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Invited Review

Recent advances in intestinal smooth muscle research: from muscle strips and single cells, via ICC networks to whole organ physiology and assessment of human gut motor dysfunction

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Abstract

Gastrointestinal smooth muscle research has evolved from studies on muscle strips to spatiotemporal mapping of whole organ motor and electrical activities. Decades of research on single muscle cells and small sections of isolated musculature from animal models has given us the groundwork for interpretation of human *in vivo* studies. Human gut motility studies have dramatically improved by high-resolution manometry and high-resolution electrophysiology. The details that emerge from spatiotemporal mapping of high-resolution data are now of such quality that hypotheses can be generated as to the physiology (in healthy subjects) and pathophysiology (in patients) of gastrointestinal (dys) motility. Such interpretation demands understanding of the musculature as a super-network of excitable cells (neurons, smooth muscle cells, other accessory cells) and oscillatory cells (the pacemaker interstitial cells of Cajal), for which mathematical modeling becomes essential. The developing deeper understanding of gastrointestinal motility will bring us soon to a level of precision in diagnosis of dysfunction that is far beyond what is currently available.

Key words: gastrointestinal motility, spatiotemporal mapping, high-resolution manometry, interstitial cells of Cajal, dysmotility

Introduction

This review is based on the keynote address given at the 61st annual Japanese Smooth Muscle Research Society meeting in Nagoya, Japan, organized by Professor Shinsuke Nakayama, and is focussed on the author's own research on the small intestine and colon. It highlights the theme of the conference which was the promotion of collaboration between clinicians and basic scientists. Smooth muscle cell research has focussed for a long time on properties of single cells or muscle strips, and changes evoked by neural activity *in vitro*.

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Communication with clinicians was hampered in part because it was not always easy to extrapolate such findings to whole organ physiology or pathophysiology let alone *in vivo* activities in the human intestine or colon. Two recent advances in smooth muscle motility research are facilitating such communication, spatiotemporal mapping and high-resolution manometry.

Spatiotemporal Mapping

Spatiotemporal mapping refers here to the detailed assessment of motility via video recording of whole organ activity or digital assessment of electrical activities via hundreds of electrodes at the same time or analysis of high-resolution manometry data from the human gut using closely spaced sensors.

Video recording that captures all the nuances of motility are converted to grayscale or color maps usually focused on changes in diameter [called diameter maps or Dmaps]. Diameter changes can show strength of the contraction underlying the diameter change, it can show propagation direction and velocity, segmentation motor patterns, duration of contraction and frequency of contraction patterns (1). Diameter maps are shown as images, with, usually, time running horizontally and distance along the intestine running vertically from proximal (top) to distal (bottom). The intensity of the Dmap is the width ("diameter") of the intestine usually from black (contracted) to white (relaxed), or colour coded. Three-dimensional representation of Dmaps gives deep insight into the characteristics of the motor patterns (2). Diameter changes focus on circular muscle, appropriate since it is the circular muscle layer that is primarily responsible for propulsive and segmenting contractions although longitudinal muscle contraction can be assessed as well for pendular contractions (3). Diameter maps can be combined with intraluminal pressure recordings, primarily in animal models, so that better insight can be obtained into what motor patterns are actually generating intraluminal pressure changes. A good example is the origin of "simultaneous pressure waves". No doubt, intraluminal pressure can be generated by many different mechanisms. It can be generated by a simultaneous contraction of large sections of the circular muscle layer, but I doubt that this is common; in that case, the term "wave" would be irrelevant. Pressure can also be generated by contractions that create a pulse pressure wave that has high velocity as this happens in the aorta (4). Importantly, we showed in the rabbit colon that a common origin of simultaneous pressure waves is a cluster of fast propagating circular muscle contractions (5); this, no doubt, happens in the human colon (6, 7). With respect to electrical activity, the recording with arrays of closely spaced electrodes offers the possibility of assessing slow wave origin and spread (8), natural properties of ICC networks, natural and abnormal dysrhythmia's: "When rhythm is the theme and puzzlement the paramount consideration, let the topic be 'dysrhythmic dilemmas'(9)".

