Physiology and pharmacology of nausea and vomiting

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Abstract

Nausea and vomiting are both very unpleasant experiences. The physiology is poorly understood; however, understanding what we do know is key to tailoring a preventative or therapeutic antiemetic regime. There are two key sites in the central nervous system implicated in the organization of the vomiting reflex: the vomiting centre and the chemoreceptor trigger zone. There are five key neurotransmitters involved in afferent feedback to these areas. These are histamine (H_1 receptors), dopamine (D_2), serotonin (5-HT_3), acetyl choline (muscarinic) and neurokinin (substance P). Postoperative nausea and vomiting will occur in around one-third of elective patients who have no prophylaxis. This can result in many detrimental effects including patient dissatisfaction, unplanned admission and prolonged recovery. It is therefore essential that clinicians understand how they can prevent and treat nausea and vomiting using either a single agent or a combination of antiemetics to target relevant receptors. Commonly used drugs include antihistamines, dopamine antagonists, serotonin antagonists and steroids. More novel agents are being developed such as aprepitant, a neurokinin receptor antagonist, palonosetron, a $5HT_3$ receptor antagonist and nabilone, a synthetic cannabinoid.

Keywords Antiemetic drugs; emetic drugs; nausea; postoperative nausea and vomiting; vomiting

Royal College of Anaesthetists CPD Matrix: 1A01, 1A02

Learning objectives

After reading this article, you should be able to:

- explain the five key stimuli for nausea and vomiting
- recognize the importance of the vomiting centre and chemoreceptor trigger zone in organizing afferent signals
- identify key receptors involved in nausea and vomiting
- describe the commonly used classes of antiemetic drugs
- tailor antiemetic regimen to treat and prevent postoperative nausea and vomiting

Background

The physiology of nausea and vomiting is still poorly understood. Much of what we know is derived from animal models, and even these are limited. Both nausea and vomiting are particularly unpleasant experiences. Approximately one-third of patients undergoing elective surgery will experience nausea or vomiting if not given prophylaxis.[1]

Understanding which physiological pathways are involved in nausea and vomiting can help clinicians guide therapy, improving patient outcomes. Figure 1 outlines these pathways and their relationship with the central nervous system.

Nausea is the unpleasant urge to vomit and both nausea and vomiting are commonly accompanied by autonomic symptoms such as sweating, pallor, hypotension and dizziness. Despite a strong association it is thought that nausea and vomiting exist as two separate entities with differing physiological pathways.

The vomiting reflex can be described in two stages. Firstly, in the pre-ejection phase, retrograde peristalsis forces contents of the small intestine and stomach back towards the oesophagus. There is deep inhalation after which the epiglottis closes in order to protect the airway. Following this, the ejection phase involves active and coordinated retching, followed by expulsion of gastric contents sometimes through the mouth and possibly the nose. This is facilitated by abdominal and diaphragmatic contraction, retrograde oesophageal contraction and dilation of the upper oesophageal sphincter.

Physiology

Two key areas are thought to organize the vomiting reflex; the 'vomiting centre' and the chemoreceptor trigger zone (CTZ). There are five key receptors implicated in vomiting. These are muscarinic (M_1), dopaminergic (D_2), histaminergic (H_1), 5-hydroxytriptamine or 5-HT_3 (serotonin), and neurokinin NK_1 (substance P).

There are five key precipitants to vomiting:

- toxic material in the lumen of the gastrointestinal tract
- visceral pathology
- vestibular disturbance
- central nervous system stimulation
- toxins in the blood or cerebrospinal fluid (CSF).

The vomiting centre

The vomiting centre is located within the medulla. It is unlikely to represent a discrete area of the brain and can be thought to encompass the nucleus tractus solitarius. It receives afferent signals from higher areas, the vagus nerve, vestibular nuclei and the CTZ.

Toxic material or irritation on the lumen of the gastrointestinal tract

Vomiting is a protective reflex allowing humans and animals to expel harmful toxins or irritants. Mucosal chemoreceptors in the gastrointestinal (GI) tract stimulate vomiting in response to toxins within the lumen or gastric irritation. Commonly these toxins are produced by bacterial or viral pathogens transmitted hand to mouth or through ingestion of food. Clinically this may occur shortly after ingestion, or may take longer to manifest such as in the case of infection with *Salmonella*.

