Gut peristalsis is governed by a multitude of cooperating mechanisms

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Huizinga JD, Lammers WJ. Gut peristalsis is governed by a multitude of cooperating mechanisms. Am J Physiol Gastrointest Liver Physiol 296: G1–G8, 2009. First published November 6, 2008; doi:10.1152/ajpgi.90380.2008.—Peristaltic motor activity of the gut is an essential activity to sustain life. In each gut organ, a multitude of overlapping mechanisms has developed to acquire the ability of coordinated contractile activity under a variety of circumstances and in response to a variety of stimuli. The presence of several simultaneously operating control systems is a challenge for investigators who focus on the role of one particular control activity since it is often not possible to decipher which control systems are operating or dominant in a particular situation. A crucial advantage of multiple control systems is that gut motility control can withstand injury to one or more of its components. Our efforts to increase understanding of control mechanism are not helped by recent attempts to eliminate proven control systems such as interstitial cells of Cajal (ICC) as pacemaker cells, or intrinsic sensory neurons, nor does it help to view peristalsis as a simple reflex. This review focuses on the role of ICC as slow-wave pacemaker cells and places ICC into the context of other control mechanisms, including control systems intrinsic to smooth muscle cells. It also addresses some areas of controversy related to the origin and propagation of pacemaker activity. The urge to simplify may have its roots in the wish to see the gut as a consequence of a single perfect design experiment whereas in reality the control mechanisms of the gut are the messy result of adaptive changes over millions of years that have created complementary and overlapping control systems. All these systems together reliably perform the task of moving and mixing gut content to provide us with essential nutrients.

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Complexity in Gut Motor Control

The motor activity of the gastrointestinal tract is critical for life. Absence of motor activity is one of the leading indications for bowel transplantation to prevent death (21). From an evolutionary point of view, it is therefore understandable that several different and overlapping mechanisms have developed to achieve mixing and propagating motor activities. For example, peristalsis of the esophagus is directed by the swallowing center in the brain, but cutting the vagus evokes immediately alternate ways of peristaltic movement: enteric neural mechanisms, including control systems intrinsic to smooth muscle cells. It also addresses some areas of controversy related to the origin and propagation of pacemaker activity. The urge to simplify may have its roots in the wish to see the gut as a consequence of a single perfect design experiment whereas in reality the control mechanisms of the gut are the messy result of adaptive changes over millions of years that have created complementary and overlapping control systems. All these systems together reliably perform the task of moving and mixing gut content to provide us with essential nutrients.

tems but rather, depending on specific stimuli, of varying domination of one or more of the control activities. Some investigators deem it advantageous to propose simplified schemes. In a recent review by Sarna (61), ICC as pacemaker cells were dismissed despite the presence of a large body of evidence to the contrary. In a recent review by Wood (76), extrinsic sensory nerves and intrinsic motor nerves were held to be responsible for the orchestration of all motor patterns in the gut. Although simplicity is advisable when creating hypotheses related to uncharted territory, is it questionable whether simplicity is advisable when scientific evidence points to complexity. The quest to keep things simple may have its root in the idea expressed by Wood that natural selection is conservative and parsimonious. In other words, why design a complex system when a simple system will do? However, control mechanisms of intestinal motor activity have not been designed from scratch but have developed over time by adding supplementary control systems to existing ones as a fitness advantage for the species. Fitness, not parsimony, is the dominant factor in natural evolution (26, 32). Nature has found complex but successful solutions to problems with the nonparsimonious result being due to both evolutionary history and a fitness advantage (32). Francis Crick wrote in his book What Mad Pursuit: ‘‘While Ockham’s razor is a useful tool in the physical sciences, it can be a very dangerous implement in
biology. It is thus very rash to use simplicity and elegance as a guide in biological research” (11). We have no choice but to embrace complexity. Complexity is a perfect word in this context since it comes from the Latin word *complexus*, which signifies entwined or “twisted together.” The different control systems of motility are unique but interconnected; evolution through natural selection has increased internal variety of control systems or functional differentiation, which leads to a higher level of control (26). Multiple overlapping systems have the obvious advantage that injury to any one system will not automatically lead to intestinal paralysis, which would lead to death. When the presence of multiple mechanisms is discussed, the term “redundant” is often used. Sometimes it is used to suggest irrelevance (76). It appears to us that it should not be used in this way, since we still have only rudimentary knowledge of the various control mechanisms. The word can also have a strong positive connotation. Denis Noble (53) used “redundancy” with a positive connotation when he pointed out the various control mechanisms that govern cardiac rhythmicity; he equated the redundancy of mechanisms with the robustness of the system; this is consistent with the thesis of this review.

