Physiology and Pathophysiology of the Interstitial Cells of Cajal: From Bench To Bedside
VI. Pathogenesis and therapeutic approaches to human gastric dysrhythmias

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Owyang, Chung, and William L. Hasler. Physiology and Pathophysiology of the Interstitial Cells of Cajal: From Bench To Bedside. VI. Pathogenesis and therapeutic approaches to human gastric dysrhythmias. Am J Physiol Gastrointest Liver Physiol 283: G8–G15, 2002; 10.1152/ajpgi.00095.2002.—This review describes recent advances in our knowledge about the pathogenesis and therapeutic approaches to human gastric dysrhythmias. A number of clinical conditions has been found to be associated with gastric slow-wave rhythm disturbances that may relate to the induction of nausea and vomiting. Human and animal studies indicate that multiple neurohumoral factors are involved in the generation of gastric dysrhythmias. Antral distension and increased intestinal delivery of lipids may cause slow-wave disruption and development of nausea. This may be mediated by cholinergic and serotonergic pathways. Similarly, progesterone and estrogen may also disrupt gastric slow-wave rhythm in susceptible individuals. Prostaglandin overproduction in gastric smooth muscle appears to mediate slow-wave disruption in diabetes and with tobacco smoking. On the other hand, central cholinergic pathways play an important role in the genesis of gastric dysrhythmias associated with motion sickness. This may be mediated by vasopressin released from the pituitary. Although it is difficult to ascribe with certainty a causative role of slow-wave rhythm disturbances in the genesis of nausea and vomiting, the search has begun for novel antiemetic therapies based on their abilities to ablate or prevent gastric dysrhythmia formation. This includes the use of prostaglandin synthesis inhibitors, central muscarinic receptor antagonists, and dopamine receptor antagonists. Finally direct gastric electrical stimulation using a surgically implanted neurostimulator has shown promise in reducing emesis in patients with gastroparesis and gastric dysrhythmias.

GASTRIC ELECTRICAL PACEMAKER activity originates from the interstitial cells of Cajal located in the greater curvature at the junction between the proximal and distal stomach. The gastric pacemaker generates rhythmic depolarizations (also known as slow waves) at a frequency of three cycles per minute (cpm) in humans. Under nonstimulated conditions, slow waves partially depolarize gastric smooth muscle but do not cause contraction. Additional depolarizations evoked by neurohumoral stimulation trigger phasic gastric contractions. Because slow waves propagate in an organized fashion from the proximal body to the pylorus, peristaltic contractions in the antrum follow the spread of slow waves. In this manner, gastric slow waves determine the frequency and direction of the stomach contractions.

Similar to the heart, ectopic pacemakers in other parts of the stomach (primarily the antrum) may generate regular or disorganized rhythms in a number of clinical conditions. Bradygastria develops when the normal dominant pacemaker fails and other oscillatory sites in the gastric body generate rhythmic depolarizations at frequencies <2 cpm. With bradygastria, the contractile efficiency of the stomach is reduced due to a decrease in the number of antral contractions during fasting and the postprandial period. Tachygastria develops when a rival pacemaker, usually in the antrum, generates an oscillatory pattern at an abnormally high frequency (>4 cpm) that overrides the rest of the stomach. Although retrograde depolarization propagates at a high frequency with tachygastria, retrograde motor activity rarely develops, because the electrical activity is of insufficient amplitude to induce contraction. Hence, during tachygastria, the stomach is atonic. Not infrequently, the ectopic pacemaker activity is highly unstable both in frequency and in location, which results in the development of tachybradyarrhythmia.

