Review

Gastrointestinal influence on the electrophysiology of the heart: induction of cardiac arrhythmic episodes by myoelectrical uncoupling within the gut

Dale POWERS

FL 34741, U.S.A.

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Abstract

It is theorized that the triggering of some arrhythmic episodes in cardiac-sensitive subjects might be directly linked to the functional uncoupling of gastro myoelectrical activity following the consumption of particular foods or by other influences on the gut. The intent of this research is to reveal the likely adverse mechanism involved through investigative analytical review. The resulting evidence shows there exists a triggering source within the visceral smooth muscle system of the gut and a mode of transmission incorporated in the autonomic nervous system mediated by the central autonomic network that could significantly affect the electrophysiology of the heart. A formal clinical study is indicated to determine the specific types of troublesome foods and other factors associated to better understand the overall process.

Key words: gastrointestinal, autonomic nervous system, cardiac arrhythmia

Introduction

This investigation was inspired by the following observations: Certain foods tended to stimulate a quivering-tingly sensation in the mid-abdominal region within minutes to hours after they were consumed. The feeling was either followed immediately by a bowel sound or, if absent, a run of heartbeats sometimes leading to paroxysmal supraventricular tachycardia (PSVT). Also, stressful stimulation such as emotional frustration or performing rigorous physical exercise shortly after a meal tended to produce that same sensation leading to PSVT. The argument begins by describing the action potential physiology of visceral smooth muscle with the goal of identifying a triggering source. Next, a comparison is made of cardiac and visceral smooth muscle, demonstrating their functional interdependence and uncovering a mode of transmission link.

“Though the answer might not seem apparent, the problem should be clear.”
Discussion

Triggering source

There are two fundamental types of action potentials formed in visceral smooth muscle: spike potentials and action potentials with plateaus (Guyton, 1986). Spike potentials can be elicited by external stimuli such as an electrical stimulus, the action of hormones on the smooth muscle, or the action of transmitter substance from nerve fibers; or spontaneously by rhythmic, slow electrical waves inherent in the smooth muscle wall of the intestine.

The later is of particular interest in that the repolarization during a plateau is delayed for several hundred milliseconds to several seconds thus allowing for a prolonged contraction in some tubular smooth muscles such as those in the gut. During this period of slow wave repolarization, frequently called pacemaker waves, excitation spikes are more likely to occur. When these pacemaker waves are coupled with local stretching, as in the distended gut, spontaneous action potentials are often generated. Once the smooth muscle has been stimulated, an action potential spreads easily along adjoining muscle fibers by direct electrical conduction without the needed secretion of any transmitter substance.

Similar to the cardiac pacemaker cells that are located mainly in the sino-atrial node, the pacemaker cell networks in the gut are also regulated by the autonomic nervous system and maintain a number of ionic channel currents in the generation of their spontaneous activity (Satoh and Takaki, 2003). Though not the only factor involved, autonomic dysfunction can cause certain arrhythmias associated with pacemaker networks.

Initiated by the interstitial cells of Cajal (ICC), gastrointestinal pacemaker waves originate within the corpus region of the stomach spreading aborally toward the pyloric sphincter (Buist et al., 2006). By activating Ca\(^{2+}\) voltage-dependant channels in the smooth muscle, these depolarization waves are responsible for the excitation-contraction coupling normally found in gastric peristalsis. The slow wave is augmented in amplitude and duration with inward currents coming from the myenteric plexus. It can also be superimposed upon by further channel-induced action potentials over the plateau.

Non-invasive electrogastrogram (EGG) can be used to record time-dependent membrane potentials of gastric electrical or myoelectrical activity (GEA). Set from experimental data, it was shown that lower resting membrane potentials existed in regions with dense ICC networks (–73 mV rest, –32 mV peak) when compared to other membrane regions (–60 mV rest, –38 mV peak). This ensures a degree of electronic coupling even while in a resting state.

