunoreactive neurones are present in the human NTS, particularly subnucleus gelatinosus (mNTS) and this is consistent with studies in both the cat and ferret (Leslie, 1985; Boissonade et al., 1996). A human brain PET study using a fluorine-18 labelled NK_1RA reported 'moderate' uptake in the NTS, the nucleus ambiguus and "other nuclei of the vagus" (not specified) (Hietala et al., 2005).

A site of action within the NTS is supported by studies showing microinjection of CP-99,994 in the "region of the NTS" inhibited, but did not completely block, cisplatin-induced acute retching and vomiting in the ferret (Gardner et al., 1994; Tattersall et al., 1996). An important point is that the NK_1RA was injected after retching/vomiting began showing that the antagonist was blocking a pathway driven by ongoing NK_1 receptor activation. The peptide NK_1RA, GR-82334 was infective against cisplatin-induced retching/vomiting when given intravenously but was effective (77% reduction) when given into the NTS (Gardner et al., 1994). Rupniak et al (1997) correlated anti-emetic activity against cisplatin in the ferret with central penetration using a range of NK_1RAs with differing brain penetration. These studies argued strongly that central penetration (at least to the NTS) is required for the acute anti-

emetic effect of an NK_1RA. Further support for an action of NK_1RA in the NTS comes from inhibition of SP (1µM)-induced discharge in NTS slices by the NK_1RA HSP-117 (10µM), without affecting baseline spontaneous neuronal discharge (ferret, Saito et al., 1998).

4.1.4.2. Dorsal motor vagal nucleus. NK_1 receptors are present in the dorsal motor vagal nucleus (DMVN; ferret, Watson et al., 1995), the site of origin of vagal efferents supplying the upper digestive tract and regulating the proximal gastric relaxation and RGC prior to the onset of retching and vomiting (Lang, 1990). In the rat, neurones in the DMVN responsive to gastric distension±24h post-cisplatin had their baseline activity altered by CP-99,994 (5µM) (Sun et al., 2017) but the results should be interpreted with caution as the efferent projection (e.g., the stomach) of the neurones was not identified (e.g., using antidromic collision, Andrews et al., 1980) and the effects of CP-99,994 were not controlled for by using its less potent 2R, 3R enantiomer, CP-100,263 (Watson et al., 1995). Although these studies show that the DMVN is a potential target for NK_1RA it should be noted that preventing the gastric relaxation and RGC will not block retching and vomiting as they can occur even in the absence of the stomach (Magendie, 1813) and when the RGC is blocked by atropine (Lang et al., 1986). An action of NK_1RA on the DMVN is therefore unlikely to explain their anti-vomiting action.

4.1.4.3. Ventral brainstem. Neurophysiological studies of fictive emesis in the dog implicate nuclei in the ventral brainstem (Fukuda & Koga, 1991, 1992; Fukuda et al., 2003; Onishi et al., 2007). When administered systemically, the NK_1RA, GR-205171 reduces vagal afferent activation (via the mNTS) of the CPG for vomiting and/or in the pathway linking the NTS to the CPG via the PSC (Fukuda & Koga, 1991, 1992); immunohistochemistry has demonstrated the presence of NK_1 receptors in both regions of the dog ventral brainstem (Fukuda et al., 2003). The CPG connects with the VRG, the location of the neurones driving the phrenic and

abdominal motor neurones involved in normal respiration as well as retching and vomiting (**Figure 4**).

Total block of transmission at either the NTS or CPG is probably not required to stop induction of vomiting; a *reduction* in transmission at either site is likely to be sufficient as triggering vomiting requires a higher frequency stimulus which also lasts for an extended time (e.g., ~20s of vagal afferent stimulation is required in dog [Koga & Fukuda, 1992] and ferret [Andrews et al., 1990]), presumably to prevent inappropriate triggering. It is particularly notable that NK_1RAs prevent the 'wind-up' of CPG neurones induced by vagal afferent stimulation and blunts the rise in firing frequency when continuous vagal afferent stimulation is used, preventing the CPG reaching a threshold for induction of the oscillatory activity required for retching and vomiting (Fukuda et al., 1999, 2003) (**Figure 5**).

4.1.5. Overview of site(s) of action against vomiting

The clinically used NK_1RAs are brain penetrant so when given systemically they can act at both the central and peripheral neuronal sites involved in retching and vomiting:

i) For ~~motion induced~~ vomiting induced by abnormal motion, the brainstem integrative pathways (NTS, CPG) are the most likely site of action.

ii) For stimuli involving abdominal vagal afferents it is possible that NK_1RA can a) block effects of any SP released from EEC cells onto NK_1 receptors on the peripheral afferent nerve terminals (Minami et al., 2001); b) reduce tachykininergic transmission between vagal afferents and the NTS (Fukuda et al., 2003; Andrews & Rudd, 2004); c) modulate the brainstem integrative pathways (NTS, CPG) sufficiently to disrupt the signals encoding induction of

vomiting (Fukuda et al., 1999, 2003; Fukuda & Koga, 1991, 1992; Watson et al., 1995-) . At present, the evidence for (b) and (c) is stronger.

iii) For stimuli acting on the AP via the circulation (or cerebrospinal fluid) including exogenous emetics and endogenous substances released for example from the digestive tract because of damage/inflammation (e.g., during the delayed phase of CINV and chronic phases of infection) (Sanger & Andrews, 2018; Andrews et al., 2021, 2023 for references), the brainstem integrative mechanisms (NTS, CPG) are the most likely sites at which vomiting is affected as there is little evidence for an action within the AP itself.

The NTS and CPG sites of action of NK_1RA are common to all stimuli inducing vomiting. However, for stimuli where abdominal vagal afferent activation occurs two additional sites of action are implicated which, if operational, would block vagal afferent input and thereby make it unnecessary for NK_1RA to act within the NTS and CPG. However, although the NK_1RA are highly effective against vomiting in a number of clinical settings, NK_1 receptors are not the only receptors involved in all of the pathways and this may explain why they may not always be fully effective in all patients. For example, SP is likely to co-transmit with a non-peptide (e.g., glutamate) with the former likely to be released by a higher frequency or different pattern of nerve firing (Svensson et al., 2019). Further, glutamate has been implicated in abdominal vagal afferent to mNTS transmission as NBQX blocked vagal afferent-induced retching in dog and ferret and the resulting mNTS activation in the dog (Furukawa et al., 2001; Onishi et al., 2007). Nevertheless, peptides, as co-transmitters, are known to be involved in network reconfiguration with release determined by both neuronal firing pattern and time (Cropper et al., 2018). Variations in the predominant transmitters in the nausea and vomiting pathways, possibly as a response to disease, especially if chronic (e.g., in chronic visceral pain

NK_1 receptor availability is downregulated; Jarcho et al., 2013), may also contribute to NK_1RAs spectrum of clinical efficacy.

5. The potential site(s) of NK_1RA action against nausea

'Anti-emetics' must not be assumed to equally affect both nausea and vomiting (Sanger & Andrews, 2022). Accordingly, we discuss the relative effects of NK_1RA against nausea and vomiting by considering specific questions about the pathways involved; this also informs directions for development of novel drugs (section 6). Direct experimental data is not available to answer all the questions raised, so some answers are speculative and hypothetical but experimentally testable.