**Peristaltic Motor Patterns**

Peristalsis is defined in the present review as gastrointestinal motor patterns involving partial or total occlusion of the lumen that move content in the anal direction, thereby in many conditions also providing a strong mixing function. This is also the use of the word in most physiology textbooks, where the words peristalsis and peristaltic waves or peristaltic contractions are interchangeably used, without the assumption that there is only one mechanism underlying the phenomenon. The peristaltic reflex, on the other hand, as defined by Bayliss and Starling (2), is only one specific form of peristalsis, orchestrated by the enteric nervous system in response to a bolus where contraction is evoked oral to the bolus and relaxation is observed anal to the bolus. This reflex has been studied extensively experimentally (10), and directional neural pathways (ascending excitatory reflexes that evoke contractions above a bolus; descending inhibitory reflexes which cause relaxations below) to elicit this response have been firmly established. However, in the human gut, most motor activity is not evoked by a bolus and even local distention does not necessarily elicit this reflex (66). In fact, the “Bayliss and Starling reflex” may not happen often in vivo (66, 75). One example in which the reflex is demonstrable is pellet propulsion in the colon of the guinea pig. Spencer et al. (67) showed that maintained circumferential stretch activated oral excitatory junction potentials and anal inhibitory junction potentials in an ongoing synchronous manner. Hence a hard-wired enteric neural circuitry is in place to cause fecal pellet propulsion. Under most conditions in the stomach, small intestine, and proximal colon there is generally no local stimulation but rather distention of a large section of the organ due to a watery mass of content. Unfortunately, in many studies or physiological essays, the mechanism underlying the “peristaltic reflex” is thought to apply to many more peristaltic activities than is justified and hence has hampered our study and understanding of most peristaltic motor activities.

All peristaltic movements involve contraction of the circular muscle layer, accomplished by means of influx of calcium into smooth muscle cells through voltage-sensitive calcium channels and calcium release from intracellular stores. In most in vitro experiments, gut muscle contraction is to a large extent served by calcium influx (blocked by L-type calcium channel blockers), likely also in vivo. Hence muscle depolarization to allow calcium channels to open is the trigger for substantial contractile activity. First, ICC provide rhythmic depolarization of most gut musculature, bringing the muscle cells periodically close to threshold for influx of calcium. The three main manners in which further depolarization can be evoked to bring the membrane potential above threshold for calcium influx and hence contraction are muscle distension, excitatory neurotransmission, or inhibition of inhibitory neurotransmission. Distention, or stretch of smooth muscle, can cause direct muscle depolarization (7) mediated by stretch-sensitive ion channels (33, 70), which can bring the membrane potential of the plateau phase of the slow wave above threshold for activation of L-type calcium channels, leading to rhythmic contractions at the slow-wave frequency. Distention also causes activation of intrinsic and extrinsic sensory nerves and subsequently activation of motor neurons.

Propagation of contractions that are governed by slow-wave pacemaker activity is due to the propagating slow wave: slow waves actively spread into more distal neighboring cells and force each subsequent cell to oscillate at this frequency, a mechanism similar in principle to the nonneural pumping contractile activity of the heart. Striking motor patterns that are dominated by slow-wave pacemaker activity are the peristaltic contractions of the antrum and duodenum (Fig. 1). Propulsive contractions at the frequency of the gastric slow-wave pacemaker sweep onto the pylorus; some content may escape into the duodenum and the rest is pushed back. This is an example of peristaltic contractile activity that will move content in anal direction and has a strong mixing function as well. The pylorus does not have slow-wave activity and thereby provides an electrical barrier between the pacemaker systems of the stomach and duodenum (39, 73). Once food enters the duodenum the distention causes motor activity that consists of peristaltic contractions at the duodenal slow-wave pacemaker frequency (Fig. 1). Although distention can cause peristaltic activity without help of neural excitation, under most circumstances the enteric nervous system will provide excitation of the musculature that is related to the force of contraction.

