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Review

Physiology of the Digestive Tract Correlates of Vomiting

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Emesis is composed of 3 independent digestive tract correlates that are individually organized by a brainstem neural network and all 3 hierarchically organized by a central pattern generator. The central pattern generator may be in the Bötzinger nucleus of the brain stem. The digestive tract sensory mechanisms that activate vomiting are the digestive tract mucosa or chemoreceptive trigger zone of the area postrema. Regardless of the initial stimulus, the area postrema may be activated in order to inhibit orthograde digestive tract motility and reflux blocking reflexes that would interfere with anterograde movement, which is the basic purpose of vomiting. The digestive tract correlates are (1) relaxation of the upper stomach and contraction of the lower pharynx, (2) retrograde giant contraction, and (3) the pharyngo-esophageal responses during retching and vomitus expulsion. The proximal gastric response allows gastroesophageal reflux, the lower pharyngeal response prevents supra-esophageal reflux, and both last the duration of the vomit process. The retrograde giant contraction empties the proximal digestive tract of noxious agents and supplies the stomach with fluids to neutralize the gastric acid which protect the esophagus from damage during expulsion. The retch mixes the gastric contents with acid neutralizer and gives momentum to the expelled bolus. During vomitus expulsion the esophagus is maximally stretched longitudinally which stiffens its wall to allow rapid transport as the suprahyoid muscles and diaphragmatic dome contract, and the hiatal fibers relax.

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Key Words

Area postrema; Central pattern generator; Digestive tract; Retrograde giant contraction; Vomiting

Introduction

The digestive tract correlates of vomiting have been studied for close to 100 years.[1,2] Although review articles on vomiting have been published recently, the last articles which reviewed the digestive tract correlates of vomiting were published over thirty years ago.[3,4] Over the past thirty years a number of significant new studies of the digestive tract correlates of vomiting have been published,[5-17] therefore, it is time for an up-to-date review.

Characteristics of the Digestive Tract Correlates of Vomiting

Vomiting consists of 3 digestive tract correlates: changes in gastroesophageal resting tension, retrograde giant contraction (RGC), and the pharyngoesophageal responses during retching and vomitus expulsion. There are other digestive tract responses during vomiting, but they are secondary to the 3 digestive tract correlates of vomiting.

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Changes in Gastroesophageal Resting Tension

The first reported responses to an emetic stimulus are relaxation of the gastric fundus[3,6,17] and LES,[9] and increased basal tension of the cricopharyngeus (CP) and cervical esophagus (Fig. 1-3).[9,14] These responses last the entire period of the vomit episode (Fig. 1-3).[9,14] It is likely that the CP and cervical esophageal contractions are longitudinal, because it has been shown that the thoracic esophagus significantly elongates (Fig. 3) during this time.[9]

Retrograde Giant Contraction

The RGC (Fig. 1-4, 6-10) is a strong single contraction of the upper digestive tract which rapidly propagates orad from the mid jejunum to the gastric antrum.[3,4,9,14,15,18,19] The RGC functions to evacuate the proximal small intestinal contents in preparation for vomitus expulsion.[3,4] Such an effect is extremely important when noxious agents have been ingested. The RGC occurs in all forms of vomiting,[3,4] even those not involving ingestion of an emetic agent, therefore, the following RGC function is more universally important.

An additional important function of the RGC is to move the digestive tract fluids into the stomach which can neutralize the gastric acid in preparation for vomitus expulsion through the esophagus.[3,4] The gall bladder contracts during the propagation of the RGC thereby pumping bile into the duodenum just prior to the arrival of the RGC.[3] Bile is composed primarily of water, bile salts, fats, bili-

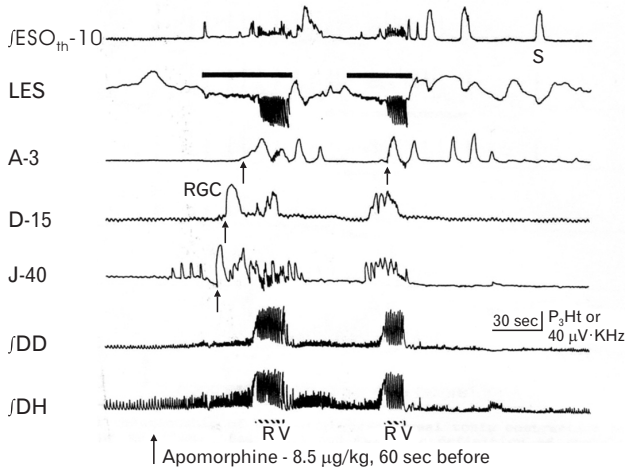

Figure 1. Temporal relationship of lower esophageal sphincter (LES) relaxation to retrograde giant contraction (RGC), retching, and vomiting. This figure shows that LES relaxation is the initial digestive tract event associated with emesis and it lasts the entire length of the process. S, swallow; R, retching; V, vomiting; ESOth, thoracic esophagus; A, antrum; D, duodenum; J, jejunum; # cm from pylorus; ∫, integral; DD, diaphragm dome; DH, diaphragm hiatus. P3Ht, mean maximum height of Phase 3 of the migrating motor complex. Solid bars indicate periods of LES relaxation associated with vomiting. The upward vertical arrow and noted time in this and all figures indicates the time of occurrence of the applied stimulus before the time of the arrow. All recordings are strain gauge recordings. Adapted from Lang.[9]