nausea; tachygastrias; gastroparesis; prostaglandin; glucose; gastric pacing

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Electrogastrography (EGG) is used for the clinical assessment of disrupted gastric pacemaker activity. EGG is performed under fasting and fed conditions. During fasting, the EGG signal typically is of low amplitude. The frequency transiently decreases, and the amplitude of the signal increases after eating, presumably caused by increases in slow-wave amplitude and generation of action potentials. Many clinical conditions are associated with gastric dysrhythmias, which may relate to the generation of nausea and vomiting (Table 1). Up to 70% of patients with diabetic gastroparesis develop tachygastria and bradygastria (20). In addition to disturbances of electrocardiograph rhythm, some diabetics exhibit a concurrent loss of the increase in signal amplitude normally observed with meal ingestion. Occurrence of gastric dysrhythmic activity frequently is accompanied by vomiting. Recovery and reoccurrence can occur spontaneously, which may partially account for the clinical observation that diabetic patients with stable motor defects frequently exhibit day-to-day variations in symptom severity (12, 31, 33). Furthermore, symptomatic improvement of nausea can occur with the successful treatment of a gastric dysrhythmia independent of resolution of a defect in gastric emptying. Recent studies (14) indicate that increases in blood glucose are associated with increased dysrhythmic activity. Conversely, it has been observed that slow-wave rhythm disturbances are minimal in patients in whom euglycemia is maintained, although defects in the meal-related increase in signal amplitude persist (13).

Gastric slow-wave dysrhythmias also occur frequently in first-trimester nausea (21), which affects 50–70% of pregnant women. Most of these individuals have mild symptoms that can be treated with support and the reassurance that spontaneous resolution will occur. However, a small fraction of pregnant women have such severe episodes that dehydration and electrolyte abnormalities supervene. This condition, termed hyperemesis gravidarum, has been estimated to affect 1 of every 1,000 live births. Recently, many of the patients with nausea of pregnancy are found to exhibit gastric slow-wave disruption, either as tachygastria or bradygastria (21, 47). Koch and colleagues (21) report that 26 of 32 pregnant women with first-trimester nausea show slow-wave rhythm disturbances, with tachygastria in 17 women, bradygastria in 5 women, and absent gastric electrical activity in 4 women. Postpartum recordings demonstrate normalization of slow-wave rhythmicity concurrent with symptom resolution. Conversely, pregnant women without active nausea and vomiting do not exhibit slow-wave dysrhythmias (47). These observations suggest a possible causative role for gastric dysrhythmias in nausea of pregnancy.

Patients with anorexia nervosa frequently experience digestive symptoms such as dyspepsia, bloating, and postprandial nausea (5). Traditionally, these symptoms have been considered to be related to the underlying emotional disturbance. A number of studies has identified gastric motility abnormalities in these patients (1, 35). Abell and colleagues (1) reported that fasting and postprandial gastric dysrhythmias are prevalent in anorexia nervosa and are associated with absent antral contractions and delayed gastric emptying. Although it is unknown whether these abnormalities are primary or secondary, it is quite likely that they may contribute to the digestive symptoms that compromise the ability of these patients to gain weight. Hence therapeutic efforts at normalizing these gastric electromechanical abnormalities may be an important aspect in the management of these patients.

Gastric dysrhythmias also are prominent during motion sickness (41). Motion sickness may be experimentally induced by the technique of circular vection, the placement of a susceptible subject within a rotating drum to produce the illusion of self rotation (41). Gastric dysrhythmias evoked by circular vection appear to be pathogenically important, because they develop 1–2 min before the initial report of nausea and their severity correlates positively with the intensity of nausea (9, 41, 50). Furthermore, both symptoms and gastric dysrhythmias are suppressed by anticholinergic agents such as atropine and scopolamine (9, 46).