Another example of collaborating control systems is the fasting intestinal motor activity. The so-called migrating motor complex (MMC) is a band of intrinsic neural excitation that travels slowly across the stomach and intestine. During this activity, a section of the gut is tonically excited and within this section of the musculature, slow wave-driven peristalsis takes place (23). Or, as Furness (19) writes, the MMC is “a migrating cluster that consists of rapidly moving slow wave-associated contractions that form a slowly moving complex.” Hence there are two levels of rhythmicity and propagation: the band of excitation propagates slowly along the intestine orchestrated by a pattern generator in the enteric nervous system that causes sequential activation of sections of the organ in anal direction (60, 64), and within the section that is excited slow wave-driven propulsive motor activity takes place (23). This is a
case in which several control systems are collaborating but are still easily distinguishable. Of course, under normal conditions, vagal and hormonal control systems may influence the MMC (24).

In addition to slow wave-driven peristalsis, peristaltic motor activity can be generated by pattern generators in the central nervous system (notably esophageal peristalsis) and the enteric nervous system can generate peristalsis independent of the slow-wave pacemaker system (6, 19). This can occur through evoking the classical reflex (14) or by pattern generators in the enteric nervous system that cause for example the mass movements in the colon (61).

**Role of ICC in Peristalsis**

Several subtypes of ICC form networks that play a role in gastrointestinal motor control. The search for understanding the role of pacemaking activity and the role of ICC in control of motor activity is not a journey into finding yet another singular mechanism that governs it all. Rather, it is a fascinating discovery of how ICC are integrated with other systems to optimally mix and transport intestinal content. Overwhelming evidence has shown the ICC to be the origin of slow-wave pacemaker activity. Structural evidence created the hypothesis (18, 71), dissection experiments on the colon indicated a relationship between presence of ICC and slow-wave activity (4, 15, 65), observation in mutant animals without ICC pacemaker cells confirmed this (30, 74), and, finally, direct evidence was obtained in the mouse small intestine (13, 31, 69).

The statement by Sarna (61) that “ICC may not pace the slow waves or help in their propagation” was in part made because smooth muscle cells can show electrical oscillatory activity without ICC. Some investigators are then inclined to conclude that ICC are not needed; the fact that functional electrical oscillatory activity can be present in the absence of the primary pacemaker cells (28, 29) is a manifestation of the presence of multiple mechanisms to mix and propel food through the gastrointestinal tract and not evidence for lack of a pacemaker role for ICC. No one would argue that the sinoatrial node is irrelevant simply because the heart is still beating and functioning without it. It is clear that peristalsis is so important that several complementary and cooperating mechanisms are in place. When ICC are damaged or absent, or in response to specific stimuli, other control systems will become dominant such as pattern generators in the enteric nervous system (14, 67) and/or control systems intrinsic to smooth muscle cells.

Mutant animals that lack specific ICC subtypes in various organs (59) have been used extensively to gain insight into the role of ICC in gut motor control. When studying these mutant animals it is important to accept the possibility that during the development of the musculature in the absence of pacemaker activity, the smooth muscle cells have adapted and gained new properties. This is relevant for the interpretation of in vivo and in vitro studies on these mutant rodents but has not been carefully studied yet. It is also evident that smooth muscle cells themselves have latent pacemaker activity. When pacemaker cells are removed from the colon, the tissue becomes quiescent