5.1. What information reaches the mNTS from the abdominal vagal afferents in the presence of NK_1RAs?

This question is relevant to both CINV and gastroparesis where abdominal vagal afferents are implicated in genesis of nausea and vomiting (Sanger and Andrews, 2018, 2023). Regardless of whether NK_1RAs reduce vagal afferent firing by acting peripherally (e.g., Minami et al., 2001) or centrally (e.g., Fukuda et al., 2003), the degree of activation, and the pattern, frequency and duration of abdominal vagal afferent activity required for induction of nausea as compared to vomiting is unknown. It is, nevertheless, a reasonable assumption that nausea requires less intense activation of afferent pathways than vomiting (see Horn 2014 for discussion in relation to the vagus). The effects of NK_1RAs on vagal afferent activity evoked by a wide range of stimulus intensities, ± substances which may sensitise the afferents (e.g., 5-HT, prostaglandins), need to be investigated directly to answer the above question. The development of vagal afferent recording techniques in humans may eventually allow direct testing of this hypothesis (Ottaviani et al., 2020).

5.2. Do differential effects of NK_1RAs on the NTS account for the differential effects against nausea and vomiting?

NK_1RA modulation of the vagal afferent drive to the mNTS and/or transmission within the NTS (vagal, AP and vestibular inputs) could contribute to a *reduction* in nausea *intensity* by decreasing the drive from the NTS to supra-medullary structures implicated in the sensation of nausea. However, the evidence for such an action is poor, as discussed below.

5.3. Are NK_1 receptors in the mid-brain and cerebral hemispheres involved in potential anti-nausea effects of NK_1RA?

In contrast to vomiting, the brain pathways responsible for nausea are not well defined. The majority of brain imaging studies are in subjects reporting nausea induced by illusory-self motion (vection; visually-induced motion sickness, VIMS), with only single studies using 'real' motion or a pharmacological challenge (see Varangot-Reille et al., 2023) making it difficult to assess whether the findings have general applicability. Cortical and sub-cortical areas consistently showing an increase in activity in healthy volunteers reporting nausea include the frontal lobe (e.g., anterior cingulate cortex), occipital lobe (e.g., posterior cingulate cortex), temporal lobe (e.g., amygdala, part of the 'limbic cortex') and basal ganglia (e.g., putamen) (Varangot-Reille et al., 2023).

NK_1RA binding in the human brain using PET shows NK_1 receptors in several brain areas implicated in nausea. For example, aprepitant has receptor occupancy of 50% in the caudate and 90% in the putamen (basal ganglia) at plasma concentrations of ~$2x10^{-9}$ M and ~$2x\ 10^{-8}$ M respectively (Bergstrom et al., 2004). Based on the striatal occupancy levels, the authors concluded that the recommended 'anti-emetic' aprepitant regime of 125mg on day 1 and 80mg on the subsequent two days in CINV would result in an occupancy of >90% (Bergstrom

et al.,2004). Hietala et al., (2005) using the same radioligand confirmed the highest uptake in the caudate and putamen and levels ~50% in regions of the occipital lobe (e.g., posterior cingulate cortex), temporal lobe (e.g., amygdala [forms the 'limbic cortex' with the hippocampus]) and frontal lobe (anterior cingulate cortex) all of which have been implicated in nausea in brain imaging studies (Varangot-Reille et al., 2023).

Pharmacological MRI studies provide additional unexpected insights. Using fosaprepitant (pro-drug of aprepitant) the NK_1 receptor distribution profile identified in the above PET studies was confirmed but in addition identified *activation* of brain areas (e.g., cerebellum, red nucleus) where there were thought to not be any NK_1 receptors, an effect attributed to "downstream pharmacodynamic effects" (Borsook et al., 2012, Fig. 2; Upadhyay et al., 2011). Such effects demonstrate that in identifying brain sites of drug action we should not only consider regions which have their activity inhibited; activation of a pathway which itself is inhibitory on the function under consideration should not be overlooked. Brain imaging studies in nausea have identified areas with both *increased* and *decreased* activity (Farmer et al., 2015).

Although we focus on areas directly implicated in nausea, as nausea involves heightened anxiety, the potential anxiolytic effects of NK_1RA (Hoppe et al., 2018) could indirectly contribute to reducing nausea scores especially in chronic conditions (e.g., gastroparesis).

Overall, NK_1RAs do not appear to have a consistent ability to reduce nausea induced by multiple stimuli despite high levels of NK_1RA binding in many of the relevant brain areas. Therefore, it is reasonable to conclude ~~that~~ that NK_1 receptors do not have a major role in transmission in the 'higher' brain regions currently implicated in nausea. We note that NK_1RA efficacy in depression (e.g., Keller et al., 2006; Ratti et al., 2013), panic disorder (Fujimura et

al., 2009), pain (Boorsook et al., 2012) and anxiety (Hoppe et al., 2018) are also variable and less than might be anticipated from NK_1 receptor distribution.

5.4. Do NK_1 RA reduce vasopressin secretion?

Relatively high plasma concentrations of arginine vasopressin (AVP) are associated with nausea induced by stimuli activating the vestibular system, AP and abdominal vagal afferents (Makwana et al., 2022). A causal link between AVP and nausea is not proven, but a credible possibility in at least some clinical scenarios involves the actions of low concentrations of AVP on gastric pacemaker activity (the interstitial cells of Cajal; ICC), synergising with actions of other nauseagenic stimuli to disrupt motility and hence, initiate vagal afferent discharge; the demonstration of synergy between two different nauseagenic stimuli (adrenaline + AVP) was used to argue that antagonism of one alone (e.g., the effects of vasopressin) might reduce but not prevent the symptom of nausea (Makwana et al., 2022). In dogs, following cisplatin administration, the NK_1RA maropitant was without significant effect on the peak [AVP] or the area under the curve whereas both were significantly reduced by ondansetron (Kenward et al., 2017). In human patients treated with cisplatin the acute rise in [AVP] was blocked by ondansetron (Barreca et al., 1996) as in the dog, but as far as we are aware similar patient studies have not been performed with an NK_1RA.

5.5. Do NK_1RA have a role in treating nausea by gastric motility modulation?

The presence of SP in the digestive tract in nerve terminals and EEC (Sanger, 2004) and of NK_1 receptors on smooth muscle cells and Interstitial Cells of Cajal (ICCs) (Lavin et al., 1998; Faussone-Pellegrini, 2006; Cheng et al., 2007; Liu & Rudd, 2023) makes the digestive tract a potential target for NK_1RA. However, an ability of NK_1RAs to affect nausea by a direct effect on gastric motility is unlikely. Thus, in healthy volunteers there is little evidence for an effect

of NK_1RA on digestive tract motility (assessed by gastric emptying or compliance, or small and large bowel propulsion) (Madsen & Fuglsang 2008; Ang et al., 2013; Jacob et al., 2017; Khanna et al., 2022). Interestingly, after a dyspeptogenic meal, aprepitant (125 mg on day 1, then 80 mg on days 2–5) increased fasting, postprandial, and accommodation gastric volume but increased aggregate symptoms, nausea, and pain scores after ingestion of the maximum tolerated volume; the authors suggested that differences between these studies may be dependent on what is measured and on the application of acute- or longer-term dosing with aprepitant (Jacob et al., 2017) but activation of TRAAK channels (see above) should also be considered.

Dysrhythmic gastric electrical activity has been associated with nausea in disorders including gastroparesis, CUNV, functional dyspepsia, gastro-oesophageal reflux disease, all linked with loss of ICCs (Koch 2014; O'Grady et al., 2021). Thus, any ability of NK_1RAs to affect ICC functions (see above) could, in theory, have an influence on *induction* of nausea although an effect on vagal afferent signalling or the NTS seems more likely based on current knowledge.

