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Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting

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Abstract

Clinical research shows that postoperative nausea and vomiting (PONV) is caused primarily by the use of inhalational anesthesia and opioid analgesics. PONV is also increased by several risk predictors, including a young age, female sex, lack of smoking, and a history of motion sickness. Genetic studies are beginning to shed light on the variability in patient experiences of PONV by assessing polymorphisms of gene targets known to play roles in emesis (serotonin type 3, 5-HT₃; opioid; muscarinic; and dopamine type 2, D₂, receptors) and the metabolism of antiemetic drugs (e.g., ondansetron). Significant numbers of clinical trials have produced valuable information on pharmacological targets important for controlling PONV (e.g., 5-HT₃ and D₂), leading to the current multi-modal approach to inhibit multiple sites in this complex neural system. Despite these significant advances, there is still a lack of fundamental knowledge of the mechanisms that drive the hindbrain central pattern generator (emesis) and forebrain pathways (nausea) that produce PONV, particularly the responses to inhalational anesthesia. This gap in knowledge has limited the development of novel effective therapies of PONV. The current review presents the state of knowledge on the biological mechanisms responsible for PONV, summarizing both preclinical and clinical evidence. Finally, potential ways to advance the research of PONV and more recent developments on the study of postdischarge nausea and vomiting (PDNV) are discussed.

Keywords

Nausea; Vomiting; Emesis; Anesthesia; Surgery; Opioid

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1. Introduction

From the beginning of the use of general anesthesia in the 1840's it was recognized that nausea and vomiting are common side effects of surgical recovery (Archer and Wells, 1960; McGill, 1873). There are widely varying estimates on the incidence of postoperative nausea and vomiting (PONV), a likely result of the diverse set of patients, surgical procedures, and chemicals used, but it is often reported to be approximately 30% (Franck et al., 2010). The incidence of PONV appears to have remained substantially unchanged since as early as the 1950s (see review, Palazzo and Strunin, 1984). However, it is now recognized that subgroups of patients with known risk factors (e.g., female, history of motion sickness; see Section 3) have an incidence of PONV as high as 80% without prophylaxis (Apfel et al., 1999).

Although PONV rarely leads to serious medical complications in the modern setting, the impact on quality of life and cost of healthcare are not insignificant. Patients report that nausea and vomiting are some of the most distressing symptoms of post-surgery and say they will theoretically pay extra to avoid these outcomes (Gan et al., 2001; Kerger et al., 2007; Wagner et al., 2007). Healthcare and hospital systems are hard pressed to develop efficient models of patient care and failure to control PONV can lead to substantial additional costs by increasing the time to discharge from the postanesthesia care unit (PACU, Habib et al., 2006). Most of the current pharmaceutical targets for the control of PONV (e.g., serotonin type 3, 5-HT₃, receptor) have been known for decades and marginal improvements in therapies focused on these approaches (e.g., a different route of administration) can sometimes lead to only marginal improvements but with a substantial increase in financial cost. Moreover, owing the paucity of well designed trials it is not clear whether PONV is efficiently controlled using the common multi-modal approaches (polypharmacy) with the potential for drug-drug interactions (Greenblatt, 1993).

The current paper focuses on reviewing the biology of PONV and discussing recent data and directions. The reader is referred to some of the large systematic reviews that are available for further details about the clinical effectiveness of particular drug regimes (Carlisle and Stevenson, 2006; Fero et al., 2011). Here we will instead present areas of substantial agreement and focus our discussion on topics where there is little biological knowledge. We also point out potential new research directions.

2. Stimuli

2.1. Clinical evidence for the role of volatile anesthetics and opioids

Before arriving for surgery, patients can have a predisposition for PONV, including female sex, history of motion sickness or PONV, non-smoker status, and younger age. These patient specific modulating variables will be discussed in Section 3 (see below). Based on clinical studies, the primary causes of PONV after surgery are the use of inhalational anesthesia (Apfel et al., 2012a; Apfel et al., 2002; Hofer et al., 2003; Moore et al., 2008; Raeder et al., 1997; Vari et al., 2010) and opioid analgesics (Apfel et al., 2012a; Binning et al., 2011). Figure 1 illustrates the potential stimuli that contribute to PONV and postdischarge nausea and vomiting (PDNV).

Inhalational anesthetic agents (e.g., sevoflurane, isoflurane) appear to have equal potency to produce PONV, and a longer duration of exposure to these agents is associated with more PONV (Apfel et al., 2002). These anesthetics increase PONV during the first 2 h after surgery in the PACU (Apfel et al., 2002). There is also an impact of nitrous oxide usage to increase PONV (Fernandez-Guisasola et al., 2010; Leslie et al., 2008). When intravenous propofol is used to replace inhalational anesthesia there is much less PONV during the first

hours in the PACU (Raftery and Sherry, 1992). Evidence suggests that propofol might also have antiemetic properties (Song et al., 1998). Although replacement of inhalational agents with intravenous propofol can reduce PONV (e.g., Raftery and Sherry, 1992), inhalational anesthesia continues to be used because it is easier to administer compared to intravenous treatments.

Opioids are commonly used in the perioperative period to control pain and thus contribute to balanced anaesthesia. Opioids, including morphine and fentanyl, are well known to induce nausea and vomiting as an independent stimulus (Apfel et al., 2012a). Intraoperative use of opioids does not appear to be a consistent stimulus for PONV (Apfel et al., 2012a). However, opioid usage for analgesia does contribute to PONV during the later period of time in the PACU and also postdischarge (Apfel et al., 2002; Apfel et al., 2012b).