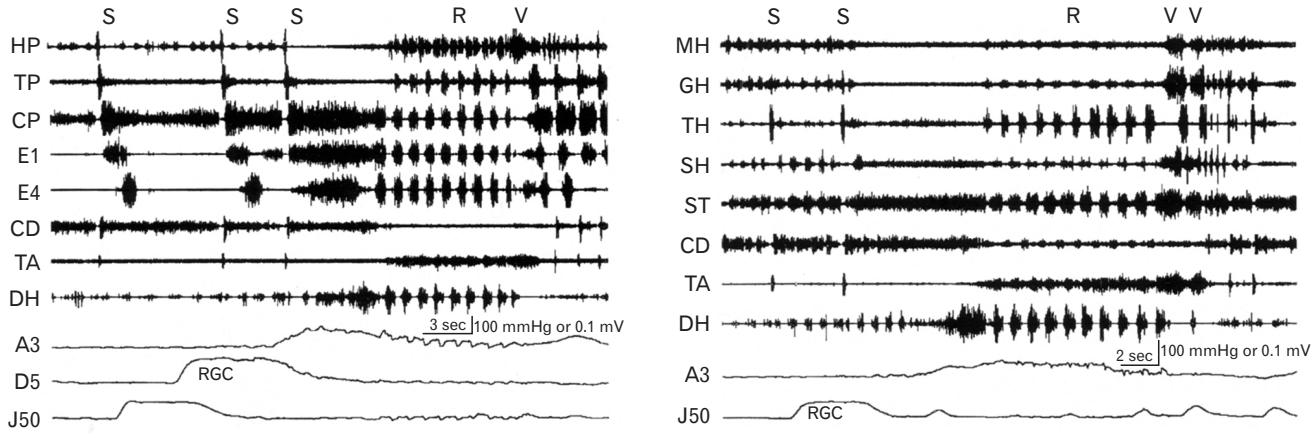

Figure 2. The relationship of digestive tract responses with the pharyngeal, laryngeal, and hyoid muscles responses associated with retching and vomiting. Note the arrival of the retrograde giant contraction (RGC) in the stomach before retching begins. Also, note the tonic activation of the pharynx, esophagus, infrahyoid muscles, and larynx; and relaxation of the suprahyoid muscles just before retching. No swallows occurred during this tonic response. S, swallow; R, retch; V, vomit; HP, hyopharyngeus; TP, thyropharyngeus; CP, cricopharyngeus; MH, mylohyoideus; GH, geniohyoideus; TH, thyrohyoideus; SH, sternohyoideus; ST, sternothyroideus; Cd, cricoarytenoideus; TA, thyroarytenoideus; DH, diaphragmatic hiatus; A3, antrum 3 cm from the pylorus; D5, duodenum 5 cm from pylorus; J50, jejunum 50 cm from pylorus. A3, D5, and J50 are strain gauge recordings and all the rest are electrical recordings. Adapted from Lang et al.[14]

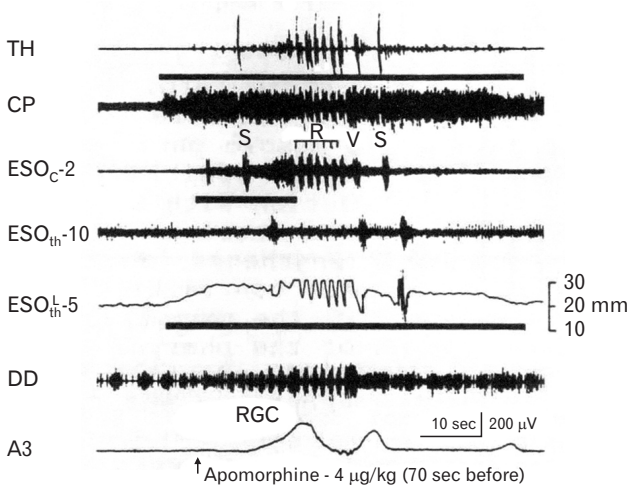

Figure 3. Correlation of thoracic esophageal stretch with tonic pharyngoesophageal contraction. Note that the thoracic esophagus stretches about 8 mm concomitant with the pharyngoesophageal tonic contraction, and that the thoracic esophagus remains relaxed throughout retching and vomiting.[9] RGC, retrograde giant contraction; S, swallow; R, retch; V, vomit; TH, thyrohyoideus; CP, cricopharyngeus; ESOc, cervical esophagus; ESOth, thoracic esophagus; A, antrum; ESOlth, thoracic esophageal length gauge; #, location of recording device # cm from the pylorus; DD, diaphragm dome. Solid horizontal bars indicate period of pharyngoesophageal tonic contraction or thoracic esophageal stretch. The ESOLth-5 and A recordings are from strain gauges and the remainder are from electrodes. Adapted from Lang.[9]