6. Concluding comments.

Irrespective of the stimulus, the effects of NK_1RA against *vomiting* are explicable by a central action on the NTS and CPG in the brain stem with potential additional peripheral effects on vagal afferent activity when activated by an emetic stimulus (e.g., HEC, some ingested toxins). NK_1RAs are not 100% effective against vomiting in humans (c.f., pre-clinical studies, **Table 1**) implicating other transmitter/receptor systems and explaining why optimal *anti-vomiting* therapy may require drug combinations (e.g., netupitant + palonosetron + dexamethasone) in treating complex situations such as HEC. An additional role for other neurotransmitters/co-transmitters (e.g., glutamate) has not yet been fully explored.

A reduction in the projection of information from the NTS to the higher brain regions by suppression of NTS pathways and the drive from the abdominal vagal afferents is likely to contribute to any reduction of nausea by NK_1RAs, no matter how sub-optimal ~~and disappointing~~ the current evidence suggests. It could be argued that the distribution of NK_1 receptors in cortical and subcortical structures implicated in nausea may predict efficacy against nausea, but it is also possible these receptors are coupled to non-nauseagenic pathways, such as those involved in fear and/ or anxiety (which nonetheless may contribute to the overall sensation of nausea).

Mechanistically, vomiting is well understood and studies with NK_1RAs show that targeting the NTS/CPG in the brainstem is a valid approach and adverse effects on the respiratory, cardiovascular and digestive systems all regulated from the brainstem appear to be avoided. The apparent specificity of NK_1RA blockade of vomiting likely reflects the functional reconfiguration of the neural network to coordinate retching/vomiting where tachykininergic signalling becomes critical (state dependence; see Doi & Ramirez 2010 for a study of NK_1 receptors and state dependent functions of pre-Bötzinger complex respiratory neurones). The NTS and CPG need investigating in emetic species using neurophysiological studies similar to those in rodents showing complex interaction between NK_1 receptor activation, glutamate and GABA release (Bailey et al., 2004) to understand how NK_1RAs are 'functionally specific' for vomiting.

Nausea remains a challenge as there are major gaps in knowledge of the cerebral pathways involved and hence in identifying potential receptor targets to identify 'broad spectrum' anti-nausea drugs. As the insular cortex is the "highest" cortical region consistently activated in subjects reporting nausea (Varangot-Reille et al., 2023) this would be a logical place to target

a drug to block nausea although the associated physiological changes (e.g., regional cold sweating, AVP secretion) may not be blocked as they involve 'lower' brain regions. An alternative approach is to selectively suppress transmission of 'nauseagenic' signals from the NTS to the mid-brain with consideration being given to the parabrachial nucleus as a potential target. Whilst this might be achieved by a combination of receptor antagonists the use of agonists (e.g., $GABA_B$, CB_1, 5-HT_{1A}, ghrelin, opioid) may provide a more fruitful approach as this makes fewer assumptions about the nature of the nauseagenic stimulus (Sanger & Andrews, 2006). A gastric inhibitory polypeptide-1 receptor agonist has been shown to block the acute vomiting induced by the chemotherapeutic agent cisplatin in the ferret (Borner et al., 2023), further extending the list of receptor agonists with 'anti-emetic' potential. The electroceutical approaches to treatment of gastrointestinal symptoms, including nausea (Horn et al., 2019; Ramadi et al., 2020), may provide a route by which this system may be controlled but further study is needed to determine the pathways and cell types involved. A final approach is to target the abdominal vagal afferents at a peripheral site but this would only be applicable when a peripheral release of SP has been demonstrated and when the original signal originates from disordered upper digestive tract function (e.g., gastroparesis; Sanger & Andrews, 2023). Research into the development of anti-nausea drugs is further hampered by the paucity of human volunteer studies using stimuli other than motion. Studies of 'anti-emetics' have been undertaken in humans using apomorphine, ipecacuanha and morphine as challenges (Proctor et al., 1978; Minton et al., 1993; Soergel et al., 2014) and a wider range of challenges could be identified from the side effect profile of licenced drugs (e.g., GLP-1 receptor agonists). The final issue is quantification of nausea. The ~~present~~ assessment tools widely used in clinical trials rely on an accurate classification of nausea by the subject, an assumption that subjects are reporting the same sensation and reliable

recollection as data may only be collected daily giving data with a low temporal resolution (see Varangot-Reille et al., 2023, Suppl. files). The heterogeneity of nausea assessment instruments was identified as an issue in a recent US, F.D.A. review of endpoints in CINV and PONV studies which identified nausea assessment as an "opportunity for continued research and development" (Gabby et al., 2021). A reliable, subject independent method for assessing nausea in real time is needed to ensure an accurate assessment of candidate drug efficacy (Andrews & Sanger, 2014).

We close by dedicating this review to a colleague and friend Wes Miner who died while we were drafting this review. Wes was co-author of the first paper demonstrating the remarkable 'anti-emetic' effect of a 5-HT_3 receptor antagonist (Miner & Sanger, 1986) and spent his career in the pharmaceutical industry. In a note to one of the authors (PLRA) in January 1999 Wes made the following insightful comment of relevance to this review regarding the Navari et al., 1999 paper reporting some of the earliest clinical data on NK_1RA: "*results are very, very good and I think this will just about wrap it up for pharmaceutical company interest in the N+V area for the next 20 years.*" As Wes predicted, there have indeed been no major advances in the development in drugs affecting vomiting and especially nausea in the last 20 plus years and as this review shows the accepted dogma that 'anti-emetics' equally affect nausea and vomiting requires challenging; a view with which we are sure Wes would concur.

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Figure legends

Figure 1. A summary of the major pathways implicated in the motor events of vomiting and the sensation of nausea. The diagram shows the major inputs (vestibular system, abdominal vagal afferents, area postrema) to the nucleus tractus solitarius (NTS) in the brainstem by which both nausea and vomiting are evoked. The mechanical events of vomiting only require activation of brainstem and spinal cord nuclei. Most notable are the dorsal motor vagal nucleus (DMVN) projecting vagal efferents to the digestive tract to induce gastric

relaxation and intestinal retrograde giant contraction, and the ventral respiratory group (VRG) of neurones driving the spinal phrenic nerve nucleus (PNN) responsible for contraction of the costal diaphragm which together with the anterior abdominal muscles (not shown) provides the main force compressing the stomach and leading to forceful oral ejection of contents. Nausea requires activation of cerebral structures and is associated with the secretion of high concentrations vasopressin (AVP) from the hypothalamic /pituitary axis but other hormones are also released (e.g., cortisol). The main sympathetic motor outputs associated with nausea are shown in the right-hand red rectangle and are a consequence of descending pathways from the "visceromotor cortex" activating the pre-sympathetic nuclei (PSN) in the brainstem which in turn drive the pre-ganglionic sympathetic neurones in the spinal cord (ILH). For details and references see text. Adapted and modified from Varangot-Reille et al., 2023.

Figure 2. The effects of the NK_1 receptor antagonist (NK_1RA) tradipant *versus* placebo on motion sickness signs and symptoms, are shown for Vomiting (left diagram) and for Nausea (right diagram). Motion sickness was provoked by motion at sea. Voyages inevitably varied in terms of the weather and roughness of waves, consequently the data are presented in terms of all data (i.e. all voyages combined) and split by lower wave motion 'calm seas' and higher wave motion 'rough seas'. Vomiting is shown as % incidence. Nausea is shown as the mean sickness rating scale, with higher scores indicating more severe nausea. Note the differences in levels of statistical significance for the different comparisons. Data were adapted from Polymeropoulos et al, 2020.