2.2. Surgical trauma and inflammation

Surgical operations can produce tissue trauma and inflammation. Increasing the duration of surgery appears to be the one consistent independent risk factor for PONV (Koivuranta et al., 1997; Sinclair et al., 1999). Several types of surgeries have been shown to put patients at higher risk for PONV. Some potentially PONV-inducing types of surgery include cholecystectomy, laparoscopic, gynecological, and ear-nose-throat (ENT) surgery (Apfel et al., 2012a). Although not directly addressed by current research, antiemetics could suppress PONV by inhibiting inflammation and not by direct actions on the neural system for nausea and vomiting (see below). Potentially this relationship might occur in the setting of abdominal surgery with a GI inflammatory response to bowel manipulation or surgical trauma, leading to local release of substance P, 5-HT, or other mediators (De Winter et al., 2012; Spiller, 2008) that could affect signaling of extrinsic afferent fibers. Notably there appears to be a relationship between postoperative ileus and intestinal inflammation (Rychter and Clave, 2013), and these conditions could be closely related with regards to a potential impact to potentiate PONV or PDNV. Antiemetics used to control PONV are also anti-inflammatory, for example, dexamethasone and 5-HT₃ and NK₁ receptor antagonists (Duffy, 2004; Faerber et al., 2007; Takao et al., 1995).

2.3. Neural systems for emetic action

Although much research has focused on defining the emetic action of opioids (e.g., Horn et al., 2012; Simoneau et al., 2001; Thompson et al., 1992; Wynn et al., 1993; Yoshikawa and Yoshida, 2002), there is significantly less insight into the effects of volatile anesthetics in this respect. First we will consider a general understanding of the neural systems for nausea and vomiting and then present evidence for the action of opioids and volatile anesthetics on specific neural sites and emetic mechanisms.

It is common to find references to the “vomiting center”; however, this label obscures the fact that the locus of the neurons that integrate sensory stimuli and produce the signals that drive emesis (and nausea) are not known. On a general level, the caudal hindbrain is undoubtedly the location of the emetic neural circuitry since the isolated hindbrain is sufficient to produce a fictive emetic episode (a pattern of neural and muscle responses consistent with emesis) (Horn et al., 2013; Miller et al., 1994; Smith et al., 2002). Rodents, including laboratory rats and mice, are of little use in studying this system because they lack an emetic reflex and therefore shrews, ferrets, dogs, and cats are the most common preclinical models (Horn et al., 2013). The neural circuitry that generates the emetic episode can be conceptualized as a central pattern generator (CPG) – a network of neural connections that produces rhythmic motor patterns. Although the command neurons (Kupfermann and Weiss, 1978) that drive the CPG for emesis are not well defined, many investigators cite the nucleus of the solitary tract (NTS) and specific nuclei in area of the

reticular formation, including the respiratory nuclear groups, as important sites for generating emesis (Fukuda et al., 2003; Horn, 2008; Hornby, 2001; Rice et al., 2010; Shintani et al., 2003). Figure 1 shows the neural pathways potentially responsible for triggering vomiting. Four pathways activate vomiting by direct projections to the NTS in the hindbrain: 1) gut vagal afferent fibers, 2) vestibular input, 3) area postrema (AP), and 4) forebrain. Vagal afferent fibers innervate the stomach and intestine and are stimulated by paracrine factors (e.g., serotonin) that are released from enteroendocrine cells that detect circulating drugs or local toxins in the lumen of the GI tract (Hu et al., 2007; Minami et al., 2003). Vestibular nuclei receive motion-related sensory input from the vestibule in the inner ear (Yates et al., 1994; Yates et al., 1998). The AP, directly adjacent to the NTS, is a circumventricular organ with a reduced blood-brain barrier that potentially detects circulating toxins (Jovanovic-Micic et al., 1989). Vomiting can also be produced by activation of one or more descending pathways from the forebrain (Beleslin et al., 1987; Robinson and Mishkin, 1968). For example, activation of the temporal lobe (which contains the amygdala) and the insular cortex by epileptic seizures can sometimes produce ictal vomiting (Catenox et al., 2008). These forebrain areas likely participate in psychogenic-related vomiting and conditioned sickness responses (Scalera, 2002).

One major roadblock to our understanding of the neurobiology of nausea is that it cannot be directly measured in non-human animals. Recently, Napadow and colleagues used fMRI to image neural responses in humans during nausea produced by visual stimulation (Napadow et al., 2012). This approach permitted the careful monitoring and control of nausea stimulation before the onset of vomiting. In their study, the dorsal pons (potentially the parabrachial nucleus; PB), amygdala, and putamen were activated prior to self-reported motion sickness (Fig. 2). The activation of the PB might be particularly important as a relay between the emetic circuitry and forebrain areas since this region receives sensory input from the NTS (Fig. 2) and demonstrates neural activity in animal models treated with emetic stimuli (De Jonghe and Horn, 2009; Horn, 2009; Horn et al., 2007; Horn et al., 2009; Suzuki et al., 2012). Furthermore, during sustained nausea the insular, cingulate, orbitofrontal, and prefrontal cortices were also recruited (Napadow et al., 2012). An earlier human study using magnetic source imaging (MSI) also showed activation of the prefrontal cortex induced by motion sickness and ingestion of ipecac, a chemical derived from a highly toxic plant (Miller et al., 1996). There are also extensively documented prodromal signs of nausea (and impending emesis) produced by activation of the autonomic nervous system. These include salivation, cold sweating, gastric dysrhythmia, and vasopressin release (see review, Stern et al., 2011). Gastric dysrhythmia and systemic vasopressin release have been used as markers of nausea in human studies (Kim et al., 1997; Koch, 1997; Stern et al., 2011). Vasopressin serves to assist in fluid homeostasis after the fluid loss from vomiting. The normal electrical response of the stomach (recorded using electrodes placed on the abdomen) progresses to dysrhythmia, bradycardia, and/or tachycardia during reports of nausea (Jednak et al., 1999; Kim et al., 1997; Lien et al., 2003). There appear to be no reports to assess the electrogastrogram and blood levels of vasopressin in relation to PONV.