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Physiological pathways involved in nausea and vomiting and their relationship with the central nervous system

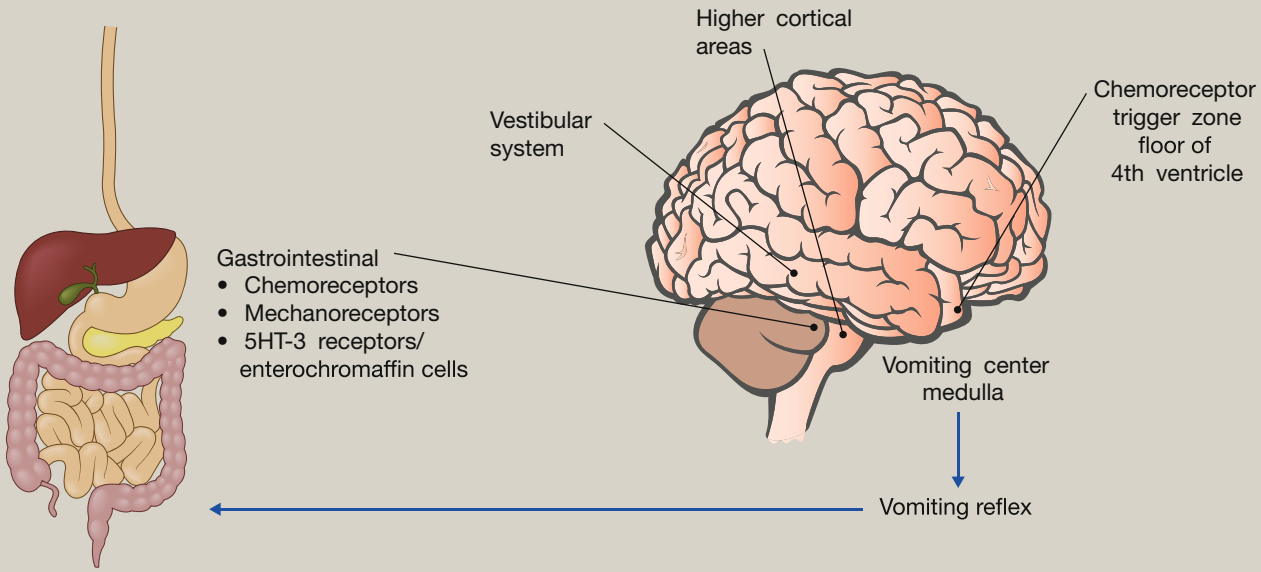

Figure 1

Afferent input from chemoreceptors is mediated by H_1 and ACh receptors from the vagus nerve and sympathetic system. These feed into the nucleus tractus solitarius and in turn the vomiting centre. While this central feedback is being processed, the enteric plexus initiates retropulsion of GI contents complementing the pre-ejection stage.

Mucosal enterochromaffin cells also play a role in the response to intraluminal damage, for example secondary to cytotoxic therapy. Enterochromaffin cells will release 5-HT_3 in response to chemical, mechanical, or hormonal stimulation; these are enteroendocrine and neuroendocrine cells which act as a transduction point for efferent and afferent nerves which do not protrude into the lumen of the GI tract. Substance P, the natural ligand for NK_1 receptors, is thought to work synergistically with 5-HT_3.

Pathological visceral stretch

Mechanoreceptors in the pharynx and GI tract can stimulate vomiting in response to stretch. This may be secondary to insufflation of the oesophagus, ileus, obstruction due to food bolus, or food being moved back due to retropulsion as described above. This is therefore a common precipitant in surgical patients.

Vestibular disturbance

Afferents from the vestibulo-cochlear system also feed into the vomiting centre and play a role in motion sickness or sea sickness. This is mediated by ACh and H_1 transmitters acting via the vestibular nuclei in the brainstem.

Visceral pathology

The nucleus tractus solitarius also receives somatic afferent signals originating from the vagus, glossopharyngeal and facial nerves. These play a role in nausea and vomiting related to cardiac stress via cardiac vagal afferents.

Central nervous system stimulation

Input from higher centres such as the limbic area may occur in response to emotional stress, distressing visual images or intense pain, helping to explain why retching, nausea or vomiting can accompany an emotional situation. Other examples of higher stimuli include raised intracranial pressure.

The chemoreceptor trigger zone

Toxins in the blood or cerebrospinal fluid

The CTZ, or 'area postrema', lies on the floor of the fourth ventricle. Interestingly, this area lies outside the cerebrospinal fluid (CSF) although it is particularly adept at detecting hormones and toxins in the CSF and blood stream due to its dense capillary network and fenestrated epithelium. It has receptors for sensing 5-HT_3, select D_2, and NK_1 (substance P).

Medication-induced vomiting is common. The CTZ can be stimulated by the drugs themselves or by the metabolites produced as the drug is broken down. Drugs can also affect gut motility leading to stimulation of stretch receptors and can irritate the gastric lining, both of which can stimulate nausea and vomiting. Drugs commonly implicated include opiates, volatile anaesthetics agents and cytotoxic drugs.

Emetics

Emetic drugs include ipecacuanha and apomorphine. Ipecacuanha comes from the dried root of the *Cephaelis ipecacuanha* plant. It stimulates vomiting via the CTZ. It is not recommended in the treatment of toxin ingestion due to an increased risk of aspiration. Ipecacuanha can, however, be found in low doses in cough syrups as an expectorant. Apomorphine is a breakdown product of morphine and interestingly has no action on opioid receptors; it is in fact a non-selective dopamine agonist. It has

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