Nausea, vomiting, and early satiety are commonly reported by patients with chronic renal failure (20). Frequently, these patients are found to have gastric dysrhythmias and a failure to increase EGG signal amplitude during the postprandial period (29). Other disorders associated with gastric dysrhythmias include ischemic gastropathy (27), chronic intestinal pseudo-obstruction (18), and nausea associated with intra-abdominal malignancy (27, 29). In addition to these well-defined clinical conditions, many patients with unexplained nausea and vomiting exhibit slow-wave disturbances without definable etiologies (51). Gastric dysrhythmias have been reported in some patients with functional dyspepsia, raising the possibility that the impaired gastric myoelectrical activity may underlie symptom development in a subset of patients (19). The association of gastric dysrhythmias with idiopathic gastroparesis suggests a possible pathogenic role for primary rhythm disruptions in this condition as well (3). In addition, some patients with functional
nausea and vomiting and normal gastric emptying exhibit EGG dysrhythmias (7, 52). It is not clear whether the gastric myoelectrical abnormalities are responsible for the pathogenesis of symptoms in this group of patients.

PATHOGENESIS OF GASTRIC SLOW-WAVE RHYTHM DISRUPTION

Multiple neurohumoral factors are involved in the generation of gastric dysrhythmias. In humans, balloon distension of the antrum evokes prominent slow-wave rhythm disruption with development of nausea, indicating the presence of mechanical dysrhythmic factors (Fig. 1) (26). On the other hand, gastric fundic distension increases EGG power similar to meals via nonserotonergic pathways. These findings indicate that gastric fundus mechanoreceptor activation may be responsible for increased electrogastrographic amplitudes after meals and suggest potential mechanisms by which antral mechanoreceptor activation may cause slow-wave disruption and development of nausea in conditions of gastric over distension. Similarly, rapid duodenal perfusion of protein and lipid solutions also evokes nausea and tachygastria, which is mediated via cholinergic and serotoninergic 5-hydroxytryptamine (HT3; Fig. 2) (25). This may provide a mechanism to explain symptom development and gastric slow-wave disruption in conditions of increased intestinal delivery with abnormally rapid gastric emptying.

Humoral factors may also play roles in gastric slow-wave rhythm disruption. Gastric dysrhythmias may be induced in nonpregnant women by administration of progesterone and estrogen in doses that reproduce plasma levels in early pregnancy (47). This suggests that gastric slow-wave dysrhythmias in pregnancy may result from the combination of elevated levels of endogenous estrogen and progesterone. Dysrhythmic capabilities also have been demonstrated for insulin, secretin, cholecystokinin, pentagastrin, and glucagon. However, the clinical implications of these observations remain unknown.

Fig. 1. Induction of bradygastria in a healthy volunteer by antral distension is shown. At baseline, normal slow-wave activity at 3 cycles per minute (cpm) is evident on the electrogastrogram tracing associated with a dominant peak in the frequency spectrum at 3 cpm. Antral distension to a pressure of 12 mmHg induced high-amplitude, low-frequency waveforms on the raw tracing, which was associated with development of nausea. Spectral analysis shows a dominant frequency of 1.5 cpm during antral distension. From Ref. 26.

Neural mediators play an important role in the regulation of gastric pacemaker activity. The effectiveness of anticholinergic medications in the treatment of motion sickness suggests a possible pathogenic role for cholinergic pathways in gastric dysrhythmias. Histochemical studies demonstrate prominent cholinergic innervation of the vestibular nuclei (43). Recent investigation of antimuscarinic agents (9) shows that gastric dysrhythmias and nausea are suppressed by atropine but not methscopolamine, a peripheral muscarinic antagonist, which does not cross the blood-brain barrier, indicating that motion sickness and gastric dysrhyth-
mias are mediated by central not peripheral muscarinic cholinergic pathways, possibly in the vestibular nuclei.

The catecholamine pathways may also play an important role in disrupting gastric slow-wave rhythm. Infusion of epinephrine induces EGG rhythm disturbances in susceptible subjects, and these are preventable by treatment with phenotolamine (11). Furthermore, experimental motion sickness is associated with increases in epinephrine and nonopinephine levels in the blood and in certain regions of the brain (22, 44). Conversely α-adrenoceptor blockade with phenotolamine reduces gastric dysrhythmias and nausea evoked by circular vection (experimental motion sickness) (9). However, it should be noted that motion stimuli that do not induce gastrointestinal symptoms also produce similar catecholamine increases in the brain, indicating that these pathways may not be pivotal (44).

