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Is there a need to identify new anti-emetic drugs?

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Abstract

Nausea and vomiting occur in a large number of disease conditions and as side effects of many drug treatments, including use of analgesics and anesthesia in surgery and chemotherapy in cancer treatment. Current anti-emetics provide relief from only some sources of vomiting, with more limited benefits for the control of nausea. Elucidation of forebrain pathways that generate nausea and brainstem circuitry controlling emesis are significant obstacles for the development of effective universal anti-nausea and anti-emetic treatments.

Introduction

Nausea and vomiting occur in many disease conditions and medical treatments, including cancer chemotherapy, radio-therapy, and pain control and anesthesia drug use associated with surgery (Box 1). There is a significant need to identify more effective anti-emetic targets because current therapeutics have limitations in controlling some sources of vomiting (Table 1) and some patients do not respond to these medicines. Most importantly, there is an even greater necessity to develop anti-nausea medications because it is clear that available anti-emetic drugs, although they inhibit emesis, are much less potent for controlling nausea. The status of this therapeutic area is the result of limited understanding of the neurobiological systems that generate nausea and vomiting. Further investments into basic biology to define these systems should not only present significant rewards for designing anti-nausea and anti-emetic drugs but also provide insight into why other classes of medicines stimulate nausea and vomiting, e.g., drugs that target nicotine receptors can produce analgesia and phosphodiesterase 4 inhibitors are anti-inflammatory but these agents also generate emesis [1;2]. Potentially, a more detailed understanding of the systems of nausea and vomiting could be used to design drugs with therapeutic benefits but with little or no effect on nausea and emesis. This report is a general overview addressing the limitations of current anti-emetics, possible new targets tested in animal models, and how we might uncover better targets. The reader should refer to recent full-length reviews for more detail on these topics [3–6]. Box 2 is a summary of outstanding issues in the area of nausea and emetic control.

Systems Neuroscience of Nausea and Vomiting

Nausea and vomiting can occur separately and nausea is not simply a low level of stimulation to the emetic system that if increased in intensity would result in vomiting. Counter-intuitively, nausea is more difficult to control using pharmacological treatments than emesis. These facts indicate that the neurobiological systems that produce nausea and vomiting are at least partially

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separate. The neural systems responsible for the perception of nausea are largely unknown but likely require activation of the cerebral cortex and other forebrain areas, e.g., the amygdala. Treatment with cisplatin, a chemotherapy agent that produces intense nausea in humans, increases Fos protein expression, a measure of neural activity, in the extended amygdala of the rat brain [7]. It is possible that brainstem circuitry, closely associated with those circuits controlling emesis, provides input to the forebrain to generate nausea. The involvement of the brainstem in the system responsible for nausea seems likely since many prodromal signs of nausea, including cold sweating, salivation, vasoconstriction, vasopressin release, and gastric dysrhythmia, are driven by neural circuits of the brainstem, and these response measures might be useful in determining the effectiveness of pre-clinical targets for control of nausea.

Emesis (the vomiting response) is produced by a central pattern generator (CPG; a collection of nuclei for generating cyclical output) located in the lower brainstem. There are at least four pathways for activation of the CPG for emesis: **1) Vagal**: chemical or mechanical activation of vagal afferent fibers innervating the gastrointestinal tract, e.g., chemotherapy agents trigger release of serotonin from the gut that stimulates the afferent vagus, **2) CPG**: direct chemical action, e.g., apomorphine, on or near the brainstem CPG or closely associated nuclei, such as the area postrema (AP), **3) Vestibular**: activation of the vestibular system by motion, and **4) Forebrain**: stimulation via descending pathways from the forebrain, including the cerebral cortex. This last pathway is the least understood and likely plays an important role in the modulation of emesis by learning, e.g., anticipatory vomiting in cancer chemotherapy. Although the inputs and outputs for emesis are reasonably well described, the CPG, and, more importantly, the final common pathway for the emetic response are not well defined. The nucleus of the solitary tract in the lower brainstem is a potential site for common input into the CPG for emesis because this region receives convergent inputs from the vagus, vestibular system, AP, and cerebral cortex. A better understanding of the emetic neural circuitry should provide a rich source of information to produce more effective anti-emetic drugs.