Lesion methods have been applied to understanding the mechanism of opioid-induced emesis, including ablation of the vagus and AP. Caution should be used in interpreting lesion effects because: 1) vagotomy and area postrema ablations can result in neuronal plasticity, and 2) anatomical verifications of these lesions are rarely reported and it is difficult to determine the extent of these ablations, e.g., to what degree is the adjacent NTS affected by AP ablation (see discussion in Andrews et al., 1990). However, reports show that AP ablation blocks morphine-induced emesis in dogs (Bhargava et al., 1981; Gupta et al., 1989). A related investigation, demonstrated that 6-hydroxy-dopamine (a dopaminergic neurotoxin), when injected into the AP of ferrets, reduced morphine-induced emesis (Yoshikawa and Yoshida, 2002). Loperamide, a μ -opioid agonist that does not cross the

blood-brain barrier, induced emesis in ferrets that was blocked by AP ablation but not affected by vagotomy (Bhandari et al., 1992). Morphine is also more effective in producing emesis when administered by injection into the fourth ventricle versus the lateral ventricle in dogs (Bhargava et al., 1981). There appear to be no reports of splanchnic nerve sectioning to assess the role of abdominal spinal afferent fibers in opioid-induced emesis. In summary, the available evidence indicates that opioids produce emesis by action on the AP.

How does inhalational anesthesia produce emesis? Studies in cell based assays indicate that isoflurane and halothane can enhance 5-HT₃ receptor function (Machu and Harris, 1994) (Parker et al., 1996). Work on anesthesia-induced emesis in animal models is limited and, as far as we know, several critical experiments to determine required pathways have not been conducted (e.g., vagotomy, AP, and splanchnic nerve ablation). An additional problem is that not all of the standard preclinical models show inhalational anesthesia-induced emesis. Recent research indicates that ferrets do not vomit to isoflurane exposure using 2 to 4% inhaled concentrations and 10 min to 6 h of exposure (Horn et al., 2011). Dogs are reported to regurgitate after exposure to halothane, isoflurane, or sevoflurane (Wilson et al., 2006). Musk shrews vomit after exposure to halothane (inhibited by NK₁ and 5-HT₃ receptor antagonists) and isoflurane (Gardner and Perren, 1998; Horn et al., 2011). Results suggest that inhalational anesthetic agents (halothane, isoflurane, and sevoflurane) stimulate vagal afferent fibers in dogs (Mutoh et al., 1998). Patients are reported to show more dizziness after sevoflurane compared to propofol, which suggests that inhalational anesthesia could affect the vestibular system (Raeder et al., 1997).

Additional insight into the molecular sites of inhaled anesthetic-induced emesis may be gleaned from a molecular understanding of the pharmacology of inhaled anesthetic action. The remarkable correlation between anesthetic potency and lipid solubility (i.e., the Meyer-Overton Rule) led to the unitary theory of narcosis that dominated the field for nearly a century (Koblin, 2005). This theory proposed that the widely diverse array of chemical compounds that are capable of inducing anesthesia all do so by nonspecific actions at the same molecular site, most plausibly the hydrophobic lipids of neuronal membranes. This theory fell out of favor in the late 20th century with the identification of chemicals that do not obey the Meyer-Overton Rule and with pioneering research supporting specific, direct actions of anesthetics on proteins (Curry et al., 1990; Dickinson et al., 2000; Mihic et al., 1997). The most direct evidence to date that inhaled anesthetics interact directly with neuronal proteins comes from X-ray crystallographic structural studies demonstrating anesthetics bound in pockets located within and between subunits of multimeric ion channel proteins (Nury et al., 2011).

Despite convincing evidence that anesthetics can directly bind to protein targets, it is currently unclear exactly which protein targets mediate the clinically desirable effects of these drugs such as immobility and amnesia (Sonner et al., 2003), let alone side effects such as emesis. Numerous neuronal proteins have emerged as potential targets of inhaled anesthetics including a wide variety of ligand-gated ion channels (e.g., receptors for GABA, glycine, NMDA, AMPA, kainite, acetylcholine, and serotonin), voltage-gated ion channels (e.g., sodium and potassium channels), metabotropic receptors (e.g., muscarinic acetylcholine, opioid, 5-HT₂, GABA_B, and α_2 adrenoreceptors), gap junctions, and others (For reviews, see: Campagna et al., 2003; Sonner et al., 2003). Despite abundant evidence that most of these plausible targets are sensitive to clinically relevant concentrations of inhaled anesthetics, definitive demonstration that any of these targets are the primary mediators of clinically important anesthetic endpoints is lacking (see Eger et al., 2008).

Even if the molecular sites of inhaled anesthetic action are conclusively established, one must be cautious. Just because antiemetic drugs counteract the adverse effects of inhaled

anesthetics, this does not necessarily mean that the molecular target of the antiemetic drugs is the same as the anesthetics.

Both opioids and inhalational anesthesia disrupt gastrointestinal function. Gastric dysrhythmias are an established biomarker for nausea and vomiting in both human and animal studies (Kim et al., 1997; Percie du Sert et al., 2010a). It is unknown whether gastric dysrhythmias precede nausea and vomiting or are the product of nausea and vomiting. A common side effect of surgery is postoperative ileus (Viscusi et al., 2009) and this action and disruptions of gastrointestinal motor rhythms could be related to the etiology of PONV.

2.4. An antiemetic role for opioids

It is often not recognized that opioid analgesics have opposing dose dependent effects on nausea and vomiting. This is most clearly evident in animal experiments where opioid dosage can be carefully controlled. For example, at low doses morphine and other opioid receptor agonists produce emesis but at higher doses emesis is inhibited – a bell-shaped dose response curve (Barnes et al., 1991; Bhandari et al., 1992; Thompson et al., 1992). Based on receptor affinity, morphine and fentanyl are likely to exert their emetic effects via μ opioid receptors but actions at kappa and delta receptor subtypes cannot be ruled out (Rudd and Naylor, 1995).