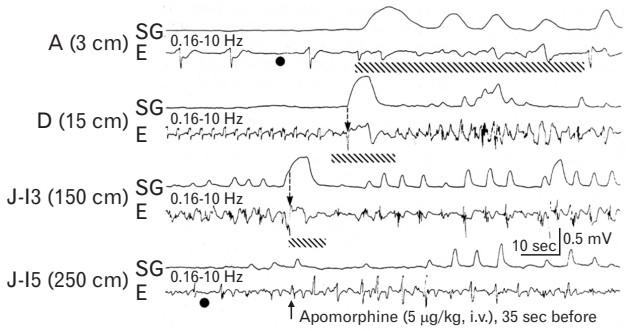

Figure 4. Simultaneous recording of myoelectric (E) and contractile (SG) activities of gastrointestinal tract from same sites during gastrointestinal motor correlates of vomiting activated by apomorphine. Hatched bars, period of electrical control activity (ECA) disruption; filled circles, initiation of ECA frequency slowing; and vertical arrows, occurrences of retrograde giant contraction (RGC) potential at upstroke of RGC. Note that the RGC potential occurs at the upstroke of the RGC, ECA disruption propagates orad ahead of the RGC, and the ECA returns after ECA disruption at a slower rate than before ECA disruption. A, antrum; D, duodenum; J-I, jenuno-ileum. The frequcncy range of 0.16-10 Hz indicates the filter used to record the electrical activity. The numbers after the letters indicate the cm from the pylorus of the strain gauge. Adapted from Lang et al.[18]

rubin, and it is usually basic (pH 7.5 to 8.05).[20] More importantly, the duodenum contains Brunner's glands whose mucous secretion is very acid neutralizing.[21] The great effectiveness of the Brunner's gland secretion in neutralizing gastric acid was demonstrated when the gastric acid was injected into the intestines of experimental animals.[22] Gastric acid had no effect when applied to the duodenum which contained Brunner's glands, but ulcerated the jejunum which did not have Brunner's glands.[22] Therefore, the RGC provides a very important function which protects the esophagus during the vomit process.

There are 2 other motor effects associated with the RGC: pre-RGC inhibition of motor activity[3,4,7,10,13] and post-RGC activation (Fig. 1, 4, 6-10) of short duration peristaltic contractions.[3,4,7-9,13,15,18,19,23,24] These 2 motor events are strongly related to the changes in electrical activity associated with the RGC. Before describing these events and the mechanism of initiation and propagation of the RGC, the gastrointestinal smooth muscle electrical activity must be discussed.

There are 2 types of electrical activity of digestive tract smooth muscle (Fig. 4), each controlling a different function.[25] The slow waves, ie, electrical control activity (ECA), are spontaneous fluctuations of the resting membrane potential of the muscle cells. Contractions occur when the membrane potential declines to the contractile threshold that allows initiation of contraction, and this is followed by increased membrane potential that inhibits contraction. Therefore, the ECA frequency controls the maximum rate of contraction. The ECA rate at more orad intestinal sites is faster than more distal sites, and the cells controlling ECA rates are connected. Therefore, the more orad sites influence the rates and occurrences of ECA at more caudad sites. This allows the gastrointestinal tract to contract at regular intervals and to generate contractions that propagate distally, ie, peristalsis, and prevents retrograde propagation. The rapid waves, ie, electrical response activity (ERA), reflect the electrical current that causes muscle contraction.

The initial myoelectric event, ie, disruption of the ECA (a period of an absence of ECA [Fig. 8]), propagates orad (Fig. 9).[4,12,15,18,26] This disruption of the ECA is necessary in order to allow a contraction to move retrogradely in the small intestine. Associated with this ECA disruption is inhibition of motor activity (Fig. 4 and 6) a few seconds before initiation of the RGC.[3,4,7,10,15,18,19,24,27] Given the loss of ECA and motor activity, it is likely that this disruption of ECA is caused by a hyperpolarization of the muscle

membrane potential. The ECA disruption lasts longer (Fig. 4 and 9) at more orad locations in the intestine.[4,12,15,18,26] A few seconds after the beginning of ECA disruption, the RGC and RGC potential occurs (Fig. 8).[15] The RGC potential is a single rapid ERA-like response (Fig. 8) that occurs at the very beginning of the RGC.[4,15,18,28] The RGC potential is initiated at the most distal ECA disruption site (Fig. 9) which is in the mid jejunum and its activation propagates orad at a slower rate (10-15 cm/sec in dog)[18] than the ECA disruption (15-25 cm/sec in dog).[18]

The second RGC related motor event is the post-RGC activation of peristaltic contractions (Fig. 1, 4, 6, 7, and 10).[3,4,7-9,13,15,18,19,23,24] After the passage of the RGC at each level of the small intestine the ECA rate returns, but at a slower rate than before ECA disruption (Fig. 4 and 9).[18] The normal intestinal ECA rate in dogs is about 15 to 20/minute, and this falls to about 10 to 15/minute after the RGC.[18] The duration of this decreased ECA rate lasts longest at more distal sites (Fig. 4 and 9)[18] and the post-RGC contractions last longest at more distal sites (Fig. 10).[19]