How effective are current anti-emetic drugs?

Table 1 includes anti-emetic targets with efficacy in humans (boldface type). Most of the information on effectiveness of anti-emetics is derived from research on chemotherapy- and postoperative-induced vomiting. The chemotherapy agent cisplatin is a common test stimulus in these studies since it has a very high emetic potential and produces acute (< 24 h) and delayed (> 24 h) emesis. The acute emetic effect of cisplatin is largely determined by activation of the vagus. Motion-induced nausea and vomiting also provides important information because control of this source of emesis might indicate the location of a target in the central nervous system. A broad spectrum or “universal” target should have efficacy to control emesis from a variety of sources.

None of the targets in Table 1 qualify as universal anti-emetics in humans since each has efficacy for only some sources of emesis. Surprisingly, antagonism of NK1 and 5-HT3 receptors in animal models typically produce a complete or near total block of emesis produced by cisplatin treatment, but these targets are less potent in humans [4]. These differences in target efficacy between human and animal testing might suggest a greater role for other mechanisms in human emetic responses, particularly psychological factors, which are difficult to control in clinical studies. For example, expectations can modulate the responses to chemotherapy. Cancer patients, after receiving several cycles of chemotherapy with less than adequate control of emesis, begin to experience anticipatory nausea and vomiting with subsequent treatments [8]. This source of modulation likely includes forebrain circuitry, such as the cerebral cortex. There are few attempts to study this type of modulation in animal models. Clinically, because of the lack of potency achieved with single agents, many of the drugs for targets in Table 1 are combined to control emesis. For example, in patients receiving highly

emetic chemotherapy agents, such as cisplatin, the standard anti-emetic protocol is a combination of a 5-HT3 receptor antagonist, NK1 receptor antagonist, and corticosteroid [9]; however, even with this cocktail some patients are refractory for control of emesis, and nausea is a persistent problem.

Drugs acting at targets in Table 1 have much less potency to control nausea than emesis. This is clearly observed in the few cases where these agents were explicitly investigated to determine the control of nausea. For example, reports indicate that antagonism of 5-HT3 or NK1 receptors produce less inhibition of nausea than of emesis [e.g., 10;11]. Much of the problem with finding a target for control of nausea is the difficulty in determining an appropriate response measure in an animal model [3] (see below).

Possible targets tested in animal models

Table 1 also lists anti-emetics with efficacy in animal models. These studies were conducted in the ferret, dog, pig, cat, monkey, and the house musk shrew (suncus murinus). It is reasonably true that treatments with anti-emetic benefit in pre-clinical studies will also show effectiveness in humans, however it is difficult to determine the extent of anti-emetic control. A common result is less efficacy for targets in humans compared to testing in other animals, e.g., the stronger potency of 5-HT3 and NK1 receptor targets in animal models versus humans. Each species tends to have a unique emetic profile. Thus, it is important in pre-clinical testing to use several species and ways of inducing emesis to confirm a target. Some of these pre-clinical targets exhibit unacceptable side effects. For example, vanilloid receptor agonists can generate hypothermia [12] and μ-opioid agonists can produce respiratory depression [13].

The most promising targets are those that inhibit emesis from a variety of sources. TRPV1 appears to be in this category but evidence suggests that this target is related to the effects of the NK1 receptor in the emetic system. Treatment of animals with resiniferatoxin, a TRPV1 agonist, depletes substance P in the brainstem and therefore less of this neuropeptide is available for activation of the NK1 receptor [14]. Although it is well known that morphine and its metabolites can produce emesis in humans (a potential source of post-operative vomiting), high levels of morphine and specific opioid receptor agonists are capable of inhibiting emesis in animal models [e.g., 15]. This dual function of opioid action on the emetic system might explain why patients begin to experience nausea and vomiting as pain medication wears off. Studies indicate the involvement of μ or k receptor subtypes in the anti-emetic property of opioids [review 4]. This mechanism might be an inhibitory neural input in the brainstem that sets the tone of the emetic CPG, but its location remains unknown. The 5-HT1A receptor target, with broad-spectrum efficacy, is an encouraging candidate but its site of action in the nervous system and efficacy in humans remain to be addressed.