Endogenous prostaglandin E₂ disrupts slow-wave rhythmicity in dogs, whereas dysrhythmias evoked by epinephrine and met-enkephalin are inhibited by the prostaglandin synthesis inhibitor indomethacin (17). Furthermore, indomethacin blunts the tachyarrhythmic response to acute hyperglycemia (Fig. 3) and to nicotine administration, raising the possibility that prostaglandin pathways mediate slow-wave disruption in diabetes and with tobacco smoking (10, 24). In vitro studies of antral smooth muscle from a woman with severe idiopathic gastroparesis with tachygastria documented an abnormally rapid spontaneous electrical oscillation, which decelerates into the normal range with indomethacin perfusion (40). This suggests that prostaglandin overproduction in gastric smooth muscle may be responsible for slow-wave rhythm disruption in some clinical settings (40). However, endogenous prostaglandin pathways do not appear to be universal dysrhythmic mediators, because slow-wave rhythm disruptions in response to circular vection in humans and glucagon administration in dogs are not blunted by indomethacin (9, 17).

Other neural pathways have been implicated in the induction of gastric dysrhythmias. Exogenously administered opiate analogs induce slow-wave rhythm disruption in animal and human models that are blocked by the opiate antagonist naloxone (17). Clinical investigation shows that vection-evoked nausea is associated with release of β-endorphins into the bloodstream, suggesting a role for endogenous opiate pathways (22). However, administration of naloxone did not reduce tachyarrhythmias or nausea evoked by circular vection (9). Thus it is unlikely that endogenous opiate release is an important factor in induction of motion sickness.

Histaminergic pathways have been postulated to play a role in motion sickness, and antihistamine agents have shown effectiveness in preventing the tachygastric response to circular vection (37, 49). However, the effectiveness of a given histamine antagonist in treating motion sickness correlates closely with its intrinsic anticholinergic activity, suggesting that the histamine pathways per se may be relatively unimportant in the response to motion stimuli.

Finally, there is evidence that hormonal and neural factors act in concert to disrupt slow-wave rhythmicity. Vasopressin is a peptide released into the peripheral circulation from the pituitary during experimental motion sickness in a time course similar to induction of nausea and gastric slow-wave rhythm disruption in human and animal models (6, 23, 50). Furthermore, when administered intravenously, vasopressin induces gastric tachyarrhythmias and nausea in susceptible individuals (18). However, gastric dysrhythmias and nausea are only observed with supraphysiological plasma levels, suggesting that central neural but not the peripheral actions of vasopressin may contribute to induction of nausea and disruption of slow-wave rhythmicity in motion sickness (18). Atropine blocks the release of vasopressin into the circulation evoked by circular vection (18). Furthermore, atropine also blunts the symptomatic and dysrhythmic effects of high-dose vasopressin infusion, suggesting at least some of the actions of vasopressin are dependent on neural cholinergic pathways as well (18).

THERAPEUTIC APPROACHES TO HUMAN GASTRIC DYSRHYTHMIAS

Previous investigations have demonstrated a clear association of gastric slow-wave dysrhythmias with human clinical conditions that produce symptoms of upper gastrointestinal dysmotility including nausea and vomiting. When carefully assessed, generation of tachygastria or bradygastria shows a close temporal

[Fig. 3. Tachygastria activity as % recording time is shown for studies of the effects of hyperglycemia on slow-wave rhythm. Hyperglycemic clamping to 230 mg/dl evoked significant increases in tachygastria compared with lower glucose levels and control studies. In contrast, euglycemic, hyperinsulinemic clamping to insulin levels that reproduced those observed at the highest plasma glucose levels did not disrupt slow-wave rhythm. Pretreatment with the cyclooxygenase inhibitor indomethacin (Indo) prevented induction of tachygastria during hyperglycemic clamping, indicating mediation of the dysrhythmic activity by endogenous prostaglandin pathways. From Ref. 10.]
correlation with induction of nausea and vomiting in experimental models of emesis. However, it has been more difficult to ascribe with certainty a causative role of slow-wave rhythm disturbances in the genesis of symptoms.

