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Slow Wave Conduction Patterns in the Stomach: From Waller's Foundations to Current Challenges

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Abstract

This review provides an overview of our understanding of motility and slow wave propagation in the stomach. It begins by reviewing seminal studies conducted by Walter Cannon and Augustus Waller on *in vivo* motility and slow wave patterns. Then our current understanding of slow wave patterns in common laboratory animals and humans is presented. The implications of slow wave dysrhythmic patterns that have been recorded in animals and patients suffering from gastroparesis are discussed. Finally, current challenges in experimental methods and techniques, slow wave modulation and the use of mathematical models are discussed.

Keywords

Dysrhythmia; ICC; gastroparesis; slow wave patterns; smooth muscle

1. The Foundations of Electrophysiology

Initial records of bioelectricity can be traced back to around 4000 BC where an Egyptian hieroglyph referred to a type of electrical catfish (Malmivuo & Plonsey 1995). While most varieties of catfish have electroreceptive organs to sense, the electric catfish also possesses an electrogenic organ capable of producing a powerful jolt of electricity to ward off predators or incapacitate their prey. Weak coordinated electrical events propagating within our bodies are critical for many functions including movement and sensing. In the gastrointestinal (GI) tract, omni-present electrical 'slow waves' are, in part, responsible for the coordinated contractions and relaxations of the musculature necessary for the efficient grinding, mixing and transportation of the food we ingest.

In the late 1700s, Luigi Galvani (1737–1798) conducted seminal experiments at the University of Bologna where he observed that placing an electrical charge in contact with the nerve fibres of dissected frog legs could make them twitch (Piccolino 1997). He hypothesised that animal tissues are endowed with intrinsic electricity that is involved in

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Conflict of Interest

None.

fundamental physiological processes such as nerve conduction and muscle contraction. Galvani's work led to the foundation of the branch of science now known as electrophysiology. Following on, Carlo Matteucci (1811–1868) began a series of experiments that showed that an electrical current accompanies each heart beat (Matteucci 1842). There is now a vast pool of knowledge in the field of cardiac electrophysiology and many cardiac electrical disorders can now be reliably treated using minimally invasive techniques. However, the corresponding knowledge and treatment options in GI electrophysiology remain relatively primitive.

This review will provide an overview of the historical developments in our understanding of motility and electrical propagation in the GI tract. There will be a particular focus on the slow wave propagation in the *in vivo* stomach in common laboratory animal models and in humans [another article in this issue by Lammers (Lammers 2015) focuses on slow wave activity in small intestine]. Finally, current challenges and future directions will be discussed.

2. Gastrointestinal Motility & Electrophysiology

Gastrointestinal Motility

Initial advances in understanding motility or movement of the gastrointestinal tract can be attributed to the seminal work of Walter Cannon (1871–1945). Although Cannon was more popularly known for the *fight or flight response* (Cannon 1915), it was while in medical school that he devised techniques for visualizing the movement of the GI tract, and thus he began his investigation of the physiology of digestion. This was a topic that occupied him for approximately 15 years and launched his career as a physiologist (Brown & Fee 2002). Cannon was the first researcher to use x-rays and ingestible contrasts to improve the understanding of swallowing mechanisms (Cannon & Moser 1898). Although image definition was poor, he was able to record his findings on static images via the use of coloured pencils and transparent paper (see Figure 1). He subsequently turned his attention to stomach and bowel contractions (Cannon 1902). As part of these studies, he noticed when his experimental animals were frightened or in some other way disturbed, peristaltic waves in the stomach sometimes ceased abruptly (Cannon 1911). It was from these initial findings that he began his fruitful research into the autonomic nervous system and the development of the fight or flight response theory.

Subsequently, using new and safer x-ray equipment, Charles Code (1910–1997) and colleagues replicated many of Cannon's experiments in dogs and humans (Carlson et al. 1966; Smith et al. 1957). These studies were able to record the real-time motions of the GI tract (Cannon was only able to record sequential static images). In addition to peristalsis in the oesophagus and stomach, and segmentation in the intestine, he observed for the first time, simultaneous contractions of the pyloric canal and terminal antrum, meaning that “instead of entering the duodenum, most of the contents were forcefully regurgitated into the proximal antrum, an action designated as retropulsion” (Carlson et al. 1966). These sheering forces grind and breakdown the particles until eventually they are less than 2 mm in size before they are able to pass into the duodenum (Meyer 1980; Meyer et al. 1979).