Spatiotemporal pressure maps obtained by high resolution manometry can provide data on motility direction (i.e., stationary, peristaltic, antiperistaltic), velocity, duration, frequency and strength of contractile motility patterns (Fig. 1). Because large sections of the organ in vivo are assessed at the same time, one can analyze interaction or simultaneous development of different motility patterns in different regions of the organ (Fig. 1) (10). The understanding of such interactions may be crucial in the evaluation of motor dysfunction.

The Gastrointestinal Musculature as a Super Network

One of the most exciting aspects of spatiotemporal mapping of whole organ activity is that one obtains an overview of mechanical or electrical activity of the entire organ at the same time and one can monitor whole organ changes over time. When studying slow wave (ICC-pacemaker) driven motor patterns (11–13) or the slow

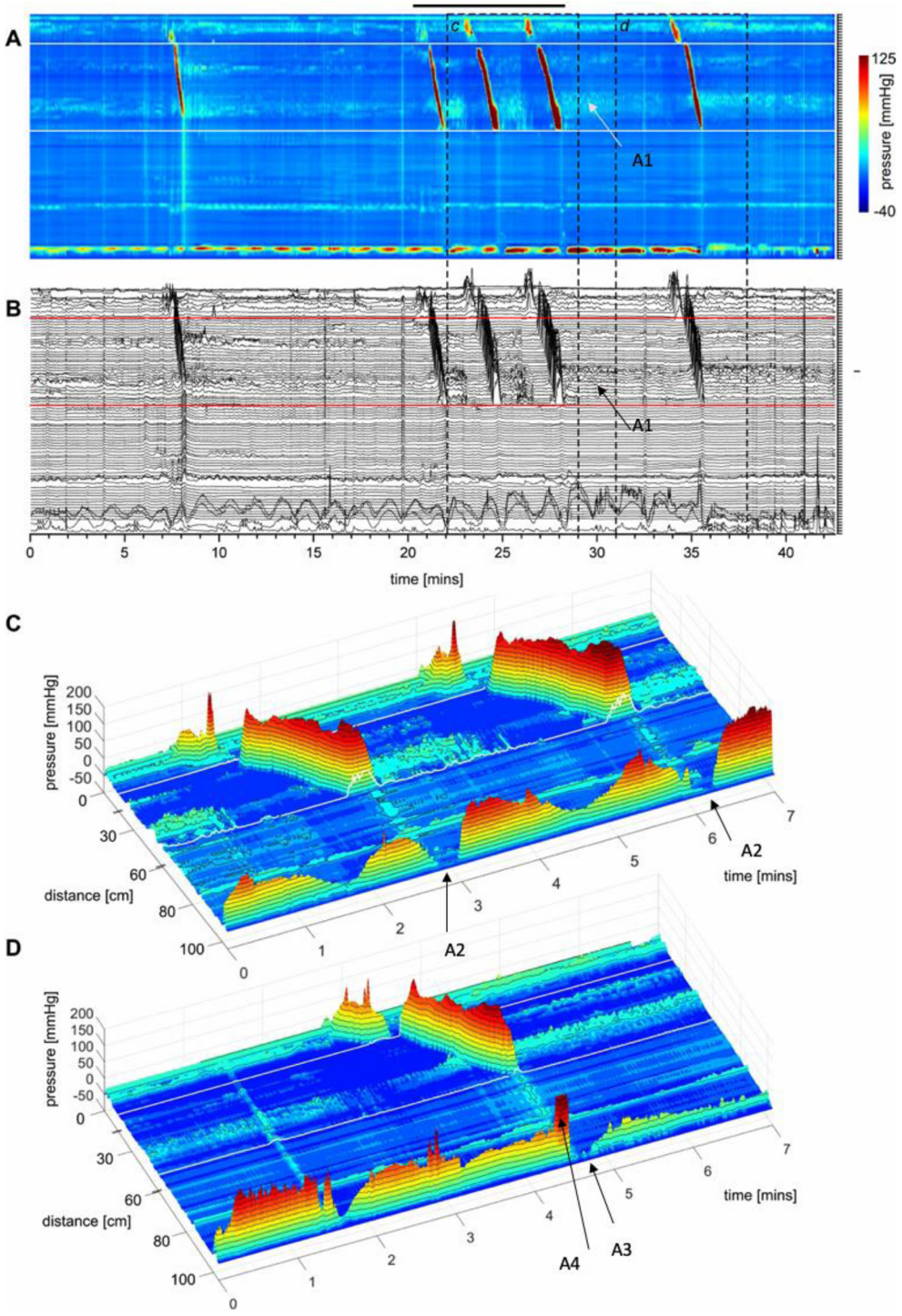

Fig. 1. High-Amplitude Propagating Pressure Waves (HAPWs) that develop into a Simultaneous Pressure Waves (SPWs) in response to proximal balloon distention (HAPW-SPWs) from (2).

A. The time period of proximal balloon distention by 240 ml air is indicated by the black line above (A). The balloon is positioned at the proximal white line. Proximal HAPWs developed into SPWs (generating HAPW-SPWs) associated with extensive anal sphincter relaxation. Extensive haustral activity (see 5, 7) is seen between 30 and 35 cm following each HAPW.

B. Same as (A), shown are the actual pressure traces.

C. Section of (A) between the first two vertical dashed lines show two HAPW-SPWs that are followed by anal sphincter relaxation. Note that the HAPW evoked by the balloon starts at the most proximal sensor or more proximal.

D. Section of (A) between the 3rd and 4th vertical dashed lines. A low amplitude SPW with anal sphincter relaxation is seen at 1.8 cm. This is followed by an HAPW-SPW and anal sphincter relaxation; the relaxation is preceded by a brief voluntary external anal sphincter contraction. For details, please consult (2).

wave activity itself by arrays of electrodes (1, 14–16), one obtains features of motility that are consequences of the network properties of the ICC and the network properties of smooth muscle cells. Slight changes in any part of the networks such as local frequency changes or a local change in the coupling strength between ICC pacemaker cells can have dramatic consequences for the entire organ motility (17–19). In organs with a pacemaker frequency gradient, from high (proximal) to lower (distal), the propagation direction will be from proximal to distal but a sudden increase in slow wave frequency in the middle of the organ, for example by local neural excitation, can initiate retrograde propulsion proximal to the frequency change.