Figure 3. A diagrammatic summary of the central and peripheral sites at which NK_1RA could act to reduce nausea and vomiting. Abbreviations: AP= Area Postrema; CPG= Central pattern Generator for vomiting; DMVN=Dorsal Motor Vagal Nucleus EC=Enterochromaffin cell; EEC=Enteroendocrine Cell; EP=Epithelial cell; HPV= Hepatic Portal Vein; ICC= Interstitial Cells of Cajal; NK_1RA= Neurokinin$_1$ receptor antagonist; NTS= Nucleus Tractus Solitarius; VNN= Vestibular Nerve Nucleus. In the periphery, NK_1 receptors located on the gastric smooth muscle, the enteric neurones and possibly the ICCs could modulate motility contributing to a reduction in nausea when disordered motility is implicated (e.g., gastroparesis). NK_1RA can prevent activation/sensitisation of both muscle mechanoreceptors and epithelial 'chemoreceptive' vagal afferents driving nausea and vomiting by locally released SP. The latter are particularly implicated in nausea and vomiting induced by anti-cancer chemotherapy, gastric irritant and some infections (e.g., rotavirus). NK_1 receptors are also implicated in inflammation the reduction of which by NK_1RA could also contribute to reducing afferent drive. The sites at which vomiting can be blocked all reside in the brainstem (particularly the NTS and CPG) although it is unclear if the AP is a site of action other than when vomiting is induced by an NK_1 receptor agonist. Induction of nausea requires activation of 'higher' brain regions and although NK_1 receptors are present at multiple sites in the mid-brain and cerebral hemispheres the data implicating them in anti-nausea effects is circumstantial. See text for details and references.

Figure 4 A-D. Diagrammatic representation of a longitudinal section through the brainstem showing the key nuclei and pathways implicated in retching, vomiting and nausea. Abbreviations: AP=area postrema; CPG= Central Pattern Generator responsible for the generation of the oscillatory pattern of activity driving the somato-motor pathways for retching and vomiting in the VRG; DMVN= Dorsal Motor Nucleus of the Vagus, origin of pre-ganglionic efferents to the digestive tract; NTS= Nucleus Tractus Solitarius; VRG= Ventral Respiratory Group of neurones; Ph= Phrenic nerve nucleus in cervical (C3-C-5) spinal cord; Ab= Abdominal muscle motor neurones in ventrolateral thoracic and lumbar spinal cord. See text for further explanation and references.

A: Resting state; B: Low level of activation of pathways inputting to the NTS resulting in activation of NTS and ascending pathways inducing nausea including secretion of anti-diuretic hormone (ADH/AVP) from the posterior pituitary; C= More intense activation of the inputs results in more intense nausea and proximal gastric relaxation, a preparatory action to accommodate refluxed material resulting from the Retrograde Giant Contraction originating in the small intestine when the input is sufficient to exceed the threshold for induction of retching and vomiting when the phrenic and abdominal motor neurones are activated. Note that The CPG and the DMV outputs must be coordinated (dotted arrow) as retching does not begin until the RGC reaches the gastric antrum.

Figure 5. Diagrammatic representation of the neuronal discharge pattern in the medial nucleus tractus solitarius (mNTS) and the Central pattern Generator (located in the compact part of the nucleus ambiguus, cAMB) in response to electrical stimulation of infra-cardia vagal afferents based on neurophysiological studies in the dog reported in Koga & Fukuda, (1992), Fukuda et al., (2003), and Onishi et al., (2007). Vagal afferent stimulation results in a uniform increase in NTS firing frequency which ceases at the end of stimulation. NTS activation results in CPG activation after a lag period and is followed by a progressive increase in frequency which is due to 'wind-up'. The CPG firing frequency reaches at threshold at which the pattern becomes oscillatory with the output driving the ventral respiratory group of neurones (VRG) which in turn drive the phrenic and abdominal motor neurones responsible for the mechanical events of retching a vomiting. The CPG oscillations causing retching are shorter and smaller magnitude than the ultimate burst of activity resulting in vomiting and continue beyond the period of vagal afferent stimulation showing a protracted effect of the initial stimulation.

Species	Neurokinin$_1$ receptor antagonist	Stimulus details	References
Cytotoxic anti-cancer drugs			
Acute phase of cisplatin			
Ferret	CJ-11,974 CJ-17, 493 CP-99,994 CP-122,721 GR203040 L-742,694 L-741,671 Netupitant SCH 619734	Given either i.p or i.v.	Duffy et al., 2012; Lau et al., 2005; Rudd et al., 2016; Rupniak et al., 1997; Shishido et al., 2008; Tattersall et al., 1996 Watson et al.,1995;
Dog	FK886 Maropitant		De la Puente -Redondo et al., 2007; Furukawa et al.,2013; Kenward et al., 2017; Vail et al., 2007
Suncus	GR203040		Gardner et al.,1995
Doxorubicin emesis (5 days)			
Dog	Maropitant	i.v.	Rau et al., 2010
Delayed phase of cisplatin			
Ferret	CJ-11, 974 Netupitant SCH619734	Given either i.p or i.v.	Duffy et al., 2012; Rudd et al., 2016; Tsuchiya et al., 2002
Cyclophosphamide			
Ferret	GR203040 GR205171	Given i.p.	Gardner et al., 1995, 1996
Pharmacological agents			
Apomorphine			
Dog	CP-99, 994 FK886	Given s.c.	Furukawa et al.,2013; Sedlacek et al., 2008; Watson et al., 1995

	Maropitant		
Ferret	CP-99,994 Netupitant SCH619734		Duffy et al., 2012; Rudd et al., 2016; Tattersall, et al., 1994; Watson et al., 1995.
Brimonidine			
Cat	Maropitant	Sedative given as eye drops	Kanda et al., 2020
Copper sulphate			
Dog	CP-99,994	Given p.o.	Andrews et al., 2001; Watson et al., 1995
Ferret	CP-99,994 Netupitant	Given p.o.	Rudd et al., 2016; Watson et al., 1995
Ethanol			
Suncus	CP-99,994	Given i.p.	Chen et al., 1997
FPL64176			
Least shrew	Netupitant	L-type Ca^{++} channel agonist	Zhong et al., 2018
GR73632			
Least shrew	CP-99,994	NK_1 receptor agonist; given i.p.	Darmani et al., 2011
Halothane/N_2O			
Suncus	GR205171	Inhaled	Gardner & Perren,1998
Ipecacuanha			
Ferret	CP-99,994 CP-122,721, GR205171, GR203040 Netupitant R116301	Given p.o.	Gardener et al., 1995, 1996; Gonsalves et al., 1996; Megens et al., 2002; Watson et al., 1995
Dog	GR203040 GR205171 Maropitant	Given p.o.	Gardner et al., 1995,1996; Sedlacek, et al., 2008
Lycorine			
Dog	Maropitant	Alkaloid from daffodils; given s.c.	Kretzing et al., 2011

2-methyl 5-hydroxytryptamine			
Least shrew	CP-99,994	5-HT_3 receptor agonist; given i.p. Note no significant effect of CP-99, 994 given at same dose that blocked NK_1 agonist (GR73632; see above)	Darmani et al., 2011
Naloxone			
Suncus	CP-99,994	Given s.c.	Rudd et al.,1999
Nicotine			
Suncus	CP-99,994 CP-122,721 RP67580	Given s.c.	Rudd et al., 1999; Tattersall et al., 1995
Opiate receptor agonists			
Ferret	CP-99,994	Loperamide; s.c.	Zaman et al., 1999
Ferret	GR203041	Morphine; s.c.	Gardner et al., 1995
Dog	Maropitant	Morphine; s.c.	Lorenzutti et al., 2016, 2017
Dog	Maropitant	Morphine; s.c.	Koh et al., 2014
Dog	Maropitant	Hydromorphone; i.m.	Claude et al., 2014
Dog	Maropitant	Hydromorphone; i.m.	Hay Kraus 2014
Dog	Maropitant	Hydromorphone; i.m. + acepromazine; i.m.	Johnson, 2014
Cat	Maropitant	Dexmedetomidine +morphine; i.m.	Martin-Flores et al., 2016
Phosphodieseterase IV Inhibitors			
Ferret	CP-99,994	R-rolipram, CT-2450, RS14203; given p.o.	Robichaud et al., 1999
Prostaglandin E_2			
Ferret	CP-99,994	Given i.p.	Kan et al., 2006
Pyrogallol			
Ferret	CP-99,994	Reactive oxygen species donor; given i.p.	Andrews & Matsuki, unpublished.
Resiniferatoxin			
Suncus	CP-99,994	Given s.c.	Andrews et al., 2000
Tranexamic acid			
Dog	Maropitant	Fibrinolytic	Kantyka et al., 2020
U46619			
Suncus	CP-99,994	TP agonist; given i.p.	Kan et al., 2003