Current theory predicts that the dual effects of opioids on emesis are the result of separately located μ receptors within the AP and those inside the blood brain barrier, potentially the NTS (see Fig. 2B) (Barnes et al., 1991). Notably methylnaltrexone, quaternary naloxone derivative, that antagonizes peripheral μ receptors (outside the blood brain barrier) blocks morphine-induced emesis in dogs without affecting its analgesic effects (Foss et al., 1993). Whereas μ opioid receptors in the AP are involved in the activation of emesis, those in the NTS provide inhibitory effects on emesis. Fentanyl, a more lipophilic opioid agonist than morphine, demonstrates antiemetic properties potentially because it quickly penetrates to μ opioid receptors within the hindbrain (e.g., NTS) (Barnes et al., 1991). There is some suggestion that sub-types of μ receptors ($\mu 1$ and $\mu 2$) mediate the emetic and anti-emetic effects although whether the findings from animal studies translate directly to humans remains to be established (see review Johnston, 2010). Furthermore, clinical studies suggest that different genetic variants in the μ opioid gene (OPRM1) and catechol-O-methyltransferase (COMT) genes produce distinct effects on the nauseogenic and analgesic potencies of opioids (Chou et al., 2006; Kolesnikov et al., 2011). It still remains possible that more targeted opioid analgesics might be engineered to retain analgesic potency but lack (or have reduced) action on nausea.

3. Patient-related risk factors

3.1. Current risk predictors

Patient-based risk predictors are the most-studied set of risk factors for PONV and are often used in clinical decisions (Apfel et al., 1999; Pierre et al., 2002). A core group of risk factors have proved reliable across multiple large groups of patients. The strongest risk factor is associated with the patients being post-pubertal females (Apfel et al., 2012a; Koivuranta et al., 1997; Pierre et al., 2002; Sinclair et al., 1999; Stadler et al., 2003; Toner et al., 1996). Non-smoking status is another independent predictor identified through regression analyses (Apfel et al., 2012a; Apfel et al., 1999; Koivuranta et al., 1997; Sinclair et al., 1999; Stadler et al., 2003). Additionally, a history of PONV and/or motion sickness is also an independent factor for increased PONV (Apfel et al., 2012a; Apfel et al., 2002; Apfel et al., 1999; Koivuranta et al., 1997; Palazzo and Evans, 1993; Pierre et al., 2002; Sinclair et al., 1999; Toner et al., 1996). Patient factors such as body mass index, physical status classification,

history of migraine, and stage of menstrual cycle are not reported to have reliable associations with increased risk for PONV (Apfel et al., 2012a).

An effort was made by Eberhart et al. to better identify risk factors for PONV in children, as many of the adult risk factors would not apply (post-pubertal female, smoking status) (Eberhart et al., 2004). Studies of pediatric risk predictors show that childhood after infancy and younger adulthood is associated with increasing risk for PONV (Bassanezi et al., 2013; Eberhart et al., 2004; Kranke et al., 2007; Sinclair et al., 1999). Additionally, a personal history of motion sickness, or even a family history of PONV or motion sickness, was an independent risk factor for pediatric PONV (Eberhart et al., 2004; Kranke et al., 2007). Bassanezi et al. used a fuzzy logic model to predict postoperative vomiting in pediatric patients undergoing oncologic surgery, which may prove to be a reliable method for PONV prediction (Bassanezi et al., 2013).

3.2. Genetics

There has been expanding interest into the role of genetics in the likelihood to develop PONV. These studies are not always easy to interpret because patients often receive antiemetic drugs and the genetic variants reported might indicate patient differences in antiemetic drug binding or metabolism. Not all of the studies are postoperative but those focusing on only opioid-induced nausea and vomiting (OINV) are also instructive because of the established role of opioids in PONV (Roberts et al., 2005). As expected, there are consistent associations with SNPs (single nucleotide polymorphisms) occurring in genes involving neural signaling and transmitter receptors in the nausea and vomiting system (Table 1). SNPs for 5-HT₃ (subunits A and B), muscarinic type 3, and μ opioid receptors are associated with PONV and OINV (Chou et al., 2006; Janicki et al., 2011; Kolesnikov et al., 2011; Laugsand et al., 2011; Pang et al., 2012; Rueffert et al., 2009; Sia et al., 2008; Zhang et al., 2011). SNPs for dopamine type 2 receptors are also related to PONV (Nakagawa et al., 2008). An association between a SNP for catechol-o-methyl-transferase and PONV (Kolesnikov et al., 2011) or OINV (Laugsand et al., 2011) could be related to the role of this enzyme in the degradation of catecholamines and potentially a change in the neuronal signaling. Alpha 2 adrenoceptors are believed to play a central role in the emetic circuitry (Beleslin and Strbac, 1987; Hikasa et al., 1992a; Hikasa et al., 1992b). Other SNPs associated with PONV and OINV, such as ABCB1 and CYP2D6 (Table 1), are more relevant to how well antiemetics, such as ondansetron (a 5-HT₃ receptor antagonist), are transported into the CNS and how quickly they are metabolized (Candiotti et al., 2005; Choi et al., 2010; Coulbault et al., 2006; Fujita et al., 2010; Wesmiller et al., 2012). Polymorphism of the gene for UDP-glucuronosyl-transferase (UGT2B7) is associated with OINV (Fujita et al., 2010). UGT2B7 plays a role in the metabolism of morphine to its main metabolites, morphine-3-glucuronide and morphine-6-glucuronide (Coffman et al., 1997).