Nevertheless, the search has begun for novel antiemetic therapies based on their abilities to ablate or prevent gastric dysrhythmia formation. Nonspecific treatments, for which gastric antiarrhythmic qualities have been proposed, include currently available prokinetic and antiemetic drugs, regimens to eradicate Helicobacter pylori infection, metabolic interventions, and acustimulation. Therapies designed to reverse intrinsic gastric smooth muscle defects believed to underlie the pathogenesis of slow-wave rhythm disturbances, including prostaglandin synthesis inhibitors, have been tested in selected experimental models but have yet to be investigated in patients with nausea and vomiting. Future investigations may focus on intrinsic physiological responses that exhibit antiarrhythmic properties to direct the pursuit of novel pharmaceutical agents. For example, meal ingestion reduces tachygastria in diabetic patients, suggesting activation of an endogenous neurohumoral pathway with slow-wave stabilizing effects. A hypothetical treatment that acts on such a pathway might prove beneficial in nauseated patients with gastric dysrhythmias. Finally, direct electrical stimulation of the gastric smooth muscle, using a surgically implanted neurostimulator, has shown promise in reducing emesis in patients with gastroparesis. However, the role of slow-wave rhythm stabilization in the symptom benefits of gastric neurostimulation is unproved.

CURRENT PROKINETIC AND ANTIEMETIC MEDICATION THERAPIES

The largest volume of investigation into gastric antiarrhythmic agents has concentrated on currently available prokinetic agents. In an early study of patients with diabetic gastroparesis, symptom improvement on treatment with the peripheral dopamine receptor antagonist domperidone has been shown to correlate better with resolution of gastric dysrhythmias than with acceleration of gastric emptying (20). Subsequent investigations report similar associations of symptom benefit with slow-wave rhythm stabilization in patients with gastroparesis and functional dyspepsia using the serotonin 5-HT3 receptor agonist cisapride. In some instances, this apparent antiarrhythmic action correlates with acceleration of gastric emptying. The gastric myoelectric effects of macrolide prokinetic agents are less certain. Some investigations have observed improvements in slow-wave rhythm with erythromycin, whereas others have reported increased dysrhythmic activity. However, erythromycin also has disparate effects on symptoms depending on the dose-reducing nausea and vomiting at low doses and evoking emesis and discomfort at higher doses.

Antiemetic drugs without prokinetic capability have also been shown to reduce gastric dysrhythmic activity in selected settings. The technique of circular vectoring has been used to evoke tachyarrhythmias, which are blocked by atropine and blunted by phentolamine, indicating mediation by cholinergic neural pathways and modulation by α-adrenoceptor pathways (9). Other investigations have demonstrated prevention of tachygastria with motion sickness after pretreatment with accepted treatments for this condition, including the antimuscarinic agent scopolamine and the antihistamine drug dimenhydrinate. Similarly, the serotonin 5-HT3 receptor antagonist ondansetron prevents bradygastria evoked by opiate administration and reduces tachyarrhythmias associated with experimental motion sickness. Finally, eradication of H. pylori is associated with reductions in tachygastria in the subset of functional dyspepsia patients with underlying gastric dysrhythmias (30). However, correlations of slow-wave stabilization with reductions in nausea and vomiting during treatment with prokinetic or antiemetic drugs do not prove that the beneficial therapeutic action of these agents stems from a specific antiarrhythmic effect. Such a conclusion awaits investigative confirmation.