Xylazine			
Cat	R116301	Given s.c.	Megens et al., 2000
Non- pharmacological stimuli			
Motion			
Cat	CP-99,994	Ferris Wheel	Lucot et al., 1997
Dog	Maropitant	Car journey	Conder et al., 2008
Suncus	GR203041 Netupitant	Horizontal motion	Gardner et al.,1995 Rudd et al., 2016
Total Body Radiation			
Ferret	GR203040 GR205171,	X-radiation	Gardner et al., 1995, 1996
Ferret	CP-99, 994	X-radiation (3 weeks post abdominal vagotomy and greater splanchnic nerve section)	Andrews & Watson, unpublished observations
Electrical stimulation of vagal afferents			
Dog (decerebrate)	GR205171	Stimulation either at the level of the terminal thoracic oesophagus or abdomen; fictive emesis measured in the decerebrate dog.	Fukuda et al., 1999; Furukawa et al., 1998
Ferret (urethane anaesthesia)	CP-99,994		Watson et al., 1995
Parvoviral enteritis-induced vomiting			
Dog	Maropitant		Yalcin & Keser, 2016
Post-neurosurgery vomiting			
Macaca fascicularis, *Macaca mulatta*	Maropitant		Steinbach et al., 2018

Compound	Efficacy against nausea in PONV	Reference
Neurokinin$_1$ receptor antagonist given alone and compared to a placebo or active comparator		
CP-122,721 (100mg, 200mg, p.o.)	In patients undergoing abdominal hysterectomy the maximum nausea score appeared to be reduced by CP-122, 721 in both dose groups compared to placebo but any effect was not statistically significant (N=20-24). VAS nausea score did not differ between ondansetron, CP-122, 721 and combination groups (N=52-53).	Gesztesi et al., 1998 (abstract), 2000.
Vofopitant (GR-205171) (25mg, i.v.)	In patients undergoing major gynaecological surgery vofopitant showed superiority compared to placebo (N=18 in both groups) for the percentage of patients without nausea (2h complete control nausea: 55% *v*. 20%) and reduced the severity of nausea over the entire 24h post -operative observation period.	Diemunsch et al., 1999.
Aprepitant (L-754,030)	Peak nausea score distribution (interquartile range) was significantly lower (P<0.05, N=280-293) for both aprepitant groups (40 /125mg) compared to ondansetron (4mg) but the percentage of patients	Diemunsch et al., 2007.

(40mg/125, p.o.)	reporting no significant nausea was only significantly higher than that ondansetron for 40mg aprepitant (62% . 53%). For vomiting both doses of aprepitant were superior to ondansetron and blocked vomiting in ~85% of patients. Open abdominal surgery.	
Aprepitant (L-754,030) (80mg p.o.)	In patients undergoing laparascopic gynaecological surgery nausea intensity was significantly lower with aprepitant compared to palonosetron on arrival in the recovery room (11.2±2.1 *v*. 19.0±2.2) and at two hours (9.7±2.1 *v*. 19.4±3.5) but not in the subsequent 46hours. The complete response rate over 48h did not differ (74% *v.* 77%)	Moon et al., 2014
Aprepitant (L-754,030) (40mg p.o.)	In patients undergoing plastic surgery compared to placebo the severity of nausea was lower (p=0.014, N=75/arm) in the aprepitant group between 0-48h post-surgery. Vomiting incidence was also significantly lower in the aprepitant group (7/75 *v.* 22/75, p=0.003).	Vallejo et al., 2012
Vestepitant (4-36mg, i.v.)	Non-emergency surgery under general anaesthesia in patients failing prophylaxis with pre-surgery ondansetron. Nausea numerical rating scale median values did not differ between ondansetron (4mg) alone and any dose of vestepitant (N=7-15/group) given subsequently but overall vestepitant was superior to ondansetron (10.1-22.9% improvement	Kranke et al., 2015

	except at a dose of 18mg when there was a -1.2 % difference.	
Fosaprepitant (150mg, i.v.)	In patients undergoing surgery requiring general anaesthesia the percentage of patients vomiting was significantly lower with fosaprpitant (N=82) than with ondansetron (N=89) at 0-2h (2% *v*. 17%),0-24h (2% *v*.28%) and at 0-48h (2% *v*.29%). However, the percentage of patients reporting nausea in the fosparepitant was higher than for vomiting at all time points (e.g., at 0-2h, nausea 41% *v.* vomiting 2%).	Murakami et al., 2017
Neurokinin$_1$ receptor antagonist given in addition to a standard treatment and compared to identify any additional benefit		
Casopitant (GW679769) (50,100,150mg, p.o.)	Only female patients, laparascopic /laparotomic gynecological procedure or laparascopic cholecystectomy. All doses of casopitant further reduced the percentage of patients with vomiting at both 0-24h (ondansetron 28.6 % *v.* casopitant + ondansetron 4.3%-9.3%) 0-48 h time points (ondansetron 32.9 % *v.* casopitant + ondansetron 6.4%-12.9%). There was no difference in the % of patients reporting nausea between ondansetron and casopitant + ondansetron groups. The % of patients experiencing nausea was higher that the % experiencing vomiting for all three doses of casopitant + ondansetron (casopitant 50 mg, nausea	Singla et al., 2010

	70.0% *v.* vomiting 9.3%; 100mg, nausea 63.6% *v.* vomiting 4.3%; 150mg, nausea 66.4% *vs* vomiting 7.1%). The intensity of nausea did not differ between the three casopitant doses.	
Aprepitant (L-754,030) (40mg, p.o.)	Craniotomy patients. No difference between nausea scores, incidence or significant nausea between aprepitant and ondansetron (4mg) up to 48h post-surgery but the study may not have been sufficiently powered to see statistical differences at all time points.	Habib et al., 2011
Vestepitant (4-36mg, i.v.)	Given to patients with breakthrough emesis; Nausea scores did not differ between patients with either complete response (no vomiting) or treatment failure and between vestepitant and ondansetron groups.	Kranke et al., 2014.
Aprepitant (L-754,030) (80mg, p.o.)	In patients undergoing bariatric surgery aprepitant increased the number of patients without nausea and vomiting (42.18% *v*. 36.67%) compared to ondansetron alone but this was not significant and nausea scores were unaffected by aprepitant.	Sinha et al., 2014.
Aprepitant (L-754,030) (80mg, p.o.)	Laparaoscopic gynaecological surgery. Significant (p=0.014) additional reduction in nausea incidence (24h) when aprepitant was given with ondansetron but no change in severity of nausea or incidence of	Ham et al., 2016.

	vomiting.	
Systematic review and Meta-analysis		
Aprepitant/rolapitant/casopitant	Systematic review and meta-analysis of 14 randomised control trials of three NK_1RAs in patients undergoing mainly either abdominal or gynaecological surgery including open abdomen approaches. Aprepitant showed an additional increase of 31% in the patients protected from nausea compared to placebo with an overall incidence of 76.1%.	Liu et al., 2015. Note that Table 2 in this paper contains a detailed summary of results from all studies included.
Aprepitant (L-754,030) (80mg, p.o.)	Systematic review and meta-analysis of 7 randomised control trials of aprepitant (80mg) in patients undergoing laparoscopic procedures. RR for nausea 0.56 v. 0.2 for vomiting compared to placebo or no anti-emetic therapy (see supplementary Figure 2,). Risk of vomiting reduced by 80% in first two hours post-operatively *vs*. 44% for nausea.	Cavaye et al., 2021. Note that Table 2 in this paper contains a detailed summary of results from all studies included.