4. Pharmacological therapies

The enormity of the PONV/PDNI problem has led to a large body of research focusing on the efficacy of individual drugs and drug combinations. The antiemetic drugs appear to be similar in efficacy when used as single agents, and differ mainly in their cost, convenience, and potential side effects. When combined, the drugs have an additive effect on the control of PONV. For example, when ondansetron and dexamethasone are administered to a patient group expected to have an 80% rate of PONV without intervention they produce a 45% rate of PONV (i.e., each agent is expected to lower the risk in this patient group by 25%). This principal appears to hold true throughout a variety of medication combinations (Apfel et al., 2004). The process by which these reducing numbers are derived is important. Antiemetic drugs are additive but it is the relative risk which decreases on the order of approximately 25% each time. Hence the absolute PONV risk will reduce by smaller and smaller amounts

with each additional drug and hence will also never be zero. This is an important concept because it underpins the current failure to eliminate PONV.

4.1. Histamine receptor antagonists

Several histamine type 1 (H_1) receptor antagonists inhibit PONV (Habib and Gan, 2005; Johns et al., 2006; Kranke et al., 2002; Lin et al., 2005). This class of agents is relatively non-specific and tends to have anticholinergic properties (Peroutka and Snyder, 1982). Commonly used agents in this class include first generation antihistaminergics, dimenhydrinate, cyclizine, and promethazine (Table 2). Drowsiness, urinary retention, dry mouth, and blurred vision are side effects of these drugs (Carlisle and Stevenson, 2006; Kranke et al., 2002) (Table 2). Compared to other antiemetics used to treat PONV, H_1 receptor antagonists are not well studied. In general, this class of agents (Table 2) is less effective than 5-HT₃ receptor antagonists (Carlisle and Stevenson, 2008).

4.2. Muscarinic receptor antagonists

Scopolamine (i.e., hyoscine) is a competitive inhibitor at postganglionic muscarinic receptors in the parasympathetic nervous system and acts directly on the central nervous system by antagonizing cholinergic transmission in the vestibular nuclei (Yates et al., 1998) (Fig. 2). Although scopolamine is a non-selective muscarinic receptor antagonist, more selective antagonism of M_3 and M_5 receptors using zamifenicin was shown to reduce motion sickness (Golding and Stott, 1997); and, therefore, these receptor subtypes might underlie the actions of scopolamine on nausea and vomiting. Due to its short half-life, it is almost exclusively administered as a transdermal patch applied prior to surgery, which delivers 1.5 mg over the course of up to 72 hours (Pergolizzi et al., 2012). This allows plasma levels to remain relatively constant for up to 72 hours after placement of the patch.

Large meta-analyses have shown that prophylactic transdermal scopolamine significantly decreases the risk of PONV (Apfel et al., 2010; Pergolizzi et al., 2012). Side effects of transdermal scopolamine can include visual disturbances, dry mouth, and occasionally sedation (Apfel et al., 2010; Pergolizzi et al., 2012) (Table 2). Patients are often cautioned to avoid touching their eyes after handling the patch, as this can cause mydriasis which may be mistaken for an acute neurologic event.

4.3. Dopamine receptor antagonists

Dopamine receptors, specifically D_2 and D_3 , are known to play a role in nausea and emesis, most likely through inhibition of adenylate cyclase (Sanger and Andrews, 2006), which alters the amount of cAMP within neurons located in the NTS and AP (Hyde et al., 1996). It is the competitive antagonism of these D_2 , and possibly D_3 , receptors that leads to the antiemetic effects of drugs such as droperidol and metoclopramide (Sanger and Andrews, 2006).

Droperidol—Droperidol is a relatively selective dopamine D_2 receptor antagonist that potently binds the D_2 receptors located in the AP (Fig. 2) (Sanger and Andrews, 2006). Droperidol has been shown to be as effective as ondansetron or dexamethasone for the prevention of PONV (Apfel et al., 2004; Carlisle and Stevenson, 2006). A recent meta-analysis showed that low-dose droperidol (1 mg or 0.15 $\mu\text{g}/\text{kg}^{-1}$) to be an effective preventative measure against PONV, with no difference in response between 0.25 mg, 0.625 mg, 1 mg, and 1.25 mg doses (Schaub et al., 2012).

With regards to side effects, low-dose droperidol increased restlessness in the PACU, but did not increase sedation (Schaub et al., 2012). Droperidol's most well-known side effect, however, is its tendency to cause QT prolongation (Lischke et al., 1994) and malignant

ventricular arrhythmias (Glassman and Bigger, 2001; Michalets et al., 1998), which led to an FDA “black-box warning” for all doses of droperidol (FDA, 2001) (Table 2). Its ability to prolong the QT interval has been attributed to its action to block the rapid component of the delayed rectifier potassium current within myocytes (Drolet et al., 1999). However, recent studies have shown that the low doses of droperidol used for PONV prophylaxis do not increase the risk for arrhythmia formation or cardiac death (Nuttall et al., 2007; Nuttall et al., 2013). This recent data suggests that the low doses used to potentially prevent PONV are likely safe.

Metoclopramide—Metoclopramide is a potent D₂ receptor antagonist and binds to D₂ receptors in the AP, as well as H₁ and 5-HT₃ receptors (Sanger and Andrews, 2006). It may also exert an antiemetic effect through its prokinetic properties within the GI tract itself, potentially mediated through antagonism of D₂ receptors and agonism of 5-HT₄ receptors (Sanger et al., 2013; Tonini et al., 1995). Metoclopramide, given in doses of 10 mg, has been shown to be an effective prophylaxis against PONV (Carlisle and Stevenson, 2006; De Oliveira et al., 2012). A recent meta-analysis showed no statistically significant amount of extrapyramidal symptoms, dizziness, headache, or sedation with this dose of metoclopramide (De Oliveira et al., 2012). In the Cochrane systematic review, droperidol was found to be superior to metoclopramide [RR=0.83 (0.71–0.97)] (Carlisle and Stevenson, 2006).