PROSTAGLANDIN SYNTHESIS INHIBITORS

Several lines of evidence point to endogenous prostaglandin production by the stomach as an important cause of gastric dysrhythmic activity. Despite these investigations suggesting a role for prostaglandin production as a modulator of slow-wave rhythmicity, no studies have been performed to test the clinical efficacy of prostaglandin synthesis inhibitors in diseases that produce nausea and vomiting. Chronic use of indomethacin and related medications is associated with significant gastrointestinal toxicity including dyspepsia and an increased risk of gastroduodenal ulcer formation. The actions of indomethacin are mediated by nonselective inhibition of cyclooxygenases-1 and -2. Recent studies have begun to focus on the abilities of agents with decreased side effect profiles to exert similar dysrhythmic effects. Administration of amtolmetin guacyl, a nonsteroidal anti-inflammatory medication relatively free of adverse effects on the gut, reverses gastric dysrhythmias resulting from ethanol ingestion in healthy human volunteers (39). However, the selective cyclooxygenase-2 inhibitor rofecoxib exhibits no antiarrhythmic activity during acute hyperglycemia in normal subjects in contrast to the actions of indomethacin. Thus the potential clinical utility of less injurious prostaglandin synthesis inhibitors in normalizing slow-wave rhythm disruptions is uncertain.

NONMEDICINAL INTERVENTIONS

Nonmedicinal interventions are associated with reductions in slow-wave dysrhythmias in different clinical disorders and experimental models of nausea and vomiting. In healthy volunteers, moderate intensity exercise on a cycle ergometer increases the electrogastrographic amplitude and increases the fraction of recording time with a normal frequency, suggesting pos-
sible benefits of physical exertion on slow-wave activity (32). In an acute study of pregnant women with first-trimester nausea and vomiting, ingestion of protein-rich meals produces greater reductions in symptoms and gastric dysrhythmic activity than equicaloric carbohydrate- or fat-rich meals, raising the possibility that dietary modifications may be useful in some conditions (15). The symptom reduction produced by improved metabolic control in diabetic patients with nausea may stem from reductions in tachygastria. In healthy volunteers, induction of acute hyperglycemia elicits gastric tachyarrhythmias at a threshold plasma glucose level of 230 mg/dl (10). Similarly, hyperglycemic clamping evokes dysrhythmias in patients with Type I diabetes. Performance of electrogastrography before and after 4 wk of aggressive glycemic control demonstrates reductions in slow-wave instability in diabetic patients (16). Furthermore, in uremic Type I diabetics, combined pancreas-kidney transplantation leads to better normalization of slow-wave function compared with kidney transplantation alone (29). Finally, acupressure and acustimulation have been shown to decrease dysrhythmic activity in several settings. In healthy subjects, acupressure at the P6 or Neiguan point reduces symptoms of motion sickness in association with decreases in abnormal slow-wave activity, whereas acustimulation increases the fraction of recording time in normal rhythm under basal conditions and during experimental motion sickness.

Ginger has long been used as an alternative medication to prevent motion sickness. Clinical studies demonstrate that ginger reduces the tendency to vomit and the incidence of cold sweats evoked by motion sickness during sailing (8). In another study, ginger was found to offer better protection against nausea and vomiting induced by circular vection, compared with dimenhydrinate and placebo (36). In a more recent study, it was shown that pretreatment with ginger reduces nausea, tachygastria, and plasma vasopressin compared with placebo (28). In this manner, ginger may act as a novel agent in the prevention and treatment of motion sickness.

In early studies, surgical excision of dysrhythmic foci produces slow-wave normalization and improves symptomatology in patients with disordered gastric motor function. With the use of gastric serosal electrodes at laparotomy, an ectopic antral tachygastriac pacemaker was initially detected in a 5-mo-old infant with severe gastroparesis and failure to thrive (45). Resection of the distal 3/4 of the stomach led to resolution of vomiting and significant weight gain. In a 26-yr-old woman with severe vomiting and weight loss, serosal electrodes recorded prominent tachyarrhythmias that were correlated with impairment of fasting gastroduodenal motor complexes and asynchrony of duodenal and jejunal motor patterns (51). After hemigastrectomy, her symptoms decreased and her weight loss stabilized. Although these surgical case histories were reported more than 20 years ago, they represent the most convincing evidence to date for a pathogenic role of gastric slow-wave dysrhythmias in the induction of nausea and vomiting.