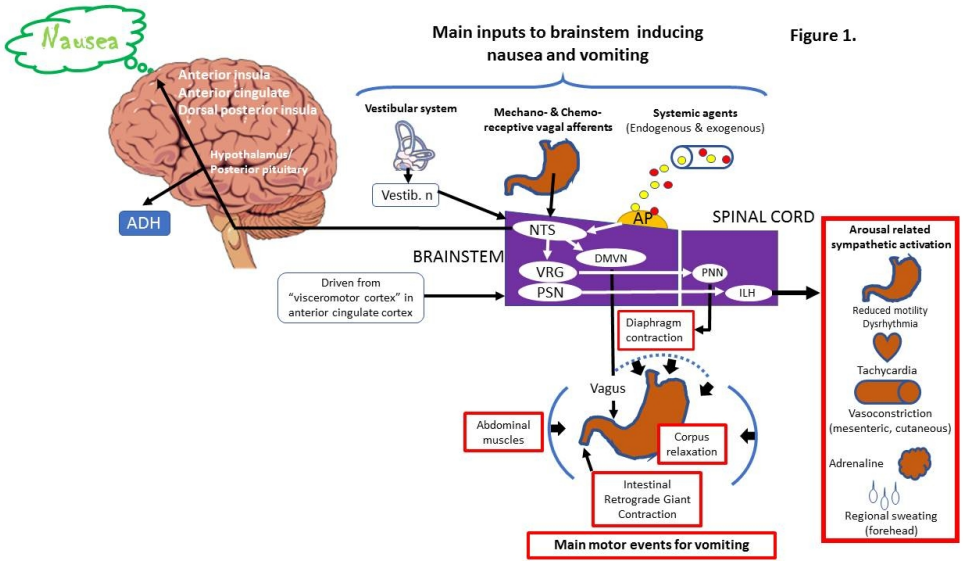

Figure 1. A summary of the major pathways implicated in the motor events of vomiting and the sensation of nausea. The diagram shows the major inputs (vestibular system, abdominal vagal afferents, area postrema) to the nucleus tractus solitarius (NTS) in the brainstem by which both nausea and vomiting are evoked. The mechanical events of vomiting only require activation of brainstem and spinal cord nuclei. Most notable are the dorsal motor vagal nucleus (DMVN) projecting vagal efferents to the digestive tract to induce gastric relaxation and intestinal retrograde giant contraction, and the ventral respiratory group (VRG) of neurones driving the spinal phrenic nerve nucleus (PNN) responsible for contraction of the costal diaphragm which together with the anterior abdominal muscles (not shown) provides the main force compressing the stomach and leading to forceful oral ejection of contents. Nausea requires activation of cerebral structures and is associated with the secretion of high concentrations vasopressin (AVP) from the hypothalamic /pituitary axis but other hormones are also released (e.g., cortisol). The main sympathetic motor outputs associated with nausea are shown in the right-hand red rectangle and are a consequence of descending pathways from the "visceromotor cortex" activating the pre-sympathetic nuclei (PSN) in the brainstem which in turn drive the pre-ganglionic sympathetic neurones in the spinal cord (ILH). For details and references see text. Adapted and modified from Varangot-Reille et al., 2023.

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Figure 2

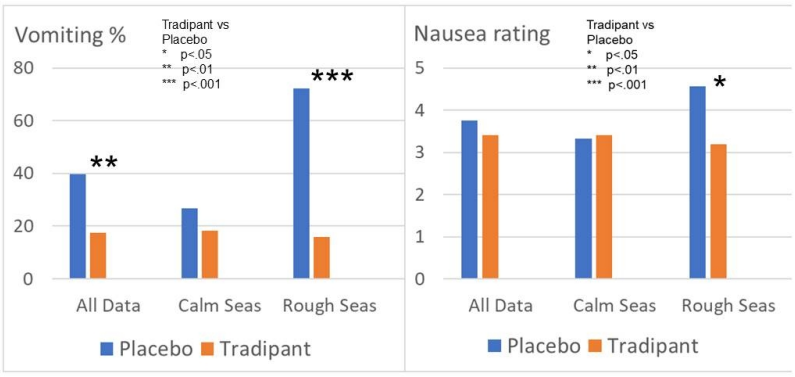

Figure 2. The effects of the NK1 receptor antagonist (NK1RA) tradipant versus placebo on motion sickness signs and symptoms, are shown for Vomiting (left diagram) and for Nausea (right diagram). Motion sickness was provoked by motion at sea. Voyages inevitably varied in terms of the weather and roughness of waves, consequently the data are presented in terms of all data (i.e. all voyages combined) and split by lower wave motion 'calm seas' and higher wave motion 'rough seas'. Vomiting is shown as % incidence. Nausea is shown as the mean sickness rating scale, with higher scores indicating more severe nausea. Note the differences in levels of statistical significance for the different comparisons. Data were adapted from Polymeropoulos et al, 2020.

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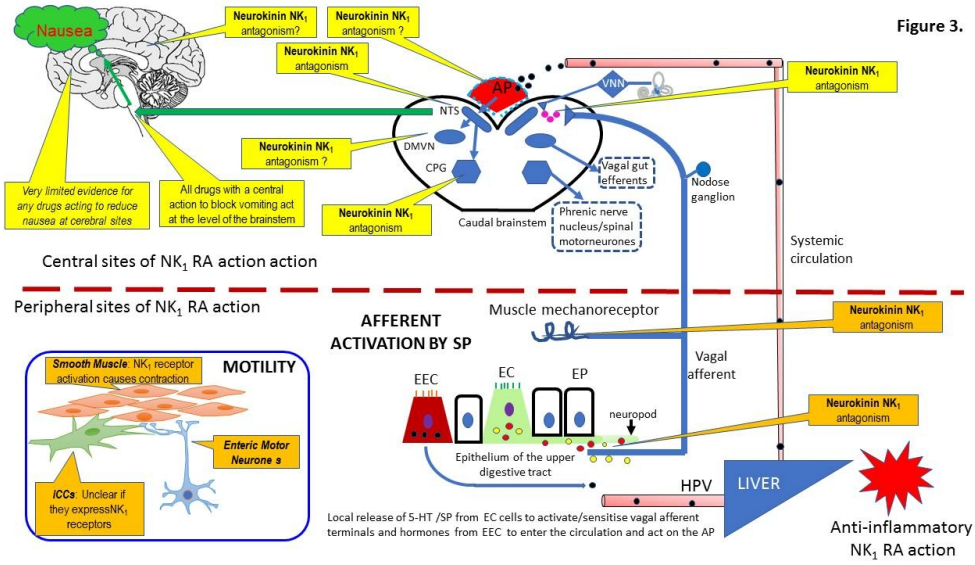