4.4. Corticosteroids

Different corticosteroids have been studied with regards to their effects on nausea and vomiting, but the most widely-studied and used corticosteroid for PONV is dexamethasone. Dexamethasone was first suggested to prevent against PONV in the early 1990's (Baxendale et al., 1993; Mataruski et al., 1990). Over the last two decades, dexamethasone was shown to decrease the incidence of PONV by approximately 25% as a single agent (Apfel et al., 2004; Carlisle and Stevenson, 2006; De Oliveira et al., 2013). Additionally, dexamethasone has been demonstrated to have an additive effect when combined with other antiemetics to prevent PONV (Apfel et al., 2004; Ormel et al., 2011).

Despite its well-established efficacy, little light has been shed on the mechanism by which corticosteroids decrease PONV. Current theories focus on the anti-inflammatory properties of dexamethasone, specifically with regards to decreased inflammation and edema (Sanger and Andrews, 2006). A well known action of dexamethasone is the prevention arachidonic acid release and then the synthesis of a host of different inflammatory mediators (Hong and Levine, 1976); some of which sensitize nerves to other commonly involved transmitters in emesis control (Grundy, 2004). Studies also suggest that glucocorticoids may have a central effect on corticosteroid receptors in the NTS (Ho et al., 2004), and may actually have a direct inhibitory effect on 5-HT₃ receptors (Suzuki et al., 2004), which may help to explain their additive effect when combined with use of 5-HT₃ receptor antagonists. Further research is needed to better elucidate corticosteroid mechanisms of action with regards to prevention of PONV.

The typical dosing of dexamethasone for PONV prevention has classically been 4 or 10 mg. Society for Ambulatory Anesthesia (SAMBA) guidelines recommends 4 mg (Gan et al., 2007b) over 10 mg, given similar efficacy and theoretically decreased incidence of side effects (see below). These recommendations are supported by a recent meta-analysis finding no differences in the range of 4 to 10 mg dosing (De Oliveira et al., 2013).

With respect to potential side effects, including postoperative hyperglycemia and wound infections, there is mixed evidence to support these concerns. First, regarding postoperative hyperglycemia, there have been multiple studies that documented postoperative

hyperglycemia in obese patients with impaired glucose tolerance (Nazar et al., 2009) or poorly-controlled diabetes (Hans et al., 2006). However, these studies used doses higher than the 4 mg recommended by SAMBA, and the clinical significance of this hyperglycemia is questionable. Further studies should be done to focus on hyperglycemia and its possible clinically-relevant side effects (metabolic disturbances, wound infection) following the SAMBA-recommended 4mg dosing. Multiple recent studies have not demonstrated an increased incidence of surgical site infections when dexamethasone is used prophylactically for PONV prevention (Bolac et al., 2013; Eberhart et al., 2011; Gali et al., 2012).

4.5. Serotonin type 3 (5-HT₃) receptor antagonists

5-HT₃ receptor antagonists are probably the most commonly used antiemetic in the perioperative setting, both for prevention of PONV and for treatment for a patient who has developed PONV in the PACU. Their mechanism of action probably involves antagonism of the 5-HT₃ receptor both peripherally in gut vagal afferents and centrally in the AP (Butler et al., 1988; Higgins et al., 1989, Fig. 2). The most commonly used 5-HT₃ receptor antagonist is ondansetron (Zofran). Typical dosing of ondansetron is 4 mg, but a meta-analysis found no difference in efficacy between 1 mg, 4 mg, and 8 mg for postoperative therapy for PONV (Tramer et al., 1997). A meta-analysis determined an approximate 25% decrease in PONV when ondansetron is given prophylactically, which agrees with multiple large studies and a Cochrane systematic review (Apfel et al., 2004; Carlisle and Stevenson, 2006). In the Cochrane review, the most common side effect of ondansetron was headache, with a relative risk (RR) of 1.16 (Carlisle and Stevenson, 2006). Other 5-HT₃ receptor antagonists include granisetron, tropisetron, and ramosetron. In comparing efficacy, tropisetron, ramosetron, and ondansetron were found to be equally effective, while granisetron was inferior to ramosetron for the control of PONV (Tramer et al., 1997). A recent investigation into ondansetron has led to new FDA warnings regarding ondansetron use in patients with prolonged Q-T intervals (FDA, 2011).

An exciting development in the 5-HT₃ receptor antagonist group is palonosetron (Aloxi); a longer-acting agent with a plasma half-life of approximately 40 h (Stoltz et al., 2004) and a much higher binding affinity for the 5-HT₃ receptor compared to other “setrons” (Rojas et al., 2008). Palonosetron may be more effective than ondansetron in high-risk patients receiving a fentanyl-based patient controlled analgesia (PCA) after surgery (Moon et al., 2012). Further studies comparing palonosetron to ondansetron (Kim et al., 2013) or ramosetron (Park et al., 2013) failed to show significant differences between the treatment regimens at longer time intervals (up to 48 or 72 h), but palonosetron did result in a lower incidence of vomiting during the 6 h after surgery compared to ramosetron (Park et al., 2013). Further research is needed to evaluate the comparative efficacy of palonosetron versus other antiemetics. Recent work suggests that palonosetron has a unique action to promote the long-term internalization of 5-HT₃ receptors in neurons (Rojas et al., 2010b) and to reduce the actions of substance P on NK₁ receptors (Rojas et al., 2010a), likely by indirect mechanisms.