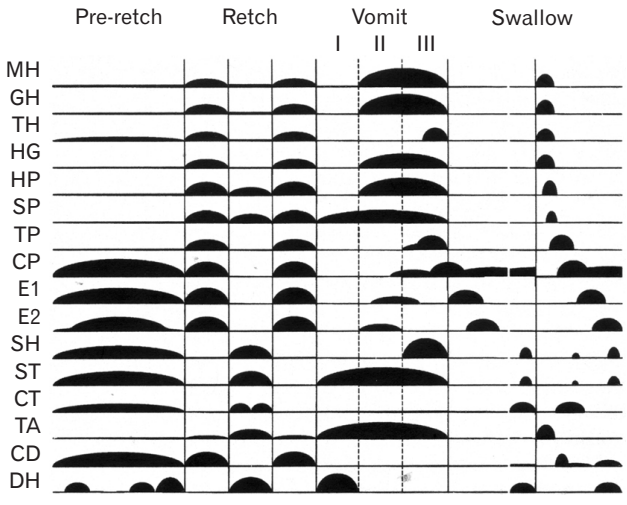

Figure 5. Schematic illustration of typical pattern of activation of pharyngeal, hyoid, and laryngeal muscles before and during retching, vomiting, and swallowing. Note the significant differences between responses during the retch and inter-retch periods and the 3 stage response during vomiting. I, II, and III, indicates phases of the vomit as described in the review. MH, mylohyoideus; GH, geniohyoideus; TH, thyrohyoideus; HG, hyoglossus; HP, hyopharyngeus; SP, stylopharyngeus; TP, thyropharyngeus; CP, cricopharyngeus; E, esophagus, #, cm from pylorus; SH, sternohyoideus; ST, sternothyroideus; CT, cricothyroideus; TA, thyroaretynoideus; CD, cricoarytenoideus dorsalis; DH, diaphragmatic hiatus. Adapted from Lang et al.[14]

Pharyngoesophageal Responses During Vomitus Expulsion

Vomitus expulsion is actually a 3-step process (Fig. 5).[14] While the 3 phases of vomitus expulsion are distinct and unique, the transitions between the phases of vomiting are mixed responses.

The initial pre-retch response is designed to prepare the esophagus and upper esophageal sphincter (UES) for the subsequent effects of retching. This first response (Fig. 2) is increased circular and longitudinal contraction of the striated muscle esophagus and UES.[9,14] This response acts to close and shorten the proximal esophagus, which helps to prevent esophago-pharyngeal reflux during retching. This set of actions moves the UES and proximal esophagus distally. Therefore, in order to maintain the normal relationship of the hyoid and larynx with the UES, the sternohyoideus

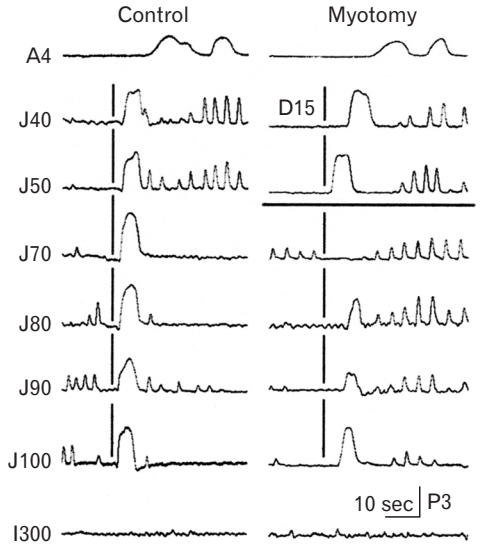

Figure 6. Effects of myotomy on retrograde giant contraction (RGC). This figure depicts the effects of myotomy at 60 cm from the pylorus on the orientation and propagation of the RGC across the small intestine. Myotomy blocked occurrence of the RGC at J70, reduced the magnitude and duration of the RGC at J80, J90, and J100, and resulted in 2 separate RGC's occurring above and below the myotomy propagating independently of each other. Myotomy had no observable effects orad of the myotomy. The control figure also provides an excellent example of the inhibition of motor activity for about 5 seconds before the RGC. The vertical lines in this figure are vertical reference lines so that direction and degree of propagation can be more easily assessed. The horizontal line in this figure depicts the location of the myotomy. P3, phase III of the migrating motor complex; A, antrum; D, duodenum; J, jejunum; I, ileum. The numbers after the letters indicate the cm from the pylorus of the strain gauge. Adapted from Lang.[15]

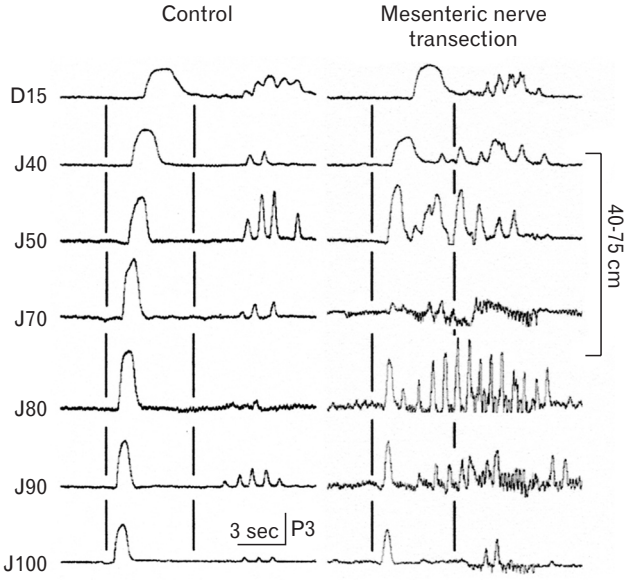

Figure 7. Effects of mesenteric nerve transection on the retrograde giant contraction (RGC). This figure depicts the effects of mesenteric nerve transection at J40 to J75 cm from the pylorus on the initiation, generation, and propagation of the RGC across the small intestine. Mesenteric nerve transection preserved the RGC over 10 cm from J40 to J50, blocked the RGC at J70, and reduced the magnitude and duration of the RGC at J80, J90, and J100. However, unlike myotomy the RGC sequence across the denervated intestine was not altered. This is unlike myotomy, as the RGC aborad of the transection did not occur after initiation of the RGC orad of the denervation. Mesenteric nerve transection had no observable effects orad of the transected intestine. Mesenteric nerve transection also blocked the intestino-intestinal inhibitory reflex that allowed non-RGC contractions to occur during the propagation of the RGC, ie, between the vertical bars, which never occurred when the mesenteric nerve was intact. P3, phase III of the migrating motor complex; D, duodenum; J, jejunum. The numbers after the letters indicate the cm from the pylorus of the strain gauge. Adapted from Lang.[15]