Just as we do not assume that any brain function is determined by a single neuron or a single linear path of action potential propagation, so are most motor patterns in the gastrointestinal tract determined by network properties of ICC and smooth muscle cells connected to networks of excitable neurons; the neural networks provide the neural programs to initiate or modulate motor patterns, involving the enteric and autonomic nervous systems. Hence, the gut muscle wall is a super-network, a massive syncytium composed of many sub-networks of excitable and oscillating cells: ICC, neurons, muscle cells and other accessory cells such as specialized fibroblasts (20, 21). Propagation can be initiated by trigger or phase waves that occur in the sub-networks of excitable and oscillatory cells, respectively (20). Trigger waves occur when excitable cells are triggered consecutively, like a set of upright dominos falling one after the other triggered by the first falling (20); or the way action potentials propagate along a nerve axon, or locally through a smooth muscle network (22). A typical example of a phase wave is a propagating slow wave in an ICC network. All ICC in a network oscillate and the synchronization of the oscillators creates an apparent propagation under certain conditions, in particular: the presence of a frequency gradient and the existence of electrical coupling between the oscillators. Noise in frequency and coupling influence motor patterns and one initiator of noise may be background activity of the enteric nervous system (19). Electrical or motor patterns can dramatically change when additional electrical events swipe through these networks. For example, if a second ICC pacemaker system such as the ICC-DMP in the small intestine generates its slow wave activity, a propulsion motor pattern can completely change into a segmentation motor pattern (23). When ICC-IM in the stomach generate its pacemaking activity, for example through vagal activation, pacemaker propagation through the entire gastric ICC networks changes (24). When cholinergic nerves are activated across a section of the ICC and smooth muscle networks, smooth muscle action potentials will appear superimposed on slow waves causing a dramatic change in contraction amplitude and propulsive force of the propagating contractions, such as phase III of the migrating motor complex (MMC) in the small intestine. The MMC is initiated by programmed neural activity; it “awakens” slow wave driven propulsive activity, illustrated in the Color Atlas of High Resolution Manometry by Conklin et al. (25). Phase III of the migrating motor complex has predominant ICC driven antegrade pressure waves with split propagation direction or segmentation patterns occasionally, but there appear to be no obvious simultaneous pressurizations (26). MMC activity is a perfect example of the joint control of motility by ICC and the nervous systems. This activity is best explained when one considers the small intestine ICC network as a system of loosely coupled oscillators, and the predominant antegrade activity is explained by the strong ICC frequency gradient in the small intestine. This system of coupled ICC oscillators allows for split propagation (18, 19, 23, 27) and segmentation (23). The major difference in the colon is that such a “permanent” strong frequency gradient is missing. This serves the purpose that propagating contractions are not the dominant myogenic motor pattern in the colon.