In addition to membrane potential, wave frequency is of major importance to normal peristaltic function. A frequency gradient exists down from the corpus curvature toward the pyloric sphincter, decreasing distally. With the highest normal generated frequency of 3 cycles per minute (cpm), the corpus region is dominant over the other membrane of the stomach. Any disruption to the frequency gradient can lead to gastric myoelectrical dysrhythmias and functional uncoupling. Dysrhythmias can occur as either high frequency waves of 4–9 cpm (tachygastrias) or low frequency waves of 0–2 cpm (bradygastrias) (Besherdas et al., 2001). Tachygastrias have been documented with absent antral contractions, whereas bradygastrias were found to could occur with either strong or absent antral contractions. Some disorders of
gastric dysrhythmias include: functional dyspepsia, nausea of pregnancy, and motion sickness.

Motion sickness has been induced in studies by increasing sympathetic activity with shock stimulus (avoidance method) and increasing parasympathetic activity using dive stimulus (forehead cooling) (Muth et al., 1999). Interbeat intervals (IBI’s) of the heart decreased greatly in response to sympathetic nervous system (SNS) stimulation, and IBI’s increased following parasympathetic nervous system (PNS) stimulation. Acute stresses can be responsible for evoking emotional arousal, subjectively ranked, and dysrythmic myoelectrical activity, most notably tachygastrias.

Gastric motility of the mid and distal stomach is governed by slow wave activity since any smooth muscle action potentials generated by excitation through distension and/or enteric neural activity are confined to the most depolarized phase of the slow wave (Huizinga, 2001). Therefore, the maximum frequency of the slow wave limits the functional frequency of peristaltic contractions. The generation of action potentials is regulated by the level of distension along with neural and hormonal inputs. However, the force of peristaltic contraction is determined by the degree of action potential generation on the plateau phase of the slow wave. It is the excitation level of the musculature that determines the threshold satisfaction for the generation of action potentials and whether to lengthen the slow wave plateau or duration.

Other factors such as stress, emotional arousal and exercise share a role in gastrointestinal function. In studies of response to stress using the mirror drawing test (MDT), in which the subject traces along the edge of a metal star reflected in a mirror, it has been shown that resting scores associated with depression had a negative linear correlation with respect to EGG frequency, while the anxiety scores demonstrated a positive linear relation with respect to EGG area power ratio (Homma, 2006). This research also showed that acute stress had a correlated effect on the GEA of visceral smooth muscle evidenced by EGG. In a different study of emotional stimuli on the GEA, there was a strong positive correlation (r=0.64) to subjective ratings of emotional arousal (Tranel and Vianna, 2006). Again another study showed that the peak amplitude of GEA could be enhanced when moderate-intensity exercise was performed alone, even with the suppressed vagal nerve activity of no meal (Kato et al., 2004).

Disruption of neural regulation could lead to functional uncoupling of the electromechanical physiology of the gut creating a condition known as a pseudo obstruction (Hubbard and Richardson, 1983). Reported as a non-mechanical condition predominantly affecting the large intestines, pseudo obstruction presents with similar symptoms to an actual physical blockage including colonic distensions and decreased motility. A more serious chronic form of idiopathic pseudo obstruction can be blamed on the impairment of the enteric nerves or enteric smooth muscle leading to dysfunctions (Bisset et al., 1992). Dysmotility of the antrum often presents with symptoms of nausea and vomiting. Tachygastrias and irregular frequencies are also common.

Within the gut exists a system of afferent nerve fibers responsible for conveying information to the central nervous system (CNS) about regulatory functions such as propulsion and emptying, and about conscious sensations like nausea and pain (Gebhart et al., 1999). These fibers are similar in function to the arterial baroreceptors in cardiovascular feedback system that help manage normal blood pressure (Olufsen et al., 2006). Responding to phasic gastric
distention-stretch associated with a constant volume peristaltic wave, mechanosensitive gastric vagal afferent fibers fire an initial burst of rate-dependent signals, followed by sustained response with or without fluctuations, then finally pause in a resting state. While in the resting state they continue to fire spontaneous impulses but only at a nominal rate until another stimulus is applied from distention. Residing in the viscera, the gastric afferent fibers terminate in longitudinal and circular muscle layers located within the stomach and duodenum then link into the myenteric plexus, mucosa, and sub-mucosa. In studies on a rat when a balloon was inflated inside the stomach, the afferent fibers produced bursts of activity that correlated with the magnitude of the distending pressure.