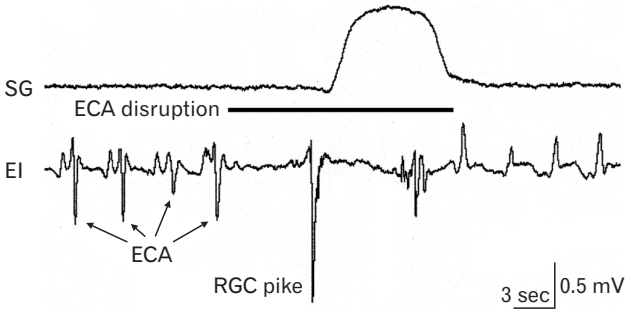

Figure 8. Intestinal pre-retrograde giant contraction (RGC) inhibition of myoelectric activity. This figure depicts the intestinal myoelectric response (EI) recorded from the same site as the strain gauge (SG) at 50 cm from the pylorus. Note that the electrical control activity (ECA) becomes disrupted, ie, ceases to occur (indicated by the downwards arrow), about 5 seconds before the start of the RGC, and that the RGC potential occurs at the upstroke of the RGC. Adapted from Lang.[15]

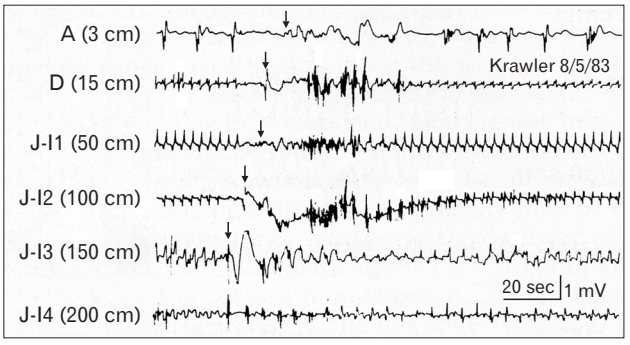

Figure 9. The retrograde transport of the retrograde giant contraction (RGC) spike potential. The figure depicts the myoelectric activity of gastric antrum (A) and small intestine recorded during a spontaneous occurrence of vomiting. In particular, note the loss of electrical control activity (ECA) just before the occurrence of the RGC spike potential (indicated at the downward arrows), and its retrograde movement through the digestive tract starting at 150 cm from the pylorus. Below the starting point of the RGC potential at 200 cm from the pylorus, the ECA rate decreases for almost 2 minutes. A, antrum; D, duodenum; J-I#, jejunum-ileum in which # is just the orad to caudad relationship of the electrodes. The numbers in parenthesis indicate the distance the electrodes are from the pylorus. Adapted from Lang et al.[18]

and sternothyroideus muscles contract (Fig. 2) pulling the hyoid and larynx distally.[14]

The second set of actions during retching are the 2 phases of retching (Fig. 5).[14] After the pre-retch response has shortened the esophagus, the first phase of the retch occurs. The diaphragm and infra-hyoid and -thyroid muscles relax, and the supra-hyoid and -thyroid muscles as well as the UES, pharynx and upper esophagus contract (Fig. 2).[9,14] Therefore, as the diaphragm relaxes the esophagus and stomach are pulled orad. This results in gastroesophageal reflux due to the relaxed LES, but with closure of the upper esophagus, UES, and pharynx, there is no esophagopharyngeal reflux.[4] After this first phase of the retch, the dome and hiatal (crural muscles) fibers of the diaphragm contract and the supra-hyoid and -thyroid muscles relax, which pulls the stomach distally and extends the esophagus (Fig. 2, 3, and 5).[9,14] The increased gastric pressure due to contraction of the diaphragm dome fibers could cause gastroesophageal reflux, but it is blocked by the diaphragm hiatal fibers contracting around the LES.[4] The basic action of the

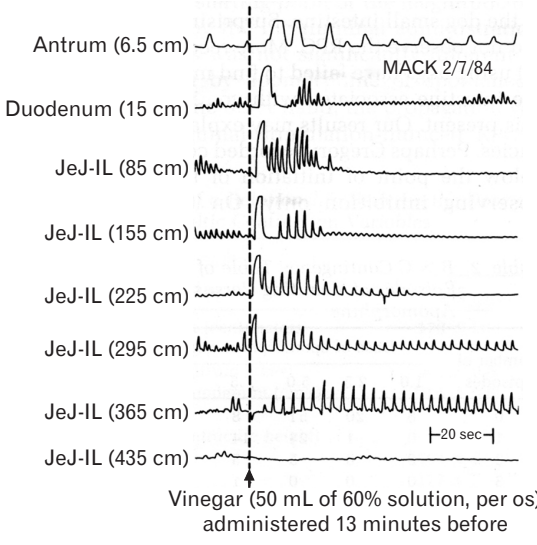

Figure 10. The post- retrograde giant contraction (RGC) activation of intestinal motor activation. This figure depicts the occurrence of the digestive tract correlates of vomiting, activated by chemical stimulation of the digestive tract, without activation of retching or vomitus expulsion. The lack of vomiting prevents respiratory artifact from fully exposing the post-RGC activation of intestinal motor activity. This figure also demonstrates the increased duration of the post-RGC activation of intestinal motility in more distal sections of the intestine, and the occurrence of these contraction in areas of the intestine caudad of the RGC (JeJ-IL [365] and [435]). JeJ-IL, jejunum-ileum. The numbers in parenthesis indicate the location of the strain gauge from the pylorus. Adapted from Lang et al.[19]