Undoubtedly many motility patterns emerge from the interaction between excitable and oscillatory cells in the super network, depending on physiological conditions (20). We have barely begun to examine these excitatory-oscillatory interactions and modulations but understanding them and the behaviour they produce in

the super-network will be achieved by careful synchrony between experiment and mathematical models (20, 28–31).

We often imagine a few neurons to trigger activity in a clump of pacemaker cells to govern motor functions, but it is likely that often large areas of an organ are stimulated at once, such as with distention. Distention will activate large areas of an organ; hence it will affect the super network. ICC-IM throughout the rectum will be activated by distention so that this massive signal can trigger essential inhibition of the anal sphincters (32); hence abnormal ICC or abnormal ICC network properties may turn out to be the cause of evacuation disorders (32). Research into the role of abnormal ICC networks in pathophysiology has started. Limited, although significant, loss of ICC in diabetic rats did not affect slow wave propagation significantly due to the very robustness of networks (33). Mathematical models further showed that effects depend on the type of loss, i.e. random or circumferential (34). In the stomach, dysthymia's may be due to loss of or abnormal ICC (35). It has been known that ICC are sensitive to inflammation (36), confirmed by a recent study on the human appendix (37). Gastroparesis (38) and chronic constipation (39) are associated with loss of ICC although the exact pathophysiological mechanisms need further study which is made complicated by the fact that ICC are rarely lost in isolation, often the enteric nervous system is also compromised.

Mathematical Modeling to Understand Network Behaviour

All subtypes of ICC form electrically coupled networks, similarly, the smooth muscle cells in both the longitudinal and circular muscle layer from coupled networks as shown by numerous electrical recordings and calcium imaging (40). The nerves in the enteric nervous system are coupled through synaptic contacts and gap junctions (41). There is no reason to assume that the advances in brain research through the study of its network properties will not be applied to the enteric nervous system. Hence the importance of a better understanding of ICC and smooth muscle network properties and their integration with neural networks cannot be overstated. Unlike the heart where a persistent propulsive activity is essential, the intestine needs a variety of motor patterns, from peristalsis, to segmentation, to quiescence. These motor patterns are triggered by luminal content requiring extensive communication between sensory and motor activities.

An illustrative example of motor patterns that are a direct result of the properties of the networks of ICC and smooth muscle cells (and of course all the cellular properties of the various cells associated with the musculature that influence the networks), is the abortion of slow waves or contraction waves that occur in the mid to distal intestine as a consequence of the frequency gradient (Fig. 2). An aborted contraction wave is followed by subtle changes in subsequent contraction waves, a pattern seen in many coupled oscillator systems such as sand waves in the desert. This pattern can be faithfully demonstrated in a relatively simple mathematical model of coupled oscillators featuring a frequency gradient and variable oscillator coupling factors (17, 19).