Figure 3. A diagrammatic summary of the central and peripheral sites at which NK1RA could act to reduce nausea and vomiting. Abbreviations: AP= Area Postrema; CPG= Central pattern Generator for vomiting; DMVN=Dorsal Motor Vagal Nucleus EC=Enterochromaffin cell; EEC=Enteroendocrine Cell; EP=Epithelial cell; HPV= Hepatic Portal Vein; ICC= Interstitial Cells of Cajal; NK1RA= Neurokinin1 receptor antagonist; NTS= Nucleus Tractus Solitarius; VNN= Vestibular Nerve Nucleus. In the periphery, NK1 receptors located on the gastric smooth muscle, the enteric neurones and possibly the ICCs could modulate motility contributing to a reduction in nausea when disordered motility is implicated (e.g., gastroparesis). NK1RA can prevent activation/sensitisation of both muscle mechanoreceptors and epithelial 'chemoreceptive' vagal afferents driving nausea and vomiting by locally released SP. The latter are particularly implicated in nausea and vomiting induced by anti-cancer chemotherapy, gastric irritant and some infections (e.g., rotavirus). NK1 receptors are also implicated in inflammation the reduction of which by NK1RA could also contribute to reducing afferent drive. The sites at which vomiting can be blocked all reside in the brainstem (particularly the NTS and CPG) although it is unclear if the AP is a site of action other than when vomiting is induced by an NK1 receptor agonist. Induction of nausea requires activation of 'higher' brain regions and although NK1 receptors are present at multiple sites in the mid-brain and cerebral hemispheres the data implicating them in anti-nausea effects is circumstantial. See text for details and references.

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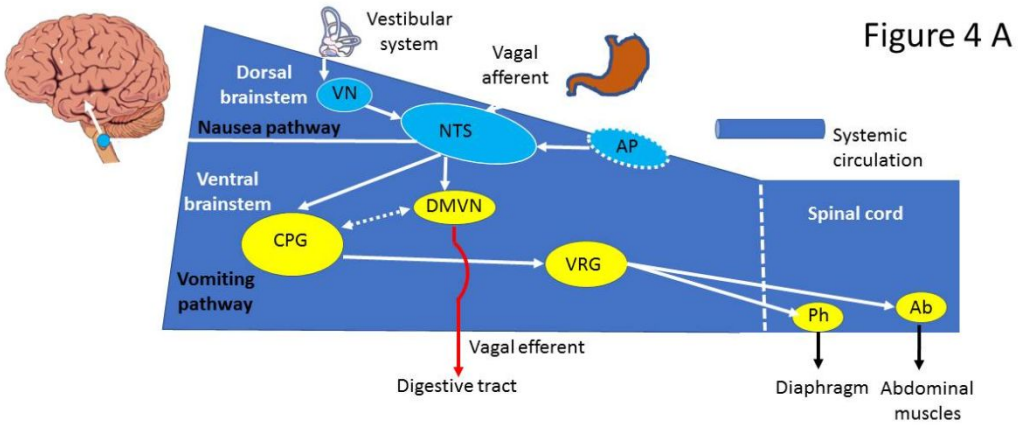
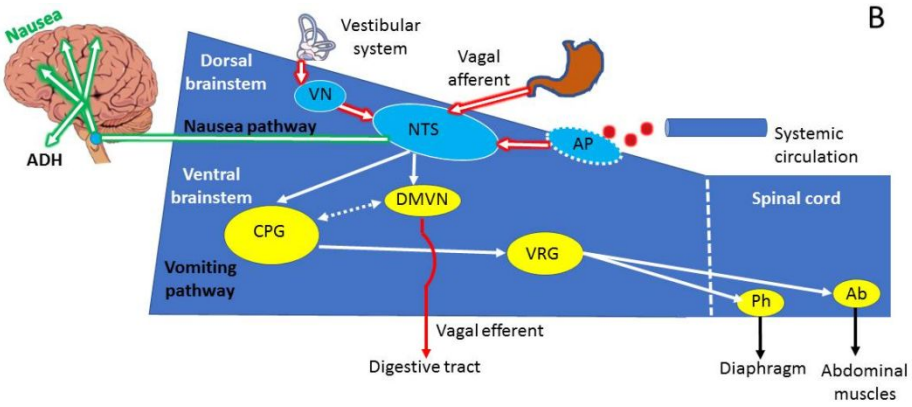
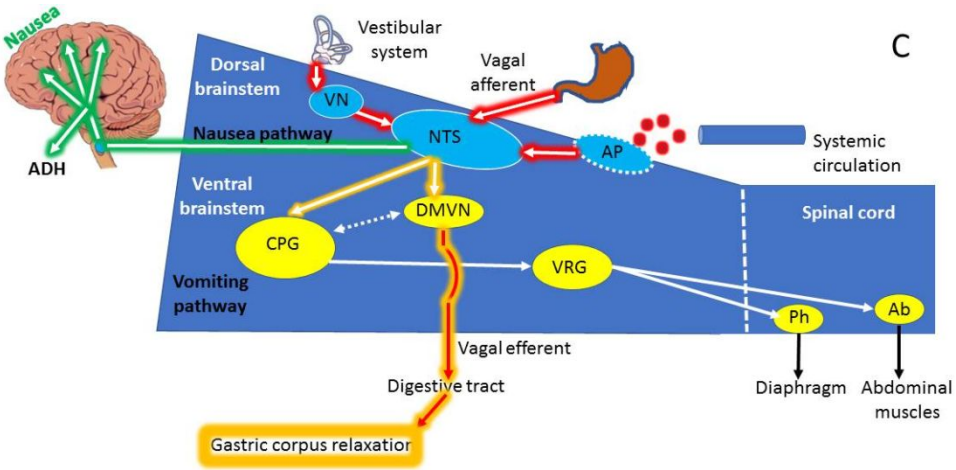


Figure 4 A
Vestibular system
Vagal afferent
Dorsal brainstem
VN
Nausea pathway
NTS
AP
Systemic circulation
Ventral brainstem
DMVN
Spinal cord
CPG
VRG
Vomiting pathway
Ph
Ab
Vagal efferent
Digestive tract
Diaphragm
Abdominal muscles


B
Nausea
Vestibular system
Vagal afferent
Dorsal brainstem
VN
Nausea pathway
NTS
AP
Systemic circulation
ADH
Ventral brainstem
DMVN
Spinal cord
CPG
VRG
Vomiting pathway
Ph
Ab
Vagal efferent
Digestive tract
Diaphragm
Abdominal muscles


C
Nausea
Vestibular system
Vagal afferent
Dorsal brainstem
VN
Nausea pathway
NTS
AP
Systemic circulation
ADH
Ventral brainstem
DMVN
Spinal cord
CPG
VRG
Vomiting pathway
Ph
Ab
Vagal efferent
Digestive tract
Diaphragm
Abdominal muscles
Gastric corpus relaxation