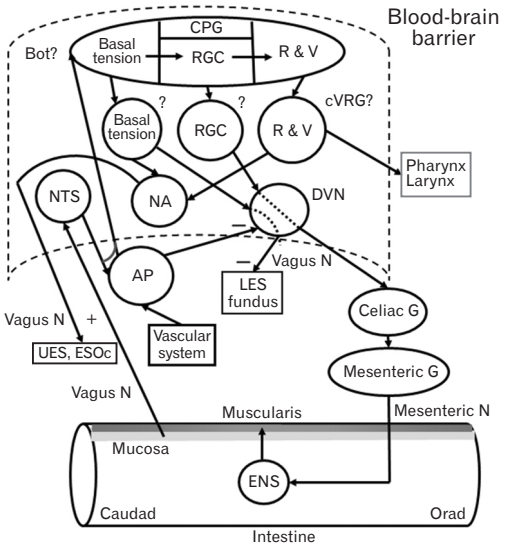

Figure 11. Neurophysiology of the digestive tract correlates of vomiting. There are 2 sensory pathways: (1) digestive tract mucosa sensing digestive tract contents with vagal afferents to the CNS and (2) the chemoreceptive trigger zone (CTZ) of the area postrema (AP) sensing blood borne agents with afferents to the central pattern generator (CPG). The AP serves multiple tasks. It not only mediates blood borne activation of the CPG, but it also transmits sensory signals from the nucleus tractus solitarius (NTS) to the CPG and inhibits dorsal vagal nucleus (DVN) mediated contraction of orthograde movement. The CPG controls the timing of the 3 basic digestive tract motor events of emesis. The first set of events is inhibition of lower esophageal sphincter (LES) and fundus which are probably controlled by the DVN, and activation of cricopharyngeus (CP) and thyropharyngeus (TP) which are probably controlled by the nucleus ambiguus (NA). The second set of responses is the retrograde giant contraction (RGC), but the CNS motor nucleus controlling this response is unknown. However, we do know that these outputs from this center are transmitted through the DVN to the vagus nerves, celiac ganglia, mesenteric ganglia, mesenteric nerves, to the intestine. The fibers then project distally 10 cm to 15 cm before innervating the intestinal musculature. The ENS is involved in this process but it is unknown at what stage of this process. The third set of responses during the retch and vomit are then activated by the CPG, but the subnucleus controlling these responses is unknown. It has been hypothesized that the respiratory movements of the retching and vomiting are controlled by the caudal portion of the ventral respiratory group (cVRG), but it is unkown what role this has in the digestive tract correlates of vomiting. Bot, Bötzinger nucleus; R&V, retch and vomit; UES, upper esophageal sphincter; ESOc, cervical esophagus; G, ganglia; N, nerve; ENS, enteric nervous system.

retching phase of vomitus expulsion is the pulling up and down of the stomach by the forces of the supra-hyoid and -thyroid muscles and diaphragm, respectively, which mixes the stomach contents (Fig. 5).[14] Another important function of retching is imparting a significant momentum to the bolus by its repetitive moving of the bolus from stomach to esophagus[4,9] in preparation for vomitus expulsion.

The third set of responses is the vomitus expulsion itself, which is composed of 5 separate actions some of which occur simultaneously (Fig. 2 and 5).[14] One set of actions is the orad pulling of the larynx and proximal esophagus by contraction of the supra-hyoid and -thyroid muscles.[14] The geniohyoideus (GH) and mylohyoideus, in particular, contract (Fig. 2 and 5) pulling the hyoid and attached proximal esophagus orad through the entire vomit expulsion process.[9,14] This also pulls the stomach orad and stretches the esophagus longitudinally.[9] Simultaneous with maximal opening of the UES caused by the relaxation of the UES, and contraction of supra- and infra-hyoid muscles which maximally pulls open the UES.[29] Both sets of responses allow esophago-pharyngeal reflux to occur. The primary force for vomit expulsion (Fig. 1-3) is then activated as the dome fibers of the diaphragm contract very strongly compressing the stomach and pulling the esophagus distally, while the hiatal fibers relax.[9,14] At the same time the GH contracts (Fig. 2) very strongly pulling the esophagus orad.[9,14]

The simultaneous pulling of the esophagus distally by the contraction of the diaphragmatic dome and orally by the contraction of the GH significantly stretches the esophagus longitudinally (Fig. 3).[9] Biomechanical data indicates that such longitudinal stretching tightens the esophageal wall in the circular direction so that it is less likely to balloon out when a bolus is pushed inside and more likely to move the bolus orad.[30-33]

As the bolus is being pushed into the esophagus, esophageal reverse peristalsis of the striated muscle esophagus occurs.[9,14] This reverse peristalsis may have minimal effects in humans as the human striated muscle esophagus is short, but this response may be very important in animals, as most have a much longer segment of striated muscle esophagus. The final stage of vomitus expulsion is the activation of swallowing (Fig. 2 and 3) after the bolus has been projected out of the mouth in order to cleanse the oral cavity and empty vomit debris from the esophagus.[9,14]

Neurophysiology of the Digestive Tract Correlates of Vomiting

The entire vomit process is controlled by the CNS. The 3 portions of the vomit process occur in well controlled sequence in hierarchical fashion,[3,4] and each controls different sets and types of muscles.[3,4,11] It is likely that each section is controlled by a separate brainstem neural network as well as a separate neural network controlling the hierarchical activation, ie, a central pattern generator of vomiting (CPG) (Fig. 11). This hierarchy of the digestive correlates of vomiting is also well illustrated by the independence of the 3 phases. The gastrointestinal correlates of vomiting can occur totally independent of the laryngeal and pharyngeal phases of the vomit process (Fig. 10).[19] All emetic agents tested have been found in low doses to be able activate only the gastrointestinal correlates of vomiting.[3,4,8,11-15,18,19,23,24,28] The review of the neurophysiology is divided into 3 sections: sensory physiology, CNS physiology, and neuromotor physiology.