4.6. Tachykinin 1 (NK₁) receptor antagonists

NK₁ receptor antagonists are a relatively new class of compounds that have been a part of treatment regimens to prevent chemotherapy-induced nausea and vomiting (CINV) since the early 2000's (Chawla et al., 2003; Warr et al., 2005). Their activity appears to occur mainly in the NTS (Tattersall et al., 2000) and possibly areas of the reticular formation (Fukuda et al., 2003), where they potently bind NK₁ receptors implicated in the emetic reflex. It is suggested that NK₁ antagonists might be more effective for inhibiting emesis than nausea (Andrews and Rudd, 2004) and this is documented in studies of CINV (Albany et al., 2012).

Aprepitant—Aprepitant is the most widely-used oral NK₁ receptor antagonist antiemetic agent. It is typically administered as a single oral dose 1–2 hours prior to induction of anesthesia. One study comparing aprepitant at 80 mg PO to no treatment found significantly decreased PONV in the treatment group (Jung et al., 2012). Another report comparing aprepitant to intravenous ondansetron found significantly lower postoperative vomiting in the aprepitant group, but no difference in nausea or use of rescue antiemetics (Gan et al., 2007a). Aprepitant was also shown to be non-inferior to ondansetron for the first 24 h after surgery, and significantly more effective than ondansetron for preventing vomiting at 24 and 48 h after surgery (Diemunsch et al., 2007). Aprepitant has also been found to be effective when used in a multimodal approach to PONV prophylaxis, particularly with respect to prevention of vomiting (Habib et al., 2011; Lee et al., 2012; Vallejo et al., 2012).

5. Future directions

5.1. Preclinical

Preclinical research should address the neural mechanisms that underlie the stimulation of nausea and vomiting by inhalational anesthesia but few studies have investigated this problem. As far as we know, only musk shrews and ferrets have been formally tested for inhalational anesthesia-induced emesis. Remarkably, the ferret, a standard model for the investigation of antiemetic drugs (particularly in the context of chemotherapy-induced emesis, Percie du Sert et al., 2010b), is insensitive to isoflurane-induced vomiting (Horn et al., 2012) and would not be a good model of the human response (Apfel et al., 2002). Indeed halothane appears to be antiemetic in ferrets (Zunini et al., 1990). However, musk shrews are emetically sensitive to isoflurane (Horn et al., 2012) and a mixture of halothane and nitrous oxide (Gardner and Perren, 1998). Halothane plus nitrous oxide-induced emesis in musk shrews is inhibited by ondansetron or the NK₁ receptor antagonist GR205171 (Gardner and Perren, 1998). Although there is a potential link between enhanced 5-HT₃ signaling and exposure to inhalational anesthetic agents (Machu and Harris, 1994; Parker et al., 1996), this has not been further explored in the context of emetic testing. Finally, dogs have been reported to regurgitate after exposure to halothane, isoflurane, or sevoflurane (Wilson et al., 2006) but were not specifically tested for emetic responses.

Although ferrets are unresponsive to isoflurane, they have well documented emetic responses to opioids, specifically morphine and its metabolites (Horn et al., 2012; Rudd et al., 1996; Sharkey et al., 2007; Simoneau et al., 2001; Thompson et al., 1992; Wynn et al., 1993). Musk shrews display a more complicated behavioral pharmacology to morphine. Although morphine alone does not to produce emesis in musk shrews (Selve et al., 1994), naloxone pre-treatment can reveal morphine-induced emesis (Javid and Naylor, 2001). Opioid receptor agonists are also well known to suppress emesis (Sanger and Andrews, 2006), usually at higher doses, and this inhibitory system is apparent in musk shrews (Javid and Naylor, 2001; Kakimoto et al., 1997; Selve et al., 1994). It is unclear whether a single animal model can be used to conduct mechanistic studies on the various aspects (i.e., summation or synergistic effects) of PONV that involve inhalational anesthesia and opioid components (Fig. 2). In this regard, it is important to realize that animal models rarely provide a model of an entire disease and that preclinical approaches are most useful when used to assess particular aspects of a neurobiological disease (see current report from the Institute of Medicine of the National Academies, Pankevich et al., 2013). Future experiments should explore the potential for inhalational anesthetic agents and opioids to affect newly defined emetic mechanisms such voltage-gated ion channels in the AP (Shinpo et al., 2012).

5.2. Clinical

Despite the fact that PONV has been extensively researched, particularly over the last two decades, it remains a very common cause of postoperative dissatisfaction among patients. Further research may be needed to elucidate why, despite our best efforts and the use of multimodal antiemetic medications, patients continue to experience PONV and PDNV.

As more and more surgeries continue to be performed on an outpatient basis in ambulatory surgery centers, more efforts may be required to differentiate between PONV and PDNV. There would be tremendous value in the development of a long-acting antiemetic regimen that would provide not only immediate benefits but also in the days after surgery, when patients have been discharged and no longer have access to potent intravenous antiemetics and fluids. The most recent development in PONV pharmacology is aprepitant, a potent NK₁ antagonist that appears to work additively with other classes of antiemetics. There have been multiple studies demonstrating its efficacy in various patient populations (Diemunsch et al., 2007; Gan et al., 2007a; Habib et al., 2011; Lee et al., 2012; Vallejo et al., 2012), but further studies are required in order to potentially contribute to updating the guidelines for controlling PONV.

Future pharmacologic treatment for PONV will undoubtedly be driven by ongoing basic science research, which is elucidating the underlying mechanisms of nausea and vomiting. Understanding the link between motion sickness and PONV, for example, may lead to novel targeted therapies that approach treatment from a different direction (modality). The same could be said for inhalational anesthetics and their tendency to increase PONV. If we are able to gain a clearer understanding of how inhalational anesthetics lead to an increased risk of PONV, we could develop strategies to treat this phenomenon. It could also prove beneficial to combine opioid antagonists with less penetration through the blood-brain barrier with morphine or fentanyl to produce analgesia but inhibit emetic activation.

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Fig. 1.