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**Fig. 1.** A: spatiotemporal mapping of motility in vivo. A “map” constructed from a video recording of barium-enriched content of the stomach and duodenum from the mouse. The short arrow lies over a propagating wave of a lumen occlusion in the stomach (white because the barium has been squeezed out); the long arrow lies over a similar wave in the small intestine. The marked rhythmicity of gastric and duodenal slow wave-driven peristalsis is convincingly displayed in such maps. The frequency and propagating velocity of these waves are identical to those of the slow wave in stomach and intestine. The arrowhead points to the pylorus that can be seen to alternately close and open. The y-axis represents time in seconds and the x-axis represents distance in centimeters. From Ref. 12. B: simultaneous recording of slow waves plus action potentials, intraluminal pressure changes, and outflow of content in a segment of the mouse small intestine. The first 3 recordings are simultaneously recorded electrical activity obtained by using extracellular electrodes showing slow waves with superimposed action potentials, recorded 1 cm apart. The next trace and the bottom trace are intraluminal pressure recordings that are measured directly underneath the electrical recordings. Between the pressure recordings, a square represents a visually observed outflow that occurred in a pulsatile manner, consistent with visually observed aboral propagation of ring contractions. This particular recording was obtained in the presence of TTX, indicating that the activities observed can occur through myogenic mechanisms. Lines indicate propagation at a velocity of 0.5 cm/s. Note that the time scale changes in the middle of the figure. From Ref. 29.
but an appropriate stimulus can evoke peristaltic oscillatory activity in the remaining musculature (15, 48). In mutant mice without pacemaker ICC, slow-wave activity is absent in vitro, demonstrating the ICC to be the primary pacemaker cells (30, 74). Isolated smooth muscle cells do not generate pacemaker activity, ICC do (31, 69). In the gastropyloroduodenal region, there is continuity of the musculature and discontinuity of the ICC pacemaker cell network, perfectly demonstrating that the ICC network hosts the dominant pacemaker system; this allows for completely independent pacemaker systems in stomach and duodenum (73) (Fig. 1). In the absence of the primary pacemaker control system, in vivo, the enteric nerves and smooth muscle cells and/or secondary ICC networks can work together to create rhythmic electrical and motor activities (25, 27–29), indicating the emergence of backup systems that can orchestrate propulsive motor patterns in the absence of the primary pacemaker cells. It is intriguing that several properties of the primary and secondary pacemaker systems are similar. This is true for the propagation velocities of esophageal peristalsis (55) and for the rhythmic contractions in the colon (48) and intestine (29). The fact that the output of motor activities due to different pacemaker systems is often similar makes for smooth and efficient cooperation. But for the investigator it may be a problem since it is often not possible to discover which control systems are operating or dominant at any given time under physiological conditions in vivo.

When slow waves are initiated in the ICC network, they actively propagate into the muscle layers (1, 49, 56). In some tissues, but not all, a reduction in slow-wave amplitude away from the site of slow-wave initiation can be observed that is due to changes in resting membrane potential (49), not evidence of passive propagation (65). The membrane potential gradient is thought to be due to gradients in ion channel properties and/or carbon monoxide (20). Active propagation indicates that smooth muscle cells have all the ion channels to regenerate a slow wave upon depolarization (52) and consequently phasic contractile activity (5). But smooth muscle cells do not have the robust mechanism to evoke slow waves spontaneously, a mechanism that is present in the ICC. Smooth muscle cells just need a trigger to get a type of slow wave going. This can be the ICC pacemaker system, or it can be sustained depolarization by cholinergic neurotransmitters, but the exact mechanism(s) of latent pacemaker activity in smooth muscle are still to be elucidated.

The Nature of Slow-Wave Propagation

An excellent technique to examine slow-wave propagation is the measurement of the electrical activity of an organ with an array of electrodes. This technique has as one of its major strengths that it can accurately determine direction and velocity of propagation. Using this technique one can witness a propagating slow wave traveling along the intestine, and one sees a front of depolarization occurring near simultaneously around the circumference and propagating relatively slowly in the anal direction (Fig. 2A). This has been measured in the small intestine of the rabbit (35), the cat (36), and the dog (44). This was recently also beautifully demonstrated by the measurement of intracellular calcium (54). A wave front of pacemaker activity could be reconstructed by locating Ca²⁺ transients in the myenteric ICC network occurring nearly simultaneously circumferentially and propagating analy at the same frequency as the propagation of slow waves (54). This refers to a propagating slow wave. When the focus is on an area where pacemaker activity is originating, then slow-wave propagation occurs with a similar velocity in all directions (42) (Fig. 2A). And so do calcium transients (54). The network of ICC is the cellular structure that allows this to happen. Upon initiation, the slow waves propagate in all directions with a similar velocity; the ICC network has the structural requirements to accomplish this but not the muscle layers. This can be demonstrated by studying the propagation of action potentials. When action potentials are initiated in the musculature they propagate much faster along the length of their cells (Fig. 2B) (42), consistent with the physical characteristics of the musculature. Calcium waves associated with contractions show the same propagation characteristics (68). Measurement of slow-wave propagation and action potential propagation simultaneously supports the notion that these two activities occur in different cellular structures (37).