The effects and symptoms associated with distention on the stomach vary with location (Hasler et al., 1998). In the less-compliant distal region gastric mechanoreceptor activation is more evident and is where nausea and dysrhythmias usually originate. Although pain and bloating can be induced from distentions in the proximal stomach, they are more easily produced with smaller pressure in the distal region. The distal mechanoreceptors are more likely to disrupt slow wave propagation leading to dysrhythmias via non-5-hydroxytryptamine3 (non-5-HT3) serotonergic, non-prostaglandin-dependent, and noncholinergic pathways. The distal stomach is distinguished by the coordinated coupling of strong phasic contractions with the initiation of pacemaker slow waves.

The peristaltic process continues into the colon where intestinal motility is dependent on the colonic reflex, which is comprised of distention-sensitive mechanoreceptors of the antrum and nutrient-sensitive chemoreceptors located in the mucosa of the small intestines (Björnsson et al., 1998). The function of the colonic reflex involves gastrocolonic responses from antral distention and duodenal lipid perfusion. Local neural reflexes modulate the colonic motor function. Impairment of the colonic reflex system is often associated with slow-transit constipation and loss of both 5-HT3-dependent and independent function (Björnsson et al., 2002). Abnormal colonic motor function manifesting in slow-transit constipation stems from neuronal dysfunction and not a smooth muscle deficit.

In the proximal colon of the mouse two distinct pacemakers and frequencies have been observed (Takaki, 2003). Associated with the higher frequency pacemaker, circular muscle (CM) contractions move proximally from the pacemaker in an antiperistalsis manner. The antiperistalsis pacemaker activity is unregulated by the enteric nervous system. The lower frequency associated contractions combine longitudinal muscle (LM) and CM to move distally toward the anus. A synchronized system of excitatory junction potentials and inhibitory junction potentials ensures the coordinated contractions and inhibitions of the CM and LM as well as net aboral propulsion (Spencer et al., 2003).

Studies of the guinea pig distal colon have indicated LM can exhibit meandering trajectories, suggesting it possesses the characteristic for chaotic electrical activity (Spencer et al., 2002). Although action potential calcium waves spread across many LM cells, a sign they are coupled, electron microscopy studies reveal little evidence for functional gap junctional (cell-to-cell) coupling with the ICC at the myenteric plexus level.

Arrhythmias can develop from ectopic activity of an individual cell, slowly propagating into ectopic waves comprised of tens to hundreds of cells (Pumir et al., 2005). They can be triggered
in a variety of ionic molecular mechanisms. Hypothetically, there exist three factors involved in network behavior and the genesis of ectopic waves: automaticity, cell-to-cell coupling; and heterogeneity. Automaticity is the myocyte’s predisposition to initiate an action potential and exhibit pacemaker-like activity or rate of spontaneous cell depolarization. Cell-to-cell coupling refers to gap junction continuity. Heterogeneity refers to the non-uniform structure of interconnected cell types in a surrounding network.

For ectopic activity to progress, local ectopic waves are a necessary step.

Mode of transmission

In the previous section, the electrophysiology of visceral smooth muscle was explored. A comparison can be made pointing out commonalities between the gastrointestinal and cardiac electrophysiological systems, beginning with shared features of the visceral pacemakers and the SA-node of the heart. First, both have a characteristic automaticity to initiate spontaneous action potentials that are activated by Ca\(^{2+}\) sparks producing pendulum-type swings from depolarization to repolarization (Satoh, 2003). Also, both possess an inherent capability to exhibit chaos in the form of arrhythmias, easily occurring under conditions of calcium overload. Additionally, they are both innervated and regulated by the autonomic nervous system. With regard to characteristic function, it is conceivable that one electrophysiological system could have influence on that of the other if a feasible mode of transmission link were found to exist.

Pacemaker automaticity in smooth muscle cells is a complex function involving the activation of ionic currents such as the Ca\(^{2+}\)-dependent K\(^+\) channels and Ca\(^{2+}\)-activated Cl\(^-\) channels for its polarization swings. The membrane must depolarize beyond threshold potential within the proper period for a spontaneous action potential to be generated. A number of time-dependent currents control the rate and duration of the pacemaker activity. In the heart this process results in heartbeat, whereas in the gut it produces motility. In gastrointestinal pacemakers, however, Ca\(^{2+}\) release comes from IP\(_3\)-dependent stores which are sensitive to signaling by autonomic neurotransmitters.