A fascinating feature of small bowel activity is the existence of slow wave plateaus, that is that although the small intestine has a slow wave frequency gradient along its length, sections of the small bowel have the same slow wave frequency followed, from oral to anal, by a transition period followed by a plateau of lower frequency. Recent studies of this phenomenon have shown that the detailed features of the plateaus as revealed by spatiotemporal mapping can best be explained by considering the ICC network as a system of weakly coupled oscillators (18). Plateaus, dislocations, interval waves and wave turbulence arise from a dynamic interplay between natural frequency and coupling in the network of interstitial cells of Cajal (Fig. 3). A dislocation, that is a termination of a contraction wave (caused by a termination of a slow wave (15)) is followed by distortions of many subsequent contraction waves together forming what we called an "interval wave" (18). The interval

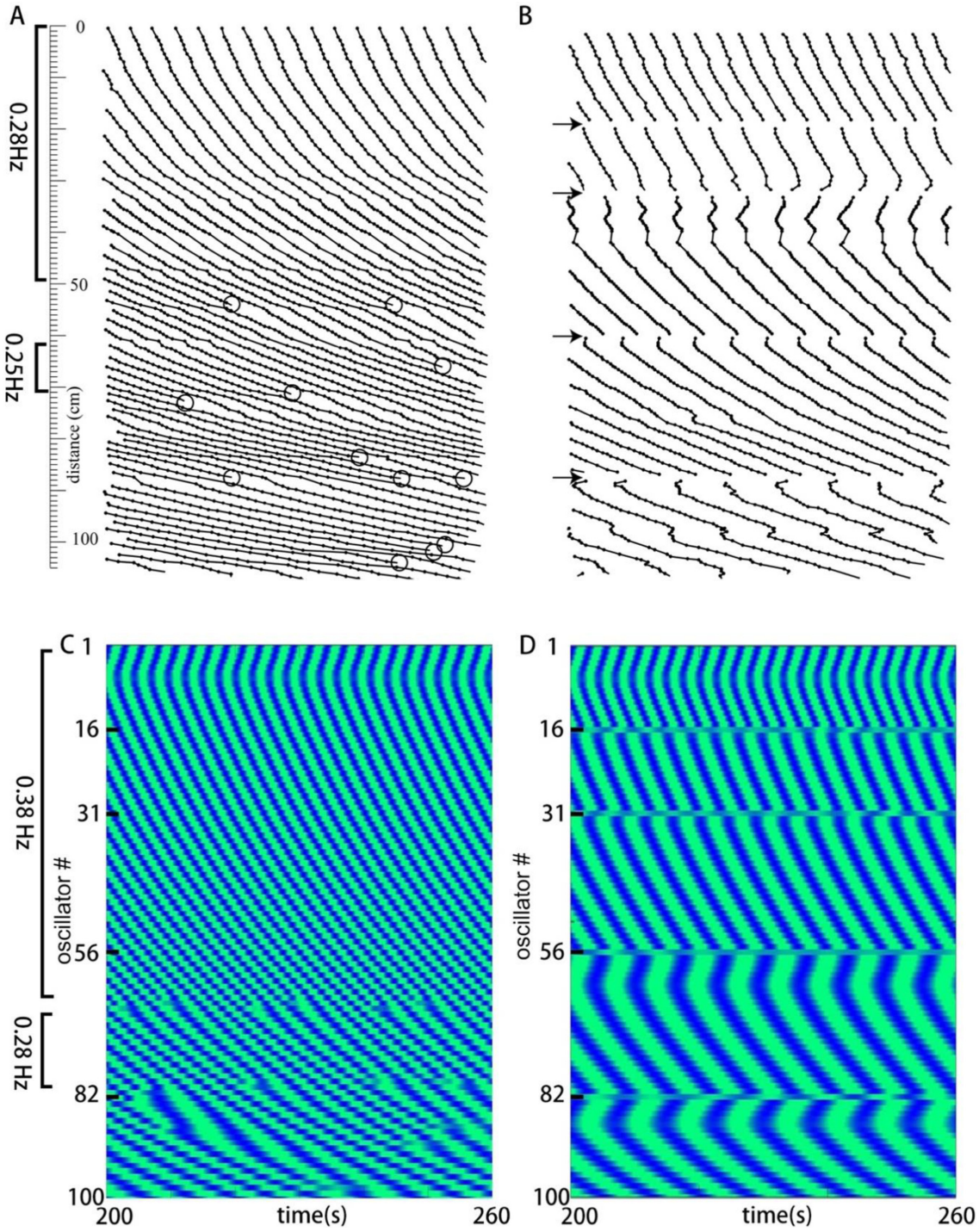

Fig. 2. Direct comparison between physiological and model data to show ICC network properties (from (34)).