GASTRIC ELECTRICAL STIMULATION

Surgically implanted devices that deliver regular, periodic electrical depolarization to gastric smooth muscle have recently been employed to treat patients with medication-refractory gastroparesis. Two distinct gastric stimulation protocols have been reported as therapies for this condition. In the first, a stimulus at or slightly higher than the intrinsic slow-wave frequency is delivered through electrodes implanted in the proximal gastric serosa to create an artificial slow wave that entrains and coordinates gastric myoelectric activity (Fig. 4). This approach has been validated in canine models of gastroparesis. In one investigation, impaired gastric emptying is induced by vagotomy plus administration of glucagon, a hormone that disrupts slow-wave rhythmicity (2). Electrical stimulation at 1–1.1 times the intrinsic slow-wave frequency normalizes the dysrhythmic activity and accelerates emptying of a solid meal. The second stimulation protocol involves delivery of a series of very brief depolarizations at a frequency four times the intrinsic slow-wave frequency also through a single set of gastric serosal electrodes. In dogs, this method produces entrainment of the intrinsic slow wave, promotes high-amplitude contractions in phase with the normal slow wave, and reduces vomiting in response to noxious stimuli.

Parallel uncontrolled investigations in humans with gastric motor dysfunction have yielded promising but inconclusive results. In nine patients with medication-resistant gastroparesis (5 diabetic, 3 idiopathic, 1 postvagotomy), serosal electrical stimulation at a rate slightly higher than the normal frequency entrains the slow wave in all individuals, corrects gastric dysrhythmias in two patients, reduces gastroparetic symptoms after 1 mo, and decreases patient requirements for enteral feedings (34). Given the small number of patients, it is impossible to determine whether

Fig. 4. Gastric slow waves measured using serosally implanted electrodes are shown before (A) and after (B) gastric electrical pacing at a frequency slightly above the intrinsic slow-wave frequency. Initiation of the pacing stimulus (dots) produced entrainment of the intrinsic slow wave within 2 min. From Ref. 34.
the presence or absence of slow-wave rhythm disruption predicts the degree of symptom improvement.

Two larger multicenter trials of patients with refractory gastroparesis (26 diabetic, 40 idiopathic, 1 postvagotomy) have been conducted employing electrical neurostimulation at four times the intrinsic slow-wave frequency (12 cpm) (48). With the use of these stimulation parameters, nausea and vomiting are markedly reduced for up to 5 yr after device implantation. Furthermore, although subtotal gastrectomy or removal of the electrical stimulator is necessary in 25% of patients, the remainder have improved weight, body mass index, and quality of life. The mechanisms of these beneficial effects on symptomatology are uncertain, because only a modest acceleration of liquid emptying is seen, emptying of solids is unaffected, and slow-wave entrainment is not reliably observed.

Mechanisms other than motor stimulation have been proposed to explain the reductions in nausea and vomiting observed in the latter studies. It is well established that some patients with functional dyspepsia exhibit exaggerated perceptual responses to gastric distension. In a preliminary investigation of gastroparesis patients, electrical neurostimulation at 12 cpm enhances their ability to tolerate noxious balloon inflation in the proximal stomach, suggesting possible mediation by inhibition of neural transmission in gastric afferent pathways (42). In a report of a canine study, electrical stimulation at the intrinsic frequency entrains the slow wave and corrects rhythm disturbances evoked by intravenous vasopressin but does not prevent vasopressin-induced emesis (38). Conversely, stimulation at four times the intrinsic frequency reduces vasopressin-evoked emesis but has no effect on slow-wave dysrhythmias. These investigations raise the possibility that intrinsic slow-wave cycling is not relevant to the benefits of gastric dysrhythmias during catecholamine infusion: dopamine and epinephrine have distinct effects on symptoms and slow wave disruption. J Gastroint Motil 5: 195, 1993.


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