It is often stated in general terms that slow-wave propagation in the circumferential direction is fast. Sarna (61) pointed out that slow waves propagate much faster in the circumferential vs. longitudinal direction and that this was incompatible with slow-wave initiation and propagation in the ICC network. Two studies were put forward to provide evidence for this state- ment. One was the study of Edwards and Hirst (16) who actually measured identical propagation velocities in all directions in the ICC network; the notion of faster propagation in the circumferential direction in this paper was based on measurements in the musculature (see below). The other study (62) used multiple recording electrodes on the dog stomach. No evidence was presented of true propagation pathways in the circumferential direction, other than the statement that transversely the direction of the phase lag depended on the relative positions of the electrodes. Several studies have recorded the arrival times of a slow wave at two electrodes located parallel to the circumference of the intestine and observed that the time difference between the two sites is minimal, which indicates nearly identical activation times but is sometimes interpreted as fast conduction velocity. However, there is actually no propagation in the circumferential direction outside the region where the slow wave is initiated, as shown in Fig. 2A (42). In a study on the stomach (16), slow waves propagated at 3.5 mm/s in all directions in the ICC network associated with Auerbach’s plexus. When an anally propagating slow wave was followed, it appeared that the propagation velocity in the circumferential direction was much higher (up to 36 mm/s), and it was shown that intramuscular ICC facilitated circumferential conduction. An alternative or supplementary explanation is that the slow wave propagates as a wave front of depolarization in the ICC-network, exciting one ICC after the other as depicted in Figs. 2 and 3. The idea that slow waves can only propagate over a short distance (59) is not correct. The ICC network is continuous in an organ and slow waves can propagate over the whole length of the organ (38, 63). After a meal, distention (63) or specific content (22) may cause the emergence of ectopic pacemaker activity. This ectopic slow wave will then collide against the normal aborally propagating slow wave, thereby interrupting its normal propagation (44). Slow-wave propagation can also be demonstrated by calcium imaging. The initiation of the slow wave in ICC, that is, the activation of the...
Fig. 2. Slow waves and action potentials (spikes) have different propagation characteristics because they travel in different cellular structures. A, left: propagation map and individual recordings of electrical activity from an area in the cat small intestine where the slow wave was initiated. First activity was detected at electrode 6 ($t = 0$) and propagated initially in a uniform manner in all directions, longitudinally and circumferentially. This is also shown in the accompanying diagram. Note that a few centimeters away from the pacemaker, the propagating wave fronts have organized themselves into circumferential rings of excitation (open arrows). Away from the pacemaker region, propagation of the slow wave occurs in the longitudinal direction, not in the circumferential direction. The situation is different in B, where the initiation and limited propagation of an action potential are presented. From the initial site of activity (at electrode 6, different experiment), conduction was rapid and reached further in the longitudinal direction than in the circumferential direction. After 200–250 ms, action potential propagation stopped, thereby exciting a relatively small area, termed a patch. Please note: isochrones in A every 250 ms; isochrones in B every 50 ms. Modified from Ref. 42.
ion channels that generate the start of the slow-wave upstroke is associated with the rhythmic release of calcium from the sarcoplasmic reticulum. Part of the subsequent upstroke is associated with influx of calcium through a non-L-type calcium channel (17, 51, 58), likely a voltage-activated T-type calcium channel (17, 45). When the electrical slow wave is evoked, it will propagate actively, that is to say regeneratively as an electrical event. The depolarization received by consecutive ICC in the propagation process will activate the T-type calcium channels causing calcium influx. Hence a wave of action potentials (spikes) can be measured. Action potentials follow the slow wave in time. An action potential that follows the slow wave excites a limited area described as a “spike patch” (Fig. 2B). Action potentials vary in number and intensity, which is associated with the degree of force of contraction. The propagation characteristics of action potentials are very different from those of slow waves. Action potentials in a patch (within the depolarized part of the slow wave) can propagate in any direction over the limited area of depolarization (34). A propagating slow wave can be associated with varying numbers of action potentials; it all depends on the depolarization experienced by the musculature while the slow wave is propagating over it. The contractions associated with this type of action potential generation are the slow wave-driven peristaltic contractions that can be very brief (resulting in mixing primarily) or long (resulting in propulsion of content when the force of contraction is strong enough to occlude the lumen). Video analysis of in vivo recorded slow wave-driven peristalsis in the stomach and small intestine show the rhythmicity of this motor pattern (Fig. 1). However, this is not the only manner by which action potentials can be generated to cause contraction. When electrical activity of the feline duodenum was measured with 240 electrodes, in addition to slow wave-associated action potentials, propagating waves of intense action potential generation were recorded that had no relationship to slow-wave activity (41). These contractions propagated orally or aborally. These were likely generated by a propagating band of excitation generated by the enteric nervous system and strong enough to depolarize the musculature to generate action potentials without the help of slow waves. In the colon, a peristaltic contraction wave often involves a propagating wave of contraction that last longer than a slow-wave cycle (46). For a period of time the whole colonic segment that was involved in the wave of contraction is tonically contracted. This was also observed in the rat ileum in vitro (3). These are examples where intense excitation by the enteric nervous systems overrules the propagating phasic slow wave. Another example is the occurrence of mass movements in the colon that are orchestrated by pattern generators in the enteric nervous system (47).