How to find new targets (and know the mechanism of current ones)

The pre-clinical development of anti-nausea and anti-emetic drugs is largely hampered by the lack of an animal model that closely mimics the human response to emetic and nauseogenic treatments. It is difficult, and perhaps impossible, to assess nausea in animal models but conditioned flavor aversion and prodromal signs might be indicators of this unique psychological state. Importantly, not all species possess the vomiting response; notably rats, mice, guinea pigs, hamsters, and rabbits lack this behavior, but rats, and probably mice, do display pica (e.g., clay ingestion) that is inhibited by anti-emetic drugs [3]. Dogs, cats, ferrets, pigs, monkeys, and house musk shrews are commonly used to test emetic responses but there is no consistent emetic sensitivity profile across these species [3]. For example, both ferrets and the house musk shrew vomit in response to cisplatin, and although apomorphine produces emesis in the ferret, it does not stimulate vomiting in the shrew [16]. Furthermore, in most

studies the potential for an anti-emetic target to act on both acute and delayed responses to a chemotherapy agent has not been investigated.

Despite these concerns, animal models have proven invaluable for developing preclinical leads, especially when several species (and several emetogenic stimuli) were used to confirm a target. Much work has focused on the sensory side of emesis, along with the pharmacology and motor outputs. There is a strong argument for the application of more advanced biological methods, e.g., high throughput data collection and analysis methods (see below), to further define the CPG circuitry of emesis. There are obvious differences in the neuropharmacology of the emetic system among species but it seems reasonable that the architecture of the neuronal wiring should be mostly conserved. If it proves possible to pinpoint the brainstem site that contains neurons receiving convergent input from the sensory systems that produce emesis it might be feasible to create a universal anti-emetic treatment, i.e., a single agent or an appropriate cocktail of medicines. Activity of these integrator neurons might be driven by a variety of neurotransmitters and neuromodulators. It remains an open question as to whether any of the current anti-emetic targets is expressed in these hypothetical nerve cells that form the final common pathway for emesis.

Work on defining the emetic CPG has been largely limited to the use of standard neuroscience approaches: single electrode electrophysiology recordings, functional neuroanatomy using Fos protein (a product of the cFos gene) as a marker of stimulation, and lesions of the emetic circuitry. Traditional electrophysiology using single electrodes cannot provide an adequate picture of the emetic system because recordings are limited to a few neurons in each recording session – the emetic CPG arguable contains many thousands of neurons whose responses produce a large spatial and temporal profile. Fos expression provides only a limited view of this system because Fos is expressed in only a subset of neurons and does not have the temporal resolution to define the patterning of the CPG. Furthermore, traditional electrolytic and chemical lesions of brain areas are difficult to interpret because these ablations tend to be non-specific and overlap adjacent regions of the brainstem, thus affecting other functions.

Several modern methods present the tools to move forward to elucidate the neural systems of nausea and vomiting, potentially forming the basis for better drug design. Large scale gene or protein arrays might assist in providing a list of candidate targets for relevant brain regions involved in the emetic response and correlates of nausea. In addition, electrode arrays and imaging methodologies could enhance the measurement of the emetic CPG, allowing the analysis of the cascade of neural events in the brainstem that generate emesis [e.g., 17]. By extension, relevant areas of the forebrain, arguably involved in nausea (e.g., insular cortex and amygdala), might also be defined using neurophysiological methods. The capability to record the ensemble of neural activity responsible for emesis, and possibly the forebrain systems engaged in nausea, would naturally allow the opportunity to test candidate drugs on these neuronal signatures. Although implementation of these methods will prove challenging, the rewards for finding the keys that control the ‘black boxes’ of nausea and emesis are very substantially, not only in the therapeutic areas of anti-emesis and anti-nausea but also in the application of this knowledge to the development of other categories of drugs that have significant nausea and emetic liabilities.

Box 1. Conditions with significant nausea and vomiting

Drug treatments

e.g., cancer chemotherapy, pain and anesthesia drugs used in surgery

Radio-therapy in cancer treatment

Motion sickness

Pregnancy

Gastrointestinal disease

e.g., gastroesophageal reflux disease, dyspepsia, irritable bowel syndrome, cancer, gastroenteritis

Cyclic vomiting syndrome

Advanced cancer

Migraine

Bulimia

Psychological stress

Box 2. Outstanding Issues

- How can we control nausea?
- What are the neural systems for emesis and nausea and how do they overlap?
- Is it possible to achieve complete control of emesis, in all conditions, with a single drug?
- What are the most appropriate animal species to model human emesis?
- How can we assess the perception, or correlates, of nausea in non-human animals?

