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Review

Neurochemical mechanisms and pharmacologic strategies in managing nausea and vomiting related to cyclic vomiting syndrome and other gastrointestinal disorders

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ABSTRACT

Nausea and vomiting are common gastrointestinal complaints which could be triggered by stimuli in both the peripheral and central nervous systems. They may be considered as defense mechanisms when threatening toxins/agents enter the gastrointestinal tract or there is excessive retention of gastrointestinal contents due to obstruction. The pathophysiology of nausea and vomiting is complex and much still remains unknown. Therefore, treatments are restricted or ineffective in many cases. Nausea and vomiting with functional etiologies including cyclic vomiting syndrome are challenging in gastroenterology. In this article, we review potential pathways, neurochemical transmitters, and their receptors which are possibly involved in the pathophysiology of nausea and vomiting including the entity cyclic vomiting syndrome.

Contents

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1. Introduction

Nausea is the unpleasant sensation of having the urge to vomit, and vomiting (emesis) is the forceful expulsion of gastric contents mediated by integrated autonomic and motor function mechanisms. They are common gastrointestinal symptoms seen in both primary care and referral settings. These symptoms dramatically affect patients' quality of life and their economic burden is believed to be considerable, primarily due to the medical costs and their effects on patients' lifestyle and employment productivity (Hasler and Chey, 2003; Scorza et al., 2007).

Food poisoning, gastrointestinal obstruction, motion sickness, etc. are among the acute causes of nausea and vomiting. Although most of the acute forms of nausea and vomiting are self-limited, they may necessitate urgent medical or surgical interventions. Chronic causes are usually observed in organic diseases like peptic ulcer disease, inflammatory bowel diseases, cholecystitis, and hepatitis. Other etiologies are termed functional when there is no organic and mechanical component as an explanation. Cyclic vomiting syndrome (CVS) is one of the functional chronic forms of nausea and vomiting which presents with recurrent and cyclic vomiting attacks with symptomless periods between the attacks (Quigley et al., 2001; Scorza et al., 2007; Hejazi and McCallum, 2011).

Treatment of nausea and vomiting should be based on the underlying pathophysiology, although empiric treatments are also an approach in many patients (Scorza et al., 2007; Quigley et al., 2001). In these settings when the pathophysiology of nausea and vomiting is not well understood, the treatment strategies are not always effective.

Understanding the pharmacopathology of nausea and vomiting helps us in developing new medications for prevention and treatment of these debilitating symptoms. Moreover, mapping the anatomical structures involved in the process of nausea and vomiting and understanding the distribution of receptors and neurochemical transmitters in the emesis circuit help us in strategizing the best available pharmacological approach in the management of nausea and vomiting.

In this article, first we discuss the underlying mechanisms of nausea and vomiting and then focus on the neurochemical mediators of these phenomena and finally discuss the currently available/potential treatments of nausea and vomiting in chronic cases with a major focus on functional forms including CVS.

2. Physiology of emesis

Emesis is a complex behavior and despite extensive studies, is only partially characterized (Darmani and Ray, 2009). There are several restrictions in studying the physiology of nausea and vomiting in general and CVS in particular with the main one being the lack of reliable animal models mimicking the neuropharmacological features of human emesis (Andrews and Horn, 2006).

Nausea and vomiting can be triggered by: (a) toxic materials within the gastrointestinal lumen which stimulate dorsal brainstem via vagal afferents; (b) absorbed toxins or drugs which act directly on the dorsal vagal complex; (c) pathologies in the gastrointestinal tract or other visceral organs (e.g. renal or cardiac) which stimulate vagal afferents; (d) stimuli within the central nervous system (CNS) including cerebral cortex and limbic system; and (e) disturbance of the vestibular nuclei and cerebellum (Sanger and Andrews, 2006; Smith et al., 2012a).

The sense of nausea is believed to be mediated by higher levels of CNS including the cerebral cortex (Miller, 1999). The key sites in the mediation of vomiting are: (a) the dorsal vagal complex consisting of area postrema, nucleus of the solitary tract and dorsal motor nucleus of the vagus, and (b) the central pattern generators. While dorsal motor nucleus of the vagus mediates emetic motor function of the gastrointestinal tract, central pattern generators coordinate prodromal activities, e.g. salivation (Darmani and Ray, 2009).

An important component of the emesis circuit is the chemoreceptor trigger zone which is located in the area postrema in the floor of the fourth ventricle. Chemoreceptor trigger zone is outside the blood brain barrier and is sensitive to chemicals in the cerebrospinal fluid and blood. The sensory signals from chemoreceptor trigger zone are sent to dorsal motor nucleus of the vagus and central pattern generators via nucleus of the solitary tract and moderate the motor and prodromal activities which mediate nausea and vomiting (Darmani and Ray, 2009; Hornby, 2001).

In response to emetic stimuli, the vagal efferent motor outputs, which are coordinated by brain-stem nuclei, supply the esophagus, stomach and the intestine, while the spinal somatomotor neurones send signals to the anterior abdominal muscles and the costal/crural regions of the diaphragm. These signals inhibit peristalsis and produce the retroperistaltic contractions beginning in the small bowel and ascending trough the duodenum and into the stomach. They also produce simultaneous contractions in the abdominal muscles and the diaphragm which generate very high amplitude pressures. In addition, autonomic stimulation of the heart and airways, salivary glands and skin causes prodromal effects such as salivation and pallor (Sanger and Andrews, 2006; Darmani and Ray, 2009; Pleuvry, 2012). The anatomical structures involved in the processing of vomiting are shown in Fig. 1.

2.1. Crosstalk between gastrointestinal tract and the brainstem emetic nuclei

The stimulators in the gastrointestinal tract are classified to: (a) nutrients, (b) mechanical stimuli, (c) toxins/irritants, (d) microbial signals and (e) antigens. These stimuli are encoded in the gut through the intrinsic primary afferent neurons, extrinsic afferent neurons, immune cells or the enteroendocrine cells (Mayer, 2011).

Enterochromaffin cells are well-known members of enteroendocrine cells. They have a major role in activating the vomiting circuit by sensing noxious contents of the gastrointestinal lumen and secreting mediators such as serotonin (5HT) and substance P. Enterochromaffin cells can directly stimulate the intrinsic or extrinsic afferent neurons or send indirect signaling to the CNS and the brainstem emetic nuclei through secreting neuroendocrine mediators into the blood (Darmani and Ray, 2009).