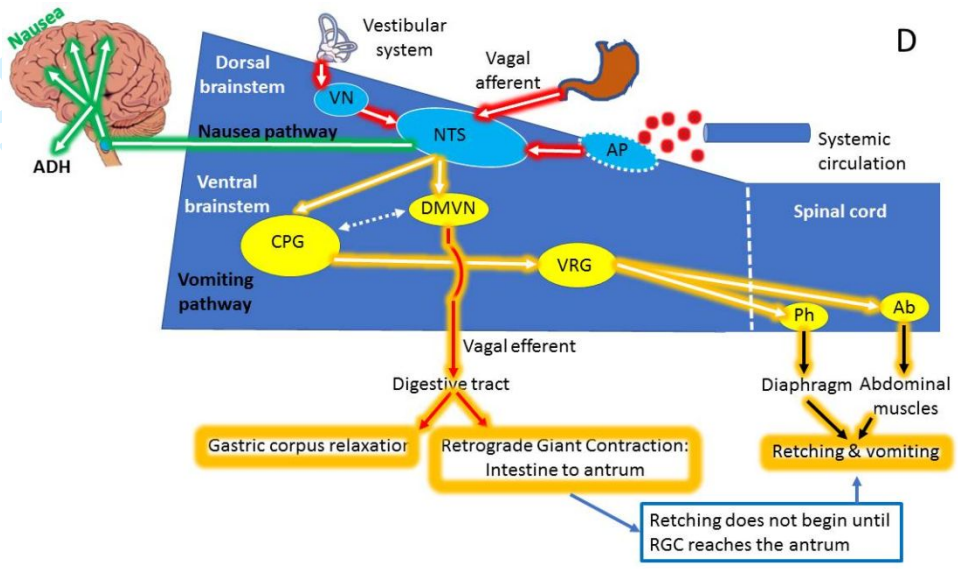


Figure 4 A-D. Diagrammatic representation of a longitudinal section through the brainstem showing the key nuclei and pathways implicated in retching, vomiting and nausea. Abbreviations: AP=area postrema; CPG= Central Pattern Generator responsible for the generation of the oscillatory pattern of activity driving the somato-motor pathways for retching and vomiting in the VRG; DMVN= Dorsal Motor Nucleus of the Vagus, origin of pre-ganglionic efferents to the digestive tract; NTS= Nucleus Tractus Solitarius; VRG= Ventral Respiratory Group of neurones; Ph= Phrenic nerve nucleus in cervical (C3-C-5) spinal cord; Ab= Abdominal muscle motor neurones in ventrolateral thoracic and lumbar spinal cord. See text for further explanation and references.

A: Resting state; B: Low level of activation of pathways inputting to the NTS resulting in activation of NTS and ascending pathways inducing nausea including secretion of anti-diuretic hormone (ADH/AVP) from the posterior pituitary; C= More intense activation of the inputs results in more intense nausea and proximal gastric relaxation, a preparatory action to accommodate refluxed material resulting from the Retrograde Giant Contraction originating in the small intestine when the input is sufficient to exceed the threshold for induction of retching and vomiting when the phrenic and abdominal motor neurones are activated. Note that The CPG and the DMV outputs must be coordinated (dotted arrow) as retching does not begin until the RGC reaches the gastric antrum.

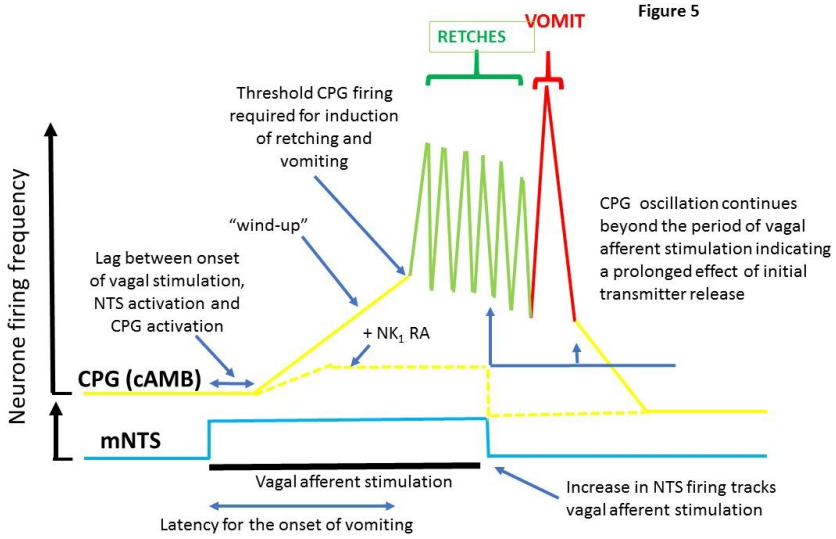


Figure 5. Diagrammatic representation of the neuronal discharge pattern in the medial Nucleus Tractus Solitarius (mNTS) and the Central pattern Generator (located in the compact part of the Nucleus Ambiguus, cAMB) in response to electrical stimulation of infra-cardia vagal afferents based on neurophysiological studies in the dog reported in Koga & Fukuda, (1992), Fukuda et al., (2003), and Onishi et al., (2007). Vagal afferent stimulation results in a uniform increase in NTS firing frequency which ceases at the end of stimulation. NTS activation results in CPG activation after a lag period and is followed by a progressive increase in frequency which is due to 'wind-up'. The CPG firing frequency reaches at threshold at which the pattern becomes oscillatory with the output driving the ventral respiratory group of neurones (VRG) which in turn drive the phrenic and abdominal motor neurones responsible for the mechanical events of retching a vomiting. The CPG oscillations causing retching are shorter and smaller magnitude than the ultimate burst of activity resulting in vomiting and continue beyond the period of vagal afferent stimulation showing a protracted effect of the initial stimulation.

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Species	Neurokinin$_1$ receptor antagonist (route)	Effect on "nausea- like behaviour" as defined by authors	Behaviour(s) measured	Additional details of stimulus	Comment	Reference
Cisplatin (low dose)						
Dog	Maropitant (i.v.)	Onset of signs of nausea delayed and VAS scores reduced at three time points between 3.7 and 4.5h post cisplatin but AUC over 7h not significantly reduced.	Composite score of lip licking, lethargy, restlessness or turning /circling signalling that vomiting is imminent.		Also showed that vasopressin secretion was reduced by maropitant.	Kenward et al., 2017
Doxorubicin (5 days)						
Dog	Maropitant (s.c.)	No effect	Appetite, protracted salivation, lip smacking		No effect on appetite	Rau et al., 2010
Opiate receptor agonists						
Dog	Maropitant (s.c.)	No effect	Ptyalism, lip licking, increased swallowing	Morphine(s.c.)	Salivation incidence unaffected; metaclopramide also no effect on "nausea - like behaviours"	Lorenzutti et al., 2016, 2017
Dog	Maropitant(s.c.)	No significant effect but reduction in incidence	Excessive lip licking and swallowing, hunched posture	Hydromorphone (i.m.)	No effect on increased panting; maropitant	Claude et al., 2014

					increased ptyalism-salivation not included in nausea score	
Dog	Maropitant (s.c.)	Significantly decreased with 60 min pre-dose	Salivation, lip-licking	Hydromoprphone (i.m.)	Effect on "N" only seen with 60min pre-dose	Hay Kraus 2014
Cat	Maropitant (s.c.)	No effect	Sialorrhea, lip licking	Dexmedetomidine +morphine (i.m.)		Martin-Flores et al., 2016
Tranexamic acid						
Dog	Maropitant (i.v.)	No significant effect on severity	Visual analogue scale	Fibrinolytic		Kantyka et al., 2020
Brimonidine						
Cat	Maropitant(p.o.)	No effect	Sialorrhea, lip licking	α_2 agonist sedative given as eye drops		Kanda et al., 2020
Motion						
Cat	CP-99,994 (s.c.)	No effect	Suri et al., 1979 symptom scale	Ferris Wheel		Lucot et al., 1997
Lycorine (s.c.)						
Dog	Maropitant (s.c.)	No effect	Increased salivation, lip licking, frequent/exaggerated swallowing motions, lethargy, restlessness and /or panting	Alkaloid from daffodils		Kretzing et al., 2011

Supplementary Table 1. A summary of the results of preclinical studies reporting the effects of neurokinin$_1$ receptor antagonists on the "nausea –like behaviours" in response to a range of emetic stimuli in species capable of vomiting.

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