The introduction of magnetic resonance imaging (MRI) has transformed the field of radiology. MRI provides an excellent medium for non-invasive imaging of internal organs without the use of radiation. However, the relatively long imaging times and limited spatial resolution has hampered their use for assessing GI motility. Recently, there has been renewed interest in the use of MRI for assessing GI motility patterns (de Zwart & de Roos 2010; Marciani 2011; Schulze 2006). MRI has now been used to image entire abdominal volume in a single breath-hold (Marciani 2011) and gastric volumes and gastric emptying rates derived from MRI have been validated against intra-gastric balloons (Boulby et al. 1997) and scintigraphy (Feinle et al. 1999). Similar techniques have also been successfully applied to assess small bowel motility (Ailiani et al. 2009; Farghal et al. 2012; Froehlich et al. 2005).

Gastrointestinal Electrophysiology

Although techniques such as scintigraphy and MRI provide detailed information about the motility patterns of the GI tract, they are unable to provide an understanding of why and how these patterns occur. To achieve this, techniques that record the underlying electrical patterns of the stomach are required.

The first recordings of electrical slow waves were made from the chicken gizzard (Marimón 1907; Szurszewski 1998) and the first recordings from mammals and humans were conducted by Walter Alvarez (1884–1978). As early as 1922, Alvarez had introduced the electrodes and the appropriate apparatus (namely a D'Arsonval instrument) that were able to reliably record the electrical activity of the digestive tract. In these studies he noted that “records can now be obtained at all times even from stomachs and bowels which seem to be motionless”. He also illustrated slow wave traces from the stomach, intestine and colon of a variety of animals including dogs, cats and rabbits (Alvarez & Mahoney 1922). The first cutaneous electrogastrogram recordings were also obtained from a “little old woman whose abdominal wall was so thin that her gastric peristalsis was easily visible” (Alvarez 1922).

Alvarez provided strong foundations of our understanding of gastrointestinal electrophysiology. The cellular origins of these electrical slow waves are described in Section 3 and our current understanding of the slow wave conduction patterns of animals and in humans is then presented in Sections 4 & 5.

3. The Origins of Slow Wave Activity

Multiple cooperating and overlapping mechanisms control GI peristalsis (Huizinga & Lammers 2009). However, it is clear that contractions are coordinated, in part, by spontaneous, cyclic electrical events originating from pacemaker cells known as interstitial cells of Cajal (ICC). ICC loss and injury is now a major research focus as it is recognized as a hallmark of a number of functional GI motility disorders (Farrugia 2008). These include gastroparesis (Grover et al. 2011; O'Grady, Angeli, et al. 2012), slow transit constipation (Wedel et al. 2002)] and intestinal pseudo-obstruction (Feldstein et al. 2003). ICCs have also been found in a variety of other smooth muscle organs that require coordinated contractions. These include the bladder, ureter, fallopian tubes and uterus (McHale et al. 2006; Thuneberg

1999; Hutchings et al. 2009). As such, an improved understanding of their function in both health and disease may have wide spread clinical implications.

ICCs are named after Nobel laureate Santiago Ramon y Cajal (1852–1934) (see Figure 2). In the late 19th century, Cajal described a new type of nerve-like branching networks interleaved among neurons embedded within the smooth muscle linings in the GI tract (Cajal 1911). However, their developmental origin and function remained unclear for many decades (Huizinga et al. 1995). Lars Thuneberg sparked a revival in ICC research by proposing that ICC are intestinal pacemaker cells (Thuneberg 1982) and subsequently showed that injury of ICC stained with methylene blue resulted in loss of slow wave activity (Liu et al. 1994). Subsequently, studies showed that mice with mutations in the Kit gene, also had a significantly reduced ICC population and an absence of electrical slow wave activity, but no apparent changes in neural pathways or SMC indicating the importance of ICC for normal pacemaking function (Ward et al. 1994; Huizinga et al. 1995).