Model of the phases and stimuli that contribute to postoperative and postdischarge nausea and vomiting (PONV and PDNV). Both inhalational anesthesia and intravenous opioids (e.g., fentanyl) can contribute to PONV, which is defined by most authors as nausea and vomiting experienced in the post-anesthesia care unit (PACU) or in-patient stay in the hospital. PDNV appears to be the result of opioid analgesic usage. Although not well understood, surgery-related effects on gastrointestinal motility (e.g., postoperative ileus) and GI inflammation might also contribute to nausea and vomiting. Patients can also develop tolerance to opioid-induced nausea and vomiting. This model is dependent on the type of surgery and may be shorter or longer periods of PONV and PDNV.,

Fig. 2. Neural pathways and pharmacology of postoperative nausea and vomiting (PONV). **A)** *Brain pathways stimulated by inhalational anesthesia and opioids.* Stimulation of three sensory pathways produce the vomiting reflex, including the vestibular nuclei (Vnu), area postrema (AP), and vagal afferent fibers from the gastrointestinal (GI) tract. These inputs project to the nucleus of the solitary tract (NTS), which potentially has output pathways to local brainstem areas to produce the vomiting reflex and projections to the mid- and forebrain for the perception of nausea. Although opioids act directly on brainstem (Barnes et al., 1991), they could also influence vagal afferent signaling by altering GI motility (Viscusi et al., 2009). Inhalational anesthetic agents could enhance 5-HT₃ signals at peripheral and central sites to produce emesis or nausea (Parker et al., 1996) (Machu and Harris, 1994). Brain pathways potentially involved in nausea include the parabrachial nucleus (PB), thalamus (Thal), amygdala (Amy), insular cortex (IC), anterior cingulate cortex (ACC), and somatosensory/viscerosensory cortex (SC) (Miller et al., 1996; Napadow et al., 2012). **B)** *Neuropharmacological targets associated with PONV.* Opioids have emetic and antiemetic effects in animals and potentially humans too; at low doses morphine produces emesis, but at high doses it acts as an antiemetic (see review, Johnston, 2010). These actions are potentially the result of stimulation of different sites within the emetic neural circuitry, separated by the blood-brain barrier (Barnes et al., 1991). As concentrations of opioids increase in the systemic circulation or if the specific opioid drug is more lipid soluble (e.g., fentanyl), there is a greater antiemetic effect via μ opioid receptors inside the blood-brain

barrier (e.g., NTS), counterbalancing the emetic action of opioids on μ opioid receptors in the AP. Other sites of antiemetic actions include serotonin type 3 (5-HT₃) receptors in the AP, NTS, and gut vagal afferent fibers (a potential target for inhalational anesthetic agents); dopamine type 2 (D₂) receptors in the AP; tachykinin 1 (NK₁) receptors in the NTS and other hindbrain nuclei; and histamine 1 (H₁) and muscarinic 3 or 5 (M_{3/5}) receptors in the Vnu.

Table 1

Candidate genes that affect nausea and vomiting

Gene	Molecule	Function	Clinical impact (References)
HTR3A	5-hydroxytryptamine type 3 receptor subunit A	Neural signaling	PONV (Rueffert et al., 2009)
HTR3B	5-hydroxytryptamine type 3 receptor subunit B	Neural signaling	PONV (Rueffert et al., 2009) OINV (Laugsand et al., 2011)
OPRM1	Opioid receptor, mu 1	Neural signaling	PONV (Kolesnikov et al., 2011; Sia et al., 2008) OINV (Chou et al., 2006; Pang et al., 2012; Zhang et al., 2011)
CHRM3	Muscarinic acetylcholine receptor 3 subtype	Neural signaling	PONV (Janicki et al., 2011) OINV (Laugsand et al., 2011)
DRD2	Dopamine type 2 receptor	Neural signaling	PONV (Nakagawa et al., 2008)
COMT	Catechol-o-methyl-transferase	Degradation of catecholamines	PONV (Kolesnikov et al., 2011) OINV (Laugsand et al., 2011)
ABCB1	Adenosine triphosphate-binding cassette subfamily B member 1	Blood-brain barrier transporter (ondansetron)	PONV (Choi et al., 2010; Coulbault et al., 2006) OINV (Fujita et al., 2010)
CYP2D6	Cytochrome P450 superfamily enzyme	Drug metabolism	PONV (Candiotti et al., 2005; Wesmiller et al., 2012)
UGT2B7	UDP-glucuronosyl-transferase	Glucuronidation of morphine to morphine 3-glucuronide (M3G)	OINV (Fujita et al., 2010)

PONV= postoperative nausea and vomiting; OINV = opioid-induced nausea and vomiting

Table 2

Common antiemetic drugs used to control PONV and their adverse effects *

Class	Representative agents	Potential adverse effects
H ₁ receptor antagonists	Dimenhydrinate (Dramamine) Diphenhydramine (Benadryl) Cyclizine (Marezine) Promethazine (Phenergan)	Drowsiness, urinary retention, dry mouth, blurred vision, extrapyramidal symptoms, vascular necrosis (promethazine)
M receptor antagonists	Scopolamine (transdermal patch; Scopoderm)	Blurred vision, dry mouth, dizziness, agitation
D ₂ receptor antagonists	Metoclopramide (Reglan) Droperidol (Inapsine) Haloperidol (Haldol) Prochlorperazine (Compazine)	Sedation, cardiac arrhythmia
Corticosteroids	Dexamethasone (Decadron)	
5-HT ₃ receptor antagonists	Ondansetron (Zofran) Granisetron (Kytril) Tropisetron (Navoban) Dolasetron (Anzemet) Palonosetron (Aloxi)	QT prolongation
NK ₁ receptor antagonists	Aprepitant (Emend)	

* This list does not represent all antiemetics and not all drugs listed are specific to one receptor target (e.g., Sanger and Andrews, 2006)