In summary, advancing our knowledge of control systems of gut motility does not require the creation of simplified models but it requires increased efforts to understand all the different

The Nature of Propagating Waves of Action Potentials and Contractions

When recordings are made with multiple electrodes on a segment of the small intestine, both slow waves and action potentials (spikes) can be measured. Action potentials follow the slow wave in time. An action potential that follows the slow wave excites a limited area described as a “spike patch” (Fig. 2B). Action potentials vary in number and intensity, which is associated with the degree of force of contraction. The propagation characteristics of action potentials are very different from those of slow waves. Action potentials in a patch (within the depolarized part of the slow wave) can propagate in any direction over the limited area of depolarization (34). A propagating slow wave can be associated with varying numbers of action potentials; it all depends on the depolarization experienced by the musculature while the slow wave is propagating over it. The contractions associated with this type of action potential generation are the slow wave-driven peristaltic contractions that can be very brief (resulting in mixing primarily) or long (resulting in propulsion of content when the force of contraction is strong enough to occlude the lumen). Video analysis of in vivo recorded slow wave-driven peristalsis in the stomach and small intestine show the rhythmicity of this motor pattern (Fig. 1). However, this is not the only manner by which action potentials can be generated to cause contraction. When electrical activity of the feline duodenum was measured with 240 electrodes, in addition to slow wave-associated action potentials, propagating waves of intense action potential generation were recorded that had no relationship to slow-wave activity (41). These contractions propagated orally or aborally. These were likely generated by a propagating band of excitation generated by the enteric nervous system and strong enough to depolarize the musculature to generate action potentials without the help of slow waves. In the colon, a peristaltic contraction wave often involves a propagating wave of contraction that last longer than a slow-wave cycle (46). For a period of time the whole colonic segment that was involved in the wave of contraction is tonically contracted. This was also observed in the rat ileum in vitro (3). These are examples where intense excitation by the enteric nervous systems overrules the propagating phasic slow wave. Another example is the occurrence of mass movements in the colon that are orchestrated by pattern generators in the enteric nervous system (47).
components separately and in combination. Advanced imaging techniques (45); advanced motor assessments in vivo (46, 73); advanced molecular techniques (50); detailed electrophysiology employed in vivo (43), in vitro (59), and in situ (72); and the creation of all encompassing models will create the enthusiasm and creativity needed to solve the fascinating control mechanisms of gastrointestinal motor activity and provide solutions for the dramatic presence of motility disorders.

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