There is now strong evidence associating compromised ICC networks and motility disorders such as gastroparesis and slow transit constipation (Farrugia 2008; Grover et al. 2011). It is estimated that up to 12% of diabetics will develop gastrointestinal motility disorders such as gastroparesis, a fact that is of particular importance due to the current diabetes epidemic and longer than average hospital stays associated with these disorders (Camilleri 2007). In fact, US hospital admissions for gastroparesis have risen an alarming 150% in the recent decade (Wang et al. 2008). As described further in Section 5, it is now known that abnormal slow wave propagation patterns are prevalent in gastroparesis patients. These abnormalities are likely to contribute to the impaired function of the stomach.

4. Slow Wave Conduction in the Animal Stomach

Alvarez's initial work was pioneered in a variety of animals including rabbits, cats and dogs (Alvarez & Mahoney 1922). Although Alvarez had, in his early studies, described that slow wave contractions occur "from two to five per minute in laboratory animals" (Alvarez & Mahoney 1922), more recent studies have refined these descriptions in a variety of laboratory animals (see Table 1). It has now been determined that certain animals have regional variations in slow wave amplitude and velocity. The dog has an increase in slow wave amplitude and velocity towards the antrum (Lammers et al. 2009; Kelly et al. 1969). On the other hand, the cat has a reduction in speed at the antrum (Xue et al. 1995), whilst the pig has limited variation between the corpus and antrum (Egbuji et al. 2010).

Both slow wave frequency and amplitudes can be accurately determined using a single (or limited) number of electrodes. However, it should be noted that slow wave amplitudes are highly dependent upon the acquisition hardware, filtering techniques and the recording electrode sizes and materials (O'Grady et al. 2013). This makes direct comparisons between studies difficult. In addition, the estimation of propagation patterns and velocities may be highly inaccurate if only low-resolution recordings was obtained. The accuracy of these estimates should be increased by the use of high-resolution, regular arrays and more sophisticated estimation techniques (Paskaranandavadivel et al. 2012; Lammers et al. 2005).

In addition, to the normal, organised slow wave conduction in the stomach, dysrhythmic slow wave patterns are an area of great interest, especially with their relationship to dysmotility (Lammers 2013). Dysrhythmias were first reported in studies conducted on dogs using low-resolution recordings (Code & Marlett 1974; Kim et al. 1987). Some of these dysrhythmias occurred spontaneously, while others were reported to be induced by drugs, diseases, surgical intervention or electrical pacing (Lammers 2013).

Although serving as a strong foundation, initial, low-resolution recording techniques had limited ability to accurately determine mechanisms underlying the initiation, maintenance or termination of these dysrhythmic patterns. The introduction of high-resolution mapping techniques provided an ideal medium for investigating these factors (Lammers et al. 1993; Cheng et al. 2013). High-resolution mapping techniques have subsequently been used to record spontaneous dysrhythmias in both pigs and dogs (O'Grady et al. 2011; Lammers et al. 2008) and subsequently in gastroparesis patients (see Section 6).

The first study to observe the spatial origin and propagation patterns of slow wave dysrhythmias in the stomach was conducted in dogs (Lammers et al. 2008). In this study, gastric dysrhythmias occurred in approximately 45% of animals studied. Dysrhythmic patterns similar to those that have been observed in the heart, such as focal origin, re-entry, circular propagation, conduction blocks and fibrillatory behaviour were reported (Lammers et al. 2008). In another study, similar dysrhythmic patterns were observed in 50% of pigs (O'Grady et al. 2011). Again, a variety of dysrhythmias were observed including: conduction block, escape rhythm, ectopic pacemakers and functional re-entry. The cause of these dysrhythmic patterns remains uncertain, and it is plausible that they may be related to anaesthesia, laparotomy or manual gastric handling. The functional consequences of the dysrhythmic patterns described in these papers are currently unknown; however, it is plausible that these disordered events may compromise normal gastric function.

5. Slow Wave Conduction in the Human Stomach

Alvarez had already determined that slow waves in humans occurred regularly at 3 cycles/min (cpm) and was already in the process of trying to localize the pacemaker region of the stomach (Alvarez & Mahoney 1922). He initially believed (incorrectly) that the pacemaker region was located on the lesser curvature