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Table 1

Anti-emetic targets

	Target	Effectiveness: Pros	Effectiveness: Cons	Representative drugs[1] and companies with current work[3]	Refs[2]
Receptor Antagonists	D2	**Postoperative**	**Motion Chemotherapy**	Thiethylperazine, Prochlorperazine, Chlorpromazine, Fluphenazine, Cyclizine, Haloperidol, Droperidol, Domperidone, Metoclopramide	[18;19]
	H1	**Motion Postoperative**	**Chemotherapy**	Dramamine, Promethazine, Cinnarizine, Cyclizine, Meclizine	[18–21]
	5-HT3	**Acute Chemotherapy Postoperative**	**Motion (Delayed Chemotherapy)**[4]	Ondansetron, Tropisetron, Dolasetron, Azasetron, Granisetron (**Hoffmann-La Roche**), Palonosetron (**MGI Pharma)**	[18;19;22]
	5-HT4	cisplatin copper sulfate	?	FK1052, GR125487, Zacopride (**Fujisawa Pharmaceutical**)	[23–25]
	M (3/5?)	**Motion Postoperative**	**Chemotherapy**	Promethazine, Dramamine, Scopolamine, Zamifenacin	[18;19]
	NK1	**Delayed Chemotherapy Postoperative**	**Acute Chemotherapy**	Aprepitant (**Merck**), Casopitant (**GlaxoSmithKline**), SCH 619734 (**Schering-Plough**)	[22;26]
Receptor Agonists	NK3	cisplatin	?	SB-222200 (**GlaxoSmithKline**)	[27]
	CB1	**Chemotherapy**	**Postoperative**	Nabilone, Marinol	[19;28]
	GABA (B?)	**Acute Chemotherapy** cyclophosphamide, morphine, nicotine	?	Gabapentin, Baclofen	[4;23;29;30]
	Ghrelin receptor	cisplatin	?	Ghrelin (**GlaxoSmithKline**)	[31]
	5-HT1A	cisplatin, copper sulfate, veratrine, motion, nicotine	?	8-OH-DPAT, Flsinoxan, Buspirone, Gepirone, Ipsaperone	[4;32]
	μ-Opioid	copper sulfate, cisplatin, cyclophosphamide, motion, morphine, apomorphine, nicotine	?	Fentanyl	[4;15]
Other & Unknown	TRPV1	Cisplatin, copper sulfate, motion, Nicotine, Morphine—6-glucuronide	?	Resiniferatoxin, Arvanil	[33;34]
	Anti-inflammatory (?)	**Motion chemotherapy postoperative**	?	Dexamethasone, Methylprednisolone	[4]
	COX-2	cisplatin	?	Indomethacin, Meloxicam	[35]
	5-HT2/ D2/5-HT3 (?)	**Chemotherapy**	?	Olanzapine	[36]
	5-HT3 (?)	cisplatin	?	Ginger derivatives	[37]
	Proton-pump inhibitor	**postoperative**	?	Esomeprazole (**AstraZeneca**)	[38]

Effectiveness: Pro = significant control and Con = little or no control of these sources of emesis. Boldface indicates human testing and regular type indicates animal testing.

D=dopamine, **H**=histamine, **5-HT**=serotonin, **M**=muscarinic, **NK**=neurokinin, **CB**=cannabinoid, **GABA**=gamma-aminobutyric acid, **TRV** = vanilloid receptor; **COX-2** = cyclooxygenase-2; number and letter designations refer to receptor subtype

[1]Many of these drugs have non-specific actions, e.g., metoclopromide targets D2 and 5-HT3 receptors.

[2]Available space limits listing of all references and in most cases a review(s) is cited.

[3]Assessments of current activity (last 5 years) in these target areas are based on public databases (PubMed.gov, ClinicalTrials.gov)

[4]Evidence suggests that palonosetron, a long-acting 5-HT3 receptor antagonist, inhibits delayed emesis in chemotherapy [39]