Sensory Physiology

Vomiting can be activated by stimulation of four sensory systems: digestive tract,[34,35] vascular system,[36,37] cerebral cortex,[38,39] or vestibular system.[12,40] However, only the digestive tract and vascular sensory mechanisms will be reviewed, because only these sensory pathways involve the digestive tract. In addition, neurophysiological studies have found that the CNS control of motion sickness[40] is different from digestive tract stimulation-induced emesis, whereas the CNS control of digestive tract-induced and chemoreceptive trigger zone (CTZ)-induced emesis are similar as described below.

Stimulation of digestive tract mucosal receptors activates sensory receptors mediated by 5-HT_3 receptors which activate vagal afferents.[41] The vagal afferents project to the nucleus tractus solitarius (NTS), and then to the CPG (Fig. 11).[42]

If the emetic agent is absorbed before activating the emetic receptors of the intestinal mucosa, receptors in the CTZ of the AP, which has no blood-brain barrier,[36,37] can be activated to initiate vomiting (Fig. 11).[36,37,40] The CTZ is activated by dopaminergic,[4,23,36,37,42-44] serotonergic,[41] or opioid[4,23,37,45] receptor stimulating agents.

Although the AP is primarily a sensory nucleus, the AP might also have a very important digestive tract motor function during vomiting. Lesions of the AP block vagal afferent-induced emesis[34,35,37,46] and it has been hypothesized that this occurs because the lesion damages a fiber pathway from the NTS to the CPG.[47] However, these studies may have disclosed an additional function of the AP, as it has been found that the AP inhibits digestive tract motility. Chemical or electrical stimulation of the AP inhibits gastric motility.[48,49] The stimulation of the esophagus under normal circumstances causes activation of the esophago-UES contractile reflex (EUCR), which blocks esophago-pharyngeal reflux.[50] If the gastric distension is rapid a belch is activated and the EUCR is inhibited.[50] However, when the AP is lesioned the very same belch stimulus now activates the EUCR.[47] Therefore, activation of the AP inhibits spontaneous orthograde gastric motility and esophageal motor reflexes that prevent esophago-pharyngeal reflux (Fig. 11). The entire purpose of vomiting is to move upper digestive tract contents anterograde, therefore, inhibiting orthograde motor events and reflux blocking effects, eg, EUCR, would be an important function during vomiting, and the AP has been shown to do this.

Central Nervous System Control

Initial studies suggested that vomiting is controlled by a CPG whose function is to temporally organize the three independent CNS centers controlling their motor responses.[51] After conducting numerous brain stimulation[52] and lesion[53] studies, more recent studies concluded that a CPG for vomiting did not exist. However, conflicting studies suggest that a true CPG is found in the ventrolateral reticular formation.[42,54,55] Emesis activates neurons in the ventrolateral reticular formation,[55,56] and more significantly, a non-respiratory set of neurons of the NTS receive convergent input from the AP and vagus nerve that project to the Bötzinger nucleus, which is in the ventrolateral reticular formation.[42] In addition, stimulation of the Bötzinger nucleus activates retching and vomiting[54] even after

lesions of the NTS.[55] Therefore, the emetic CPG may be the Bötzinger nucleus. However, since the digestive tract correlates were not recorded in these studies, it is possible that the Bötzinger nucleus is the retch and vomit CPG and not the general emetic CPG.

While the AP has opiate receptors that activate vomiting, opioid agents also inhibit vomiting. Opioid agents which rapidly cross the blood-brain barrier, eg, fentanyl, inhibit rather than activate vomiting.[23] Fentanyl can block digestive tract or AP stimulated vomiting,[23] therefore, these opiate receptors may be in the CPG.

Neuromotor Physiology

Changes in gastroesophageal resting tension

The relaxations of the LES and hiatal fibers of the diaphragm during vomiting are very similar to the relaxations of these muscles during belching[57] and the transient lower esophageal sphincter reflex (TLESR).[57,58] Relaxation of the fundus is a significant part of this phase of vomiting, but fundus relaxation has not yet been demonstrated during belching or TLESR. Given the similar responses of these reflexes, they may all be generated by the same brainstem motor nucleus.

Interestingly, a motor nucleus has been identified which that electrically stimulated activates both motor responses. Stimulation of the caudal subnucleus of the dorsal vagal nucleus (DVN) relaxes the LES and fundus.[59] These responses were blocked by vagotomy.[59] Therefore, the DVN may be the brainstem motor nucleus mediating this first response during the vomiting process (Fig. 11).