A. Slow wave activity across the entire cat intestine, recorded for 60 s. Two frequency plateaus are marked.

B. Slow wave activity across the entire cat intestine after ligation at four sites indicated by arrows, recorded for 60 s.

C. Mathematical model of weakly coupled oscillators with parameters from A: intrinsic frequency gradient of 17 cycles/60s (proximal) to 6 cycles/60s distal, using 6 × 100 oscillators with the values of the 6 circumferential averaged. Noise was added to the cycle intervals randomly between −0.5 s to +0.5 s. Coupling strength gradient of 5 (proximal) to 0.5 (distal). Two frequency plateaus are marked.

D. Mathematical model of weakly coupled oscillators with parameters from B: coupling strength gradient of 5–0.5 with frequency noise, columns 16, 31, 56, and 82 were taken out (all oscillators in the column were taken out, isolating the different sections).

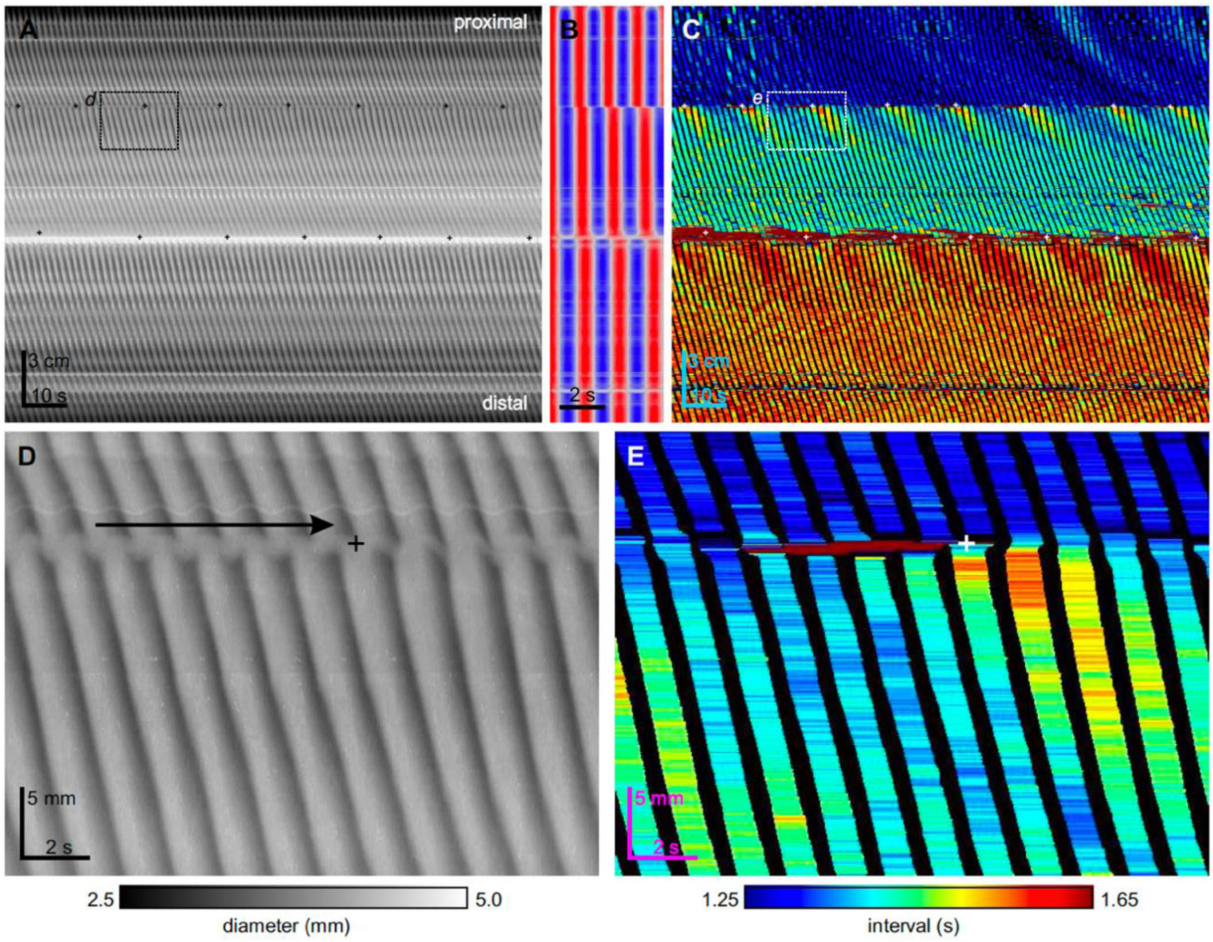

Fig. 3. Dislocations cause interval waves (from (18)).