A predisposition for dysrhythmias to occur in smooth muscle has been well documented. In a study of ectopic surface in the heart, it has been reported that gap-junction uncoupling led to contained ectopic waves that, when cell-to-cell coupling returned, exited at multiple sites creating disorganized patterns and arrhythmias (Arutunyan et al., 2003). Likewise, when an intestinal obstruction occurs, gross distention can halt gastric contractility, then propagating into a chaotic electrogastrogram (Gerring and King, 1989). This effect can be reversed immediately upon decompression of the stomach. From surgical observations, nearly simultaneous contractions and distentions have been noted both proximally and distally to an obstruction resulting in abnormal motility complexes (Condon et al., 1980). Dysrhythmias in either the heart or the gut can result from functional uncoupling and then develop into ectopic behavior.

The autonomic nervous system (ANS), consisting of sympathetic and parasympathetic divisions, is responsible for governing the involuntary actions associated with cardiac and visceral smooth muscle. Whereas the sympathetic division can increase heart rate in the cardiovascular system, it decreases motility in the gastrointestinal system (Axelrod et al., 2006).
The parasympathetic division has just the opposite effect of decreasing heart rate while increasing motility. A number of functional gastrointestinal disorders presenting with abnormal motility or visceral hyperalgesia are produced by the ANS through the brain-gut axis. Other autonomic disorders known as hereditary sensory and autonomic neuropathies (HSAN) involve the peripheral and central autonomic networks (CAN). One such CAN, stemming from the insular and medial prefrontal cortices, is the high-order autonomic control, which takes input from gastric mechanoreceptors, arterial chemoreceptors, and baroreceptors. Interestingly, its HSAN clinical manifestation is cardiac arrhythmia, thus establishing a mode of transmission link.

Essential for survival, the CAN makes up an integral brain-controlled component of the ANS (Benarroch, 1993). It is comprised of the insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus of the tractus solitarius, and the ventrolateral medulla. Its structures are linked through reciprocal interconnections, parallel organization, state-dependent activity, and neurochemical complexity. The CAN manages multiple inputs including viscerosensory signals from the gut and responds through mixed neuronal populations of the paraventricular and other hypothalamic nuclei to control specific subsets of preganglionic sympathetic and parasympathetic neurons. Many autonomic disorders are associated with the CAN including high-order, hypothalamic, and medullary controls.

A clinical indicator of ANS performance can be observed utilizing the transfer function analysis of the heart rate variability (HRV) and respiration. In addition, by studying respiratory sinus arrhythmia (RSA) together with EGG, a correlation between myoelectrical activity of the gut and the ANS is further demonstrated (Chen et al., 2004). It was shown that following the ingestion of 500 ml water there was linearity between HRV and EGG power. An explanation for this is that while fasting motor activity is modulated by the enteric nervous system, the fed state vagal nervous activity contributes to phasic motility and reflects vagal influence on the heart. By observing these subtle changes with this technique, a useful method of understanding neuropathies of the ANS is made available.

There are a number of autonomic disorders that have presented themselves in varying degrees of orthostatic intolerance (Grubb, 2005). Among them is a reflex-type disorder known as neurocardiogenic syncope (NS), formerly called vasovagal syncope. It manifests itself by a loss of the body’s ability to maintain homeostasis due to a drop in cardiac stroke volume during sudden standing. Although the cause of NS is not clear, it has been theorized to be related to prolonged orthostatic stress, marked by increased peripheral venous pooling. When this occurs, the venous return to the heart drops precipitously to the point of ventricular inotropy leading to a hypercontractile state, thus, paradoxically, activating mechanoreceptors mimicking the condition of hypertension. The medulla reacts to the sudden influx of neural signals by inhibiting sympathetic activity thereby inducing hypotension and syncope. Though the ANS appears functionally adequate in these patients, it could be insufficient to support proper vascular tone in certain circumstances.

A different subgroup of orthostatic hypotension is referred to as postural tachycardia syndrome (POTS), characterized by tachycardia associated in the upright position. The more commonly seen of this syndrome is the peripheral (partial) dysautonomic form. Symptoms
include: heart rates of 160 bpm or greater while standing, complaints of severe fatigue, exercise intolerance, light headedness, dizziness, palpitations, and near syncope. A second less common form of the POTS syndrome is referred to as “central” or “β-hypersensitivity”. Symptoms of this form include simultaneous orthostatic hypertension together with tachycardia. The cause of this central form is believed to be from an inadequate feedback process above the level of the baroreflex. Due to its onset, POTS has been reported to be an early indication of autonomic dysfunction.