However, changes in gastro-esophageal resting tension also include increased tension of the CP and cervical esophagus, which do not occur in belching[57] and the motor nucleus of these striated muscles is the nucleus ambiguous, not the DVN.[60] Therefore, the DVN may simply be the motor nucleus of the smooth muscle components of this part of vomiting process and not the CPG of this initial portion of the vomit process.

Retrograde giant contraction

The vagus nerve mediates activation of the RGC and its associated pre- and post-RGC motor events,[3,4,10,18,19,28] but sympathectomy has no effect on any digestive tract correlate of vomiting.[28] Atropine blocks only the RGC and the RGC potential,[3,4,18,19,28] but hexamethonium blocks all 3 motor and myoelectric responses associated with the RGC.[3,4,23] Therefore, the RGC is mediated by muscarinic cholinergic receptors on the smooth muscle and all of the responses are mediated by nicotinic cholinergic receptors of the enteric nervous system (ENS). No adrenergic,[8] serotonergic,[4,23] opioid,[4,23] or dopaminergic[4,23] receptors have been shown to mediate the motor responses of the RGC and its associated responses peripherally. Considering that atropine only blocks the RGC and no other non-enteric blocker has been found to inhibit the other motor events associated with the RGC, it has been hypothesized that a non-adrenergic and non-cholinergic receptor mediates these responses.[4] However, no such receptor has yet been identified.

The neural pathway mediating the vagal control of the digestive tract intestinal correlates of vomiting has been determined. It was found that transecting the celiac branch of the vagus[10] or the mesenteric[15] nerves blocked all of the intestinal correlates of vomiting. However, the pathway within the intestine was more complex. Studies in dogs found that when the mesenteric nerves innervating a segment of the intestine were transected, the RGC was not blocked (Fig. 7) in the first 15 cm of the orad portion of the denervated segment, but was significantly inhibited in magnitude and duration distal to this position.[15] Similarly, myotomy totally blocked the initiation of the RGC (Fig. 6) for about 10 cm distal to the myotomy, and reduced the amplitude and duration of the RGC for about 40 cm further distally.[15] Neither surgery had any effect on the digestive tract correlates of vomiting orad of the neurotomies.[10,15] Therefore, the mesenteric fibers entering the intestine carrying the RGC signal, move about 15 cm distally before innervating the muscle (Fig. 11). While the ENS mediates the innervation of the intestinal muscle, the role of the ENS in directing this distal projection is unknown.

Studies suggest that the primary response that generates the RGC and RGC potential is ECA disruption.[3,15,18,28] The orad velocity and magnitude of the RGC are highly variable, whereas the orad velocity of ECA disruption is very stable and consistent.[18] Other evidence that the primary response controlling the RGC is ECA disruption is that after myotomy the ECA rate of the intestine distal to the myotomy decreases significantly as well as the RGC propagation velocity.[15] In addition, the RGC never occurs without ECA disruption.[15] Therefore, the primary effect that initiates and controls the propagation of the RGC is ECA disruption. It has been hypothesized that the RGC is a rebound effect of the ECA disruption and the inhibition of intestinal motor activity.[15] The mechanism of the orad propagation of the RGC and myoelectric correlates are discussed below.

The relative roles of the CNS and ENS in controlling the activation and orad propagation of the RGC, RGC potential and ECA disruption have been determined. It was found that splitting the length of the small intestine into 3 segments and sewing them back together in different order did not alter the order of occurrence of the RGC in each segment.[17] This study clearly showed that

the RGC initiation and propagation were controlled by the CNS. However other studies found this conclusion to be incomplete as local factors, ie, ENS, had significant effects on generation, magnitude, and propagation of the RGC and its associated responses.

It was found that after myotomy of the upper small intestine, ECA disruption occurrence was not altered, but 2 RGC's occurred simultaneously that moved independent of each other (Fig. 6).[15] An RGC began in the usual position at mid jejunum and the other began just orad of the myotomy. The RGC which started at mid-jejunum traveled orad slower than the one that began at the location orad to the myotomy so that 2 RGC's were propagating orad at the same time. The distal RGC propagated orad more slowly even though the ECA disruption rate was not altered. In another set of studies it was found that intravenous administration of high doses of CCK activated ECA disruption, RGC potential, and the RGC, but all responses at different portions of the intestine occurred at the same time, and none of these responses were blocked by vagotomy.[28] Therefore, CNS controls initiation and propagation of ECA disruption, but the ENS generates the RGC and controls its magnitude, and can adjust the orad propagation velocity of the RGC. The second portion of the RGC, ie, the post-RGC peristalsis, is just the return of normal peristaltic contractions at a slower rate due to the slower ECA rate.

No studies have defined the specific brainstem nuclei controlling initiation and propagation of the RGC.

Pharyngoesophageal responses during vomitus expulsion

All of the recorded digestive tract motor correlates of vomitus expulsion are mediated by striated muscles of the pharynx and proximal esophagus, and all are mediated by their motor nerves through cholinergic receptors.

No CNS nucleus controlling the digestive tract correlates of vomitus expulsion has been identified, but a possible motor nucleus for the respiratory movements of retching and vomiting may have been identified. It was found that during emetic stimulation, neurons of the CPG directly drive the respiratory output of the caudal portion of the ventral respiratory group to produce fictive retching movements (Fig. 11).[61] However, the digestive tract correlates were not recorded, therefore, it is not known whether this is purely a respiratory control center or a general vomiting expulsion control center.

Conclusion

The digestive tract correlates of vomiting and their peripheral control mechanisms have been well documented, but there is much investigation of the central control mechanisms that needs to be conducted as illustrated in Figure 11.

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