In a DMap of the mouse small intestine (A) contraction waves travel from its proximal end to its distal end and terminate periodically (plus signs) at two positions. Looked at close-up (D) a termination has a fork-like appearance. This is called a dislocation. It should be expected that contraction wave frequency changes at a dislocation as it removes one wave. This can be shown by autocorrelation of the DMap (B). Autocorrelation is the correlation of a signal with itself shifted by varying amounts or "lags". The y-axis in (B) corresponds to the same axis in the DMap and the x-axis is the lag (from 0 to 5 s). The correlation is color coded with red as positive correlation and blue as negative. A rhythmic signal results in a series of correlation peaks as a function of lag, the red bands in (B). The first band, at zero lag is the correlation of the unshifted signal and so will be 1. Successive bands indicate the correlation between every wave, every second wave, every third wave, etc., etc. It can be seen that the bands are mostly vertical, but step to the right (interval increases, frequency decreases) at the positions where dislocations occur. Thus there are frequency steps at these positions. In the section between the frequency steps, the frequency is constant: this is referred to as a frequency plateau. Interval maps (C and E) show that the contraction interval increases in a comet-shaped wave at each dislocation.

wave is formed due to the fact that a contraction wave that follows a terminated wave temporally increases it apparent propagation velocity, an increase that slowly diminishes with subsequent contraction waves. This is a typical consequence of network activity that can be faithfully shown by a mathematical model of coupled oscillators (18). This phenomenon is most clearly observed after block of spontaneous neural activity, hence when activity is dominated by ICC network activity (frequency gradient, and noise in coupling and frequency). It is very likely that this noise is created in part by background enteric nervous system activity.

High Resolution Manometry Combined with Spatiotemporal Mapping

The quality of spatiotemporal mapping depends on its resolution, and *in vivo* human motility studies started to reveal unprecedented detail when high-resolution manometry entered esophageal motility clinical practice. Since human colon motility is so much more complex compared to esophageal motility, high-resolution colonic manometry will revolutionize assessment of colon motor function and dysfunction. It started with the pioneering work of Dinning and Cook with multiple sensors, 7.5 cm apart (42) and later with true high-resolution, that is with sensors 1 cm apart (43). One cm spacing is probably enough to assess most clinically important motor patterns but certain details such as intra-haustral activities (Fig. 1) probably require even higher resolution that will no doubt come in the future. Since the colon may be quiet for hours, to study motility in a limited time span, it is essential to stimulate the colon to evoke motor patterns, and ideally the stimulus should evoke a reliable motor pattern in healthy volunteers so that in patients a potential dysmotility might be detected. This is no easy goal since physiologically relevant stimuli such as eating a meal show quite variable responses in humans (44). The objective to find ideal stimuli has therefore not yet been achieved although significant insights have already been accomplished (2, 7, 45–48).

Interestingly, one of the earliest colonic motor stimuli, bisacodyl, is still one of the most reliable and is extensively in low resolution colonic manometry as that is practiced today (49). But even bisacodyl does not give truly consistent motor patterns in healthy volunteers (50). Current practice administers bisacodyl in the proximal colon via a catheter to evoke the best characterized colonic motor pattern most often called the High Amplitude Propagating Contraction. In early studies it was referred to as pressure waves (51, 52), a term now often abandoned and replaced by contraction, unfortunately, since manometry measures pressure and not contraction directly. This might be problematic since pressure can be generated in many different ways and to "automatically" associate pressures or pressure waves with equivalently shaped contraction waves will obscure the true origin of some pressure patterns. This is why we prefer the terms High Amplitude Propagating Pressure Waves (7) and Simultaneous Pressure Waves (7, 53) for the two most prominent propulsive motor patterns of the human colon.