Positive stimulation to the parasympathetic nervous system has long been known to have a vasovagal effect on the heart. The relationship between esophageal dysfunction (dysmotility) and cardiopulmonary responses with “near miss” sudden infant death (SIDS) symptoms has also been associated with neurological function (Cambell et al., 1981). Other viscera and somatic triggering sites have been indicated including the larynx, pharynx, and of particular interest, the intestines. The pathway for the vasovagal response begins with stimulation to the mechanoreceptors, sending bursts of signals from numerous afferent fibers into the mid-brain reflex centers where they are modified by high-brain centers before being redirected to the heart. The effects of esophageal dysfunction can be complicated in premature infants because of an underdeveloped high-brain function that is sometimes incapable of moderating excessive outbursts of afferent input to the brainstem.

To emphasize and mark the routes involved in gastrointestinal innervation, a study of Scrapie is presented, though no other implications are made. ANS transmission of Scrapie, a degenerative encephalopathy usually associated in sheep, uses synaptically linked autonomic ganglia via the enteric nervous system (ENS) and vagus and splanchnic nerves to target sites in the brain and spinal cord (Beekes et al., 2001). The most likely portal of natural entry for Scrapie and other transmissible spongiform encephalopathy infections is through the gastrointestinal tract via the food chain. Once inside the intestines, Scrapie moves through the ENS then through the PNS using autonomic ganglia and efferent fibers along the vagus and splanchnic nerves until eventually infecting the CNS, notably the hindbrain and spinal cord. The spread continues to move cranially and caudally as it progresses along the neural pathways.

**Process Summation**

A set of linking characteristic behaviors is proposed to help explain the causes that can lead to the onset of cardiac arrhythmia in certain susceptible subjects. First, two givens should be assumed: 1) the subject has a propensity for cardiac arrhythmia in some form, paroxysmal or otherwise; 2) the cardiac arrhythmias follow some gastrointestinal stimulation, such as after a meal or from emotional stress.

It is thought that the triggering process begins in the gut with the halting of a peristaltic wave contraction. This could be the result of either a slow-moving bolus creating gross distention or by a neural disruption attributable to external stress. Following the functional uncoupling of the wave, the automaticity of ectopic behavior can propagate into dysrhythmic activity.

The origination of the uncoupling is presumed not to be from the stomach since
dysrhythmias in the antral region would also be complicated by nausea or vomiting, generally unassociated in this case. A more likely point for uncoupling to occur is in network with colonic longitudinal smooth muscle which has been shown to exhibit a propensity for meandering trajectories and chaotic behavior.

Once dysrhythmias in the colon have been initiated, distention increases, causing more stretching of the mechanoreceptors. The initial autonomic response is to increase peristaltic activity by stimulating adjacent visceral smooth muscle. Paradoxically however, due to the current state of uncoupling, the additional stimulation only evokes further widespread distentions, deluging the afferent pathways with multiple bursts of signals.

It is theorized next that the CAN mismanages its reaction to the sudden increase in afferent activity in one of the following ways. Responding to an apparently overactive bowel, the CAN mediates by quickly inhibiting parasympathetic stimulation and tone, considered normally strong in the gut. It is suggested that the command to decrease parasympathetic activity might be shared along another pathway linking it with the heart. Though parasympathetic control functions are usually quite specific, they sometimes ally together. For example, though capable of independent production, salivary and gastric secretions are often produced concertedly. Also, bladder and rectum emptying can occur independently or be simultaneously initiated.

Another possibility suggests that a crossover mechanism of the high-order autonomic control might allow for overriding during a crisis situation. Some higher control centers in the brain such as the hypothalamus can activate lower brain stem areas like the medullary cardiovascular control center acting as a relay in influencing the heart. Although the moderation function of the CAN is not fully understood, its role in mismanaging a response has been demonstrated by its inherent perturbations, dependencies and dysfunctions. Regardless of the method, a marked decrease of parasympathetic tone on the heart can quickly precipitate into an arrhythmia in the cardiac-sensitive subject.

References