High resolution manometry combined with spatiotemporal mapping has given us increased insight into the characteristics and origins of human colon motor patterns. One of these motor patterns is the HAPW-SPW (2, 48), a high amplitude propagating pressure wave that starts in the proximal colon and changes into a simultaneous pressure wave in the mid or descending colon (Fig. 1). The exact origin of the simultaneous pressure wave is still to be elucidated and it may be a combination of several mechanisms, but it is not logical to assume that it is caused by a "spastic" simultaneous contraction of the circular muscle distal to the end of the HAPW. Simultaneous events are a natural occurrence is systems of coupled oscillators without, or with a low frequency gradient. A common motor pattern in the human colon is a fast propagating circular muscle contraction (54, 55) and such a contraction is likely to result in a simultaneous pressure wave, that it is too fast to measure its velocity in spatiotemporal maps. We proved this to be the case in the rabbit colon using ultra-high resolution with sensors 0.25 cm apart (5). It is also possible that some pressure is generated by contraction similar to the pulse pressure wave in the aorta (4). We have heard the argument that pressure might be generated by contractions due to the so-called common cavity effect, that is, a contraction in a part of a common cavity will cause a pressure change in the rest of the cavity. But the colon is not a common cavity, otherwise strong contractions would always cause pressure changes in the rest of the colon and this is not the case (Fig. 1). For example, strong proximal HAPWs very often do not cause any pressure changes distal to the contraction. It maybe that haustral boundaries contribute to the prevention of the phenomenon of the common cavity.

From Basic Science to the Clinic and Back Again

The current extensive basic science knowledge of smooth muscle cells, neurons and ICC, to which Japanese scientists have made such an impressive contribution, e.g. (56–64), to name just a few, make it possible to begin to interpret gastrointestinal motor patterns as they emerge from high resolution mapping. Similarly, the detailed pictures that are now emerging from spatiotemporal mapping of high-resolution data of the gastrointestinal tract, electrical, diameter changes, pressure, etc., make it possible to predict the cellular behaviour underlying the electrical or motor patterns, and such hypotheses can be pursued in further human studies or animal models. An example is the study on the origin of simultaneous pressure waves in the human colon which was pursued in the rabbit colon as referred to above (5). Another example is the study of abnormal cyclic motor patterns in the human colon after surgery (65). An interesting study by Lindley et al. attempted to correlate ICC abnormalities with abnormalities in motor patterns revealed by high resolution manometry in pediatric slow transit constipation (48). Continuing discussions about interpretations of animal model data for understanding of human physiology and pathophysiology is of critical importance and recently a first attempt to obtain consensus was successful (47). Many more studies are needed that study human high-resolution spatiotemporal maps under many conditions, before a simplified scheme can be constructed for clinical use to identify pathophysiology. Many more studies on healthy human volunteers are also needed since the correct identification of normal motor patterns in patients may be just as important and clinically useful as abnormal motor patterns. An interesting example is the revealing study by Angeli et al. (66) on the behaviour of electrical pacemaker activity in the human small intestine. It was found that slow wave propagation patterns were “disordered”, to varying degrees in all volunteers, including variable propagation directionality (antegrade, retrograde, and circumferential), wavefront collisions between “dissociated” propagating events, breakout and entrainment of “ectopic” pacemakers, and functional conduction blocks (66). To distinguish normal disorder from functionally important abnormal disorder will be a major challenge. Disorder can be an essential normal feature, as we know from, for example, heart rate variability (67).

Conclusions

Spatiotemporal mapping of diameter changes observed through video recording, of pressure patterns obtained by high-resolution manometry or of electrical activities measured by closely spaced arrays of electrodes throughout the gastrointestinal tract has given us unprecedented detail of motor and electrical activities, such that hypotheses about underlying cellular behaviour can now be pursued based on our vast basic science knowledge of smooth muscle, ICC and neurons, tested by human or animal research and/or mathematical modeling. This deeper understanding of gastrointestinal motility brings us very soon to a much higher level of precision in diagnosis of dysfunction than is currently available.

Conflict of Interest

The author declares that there is no conflict of interest.

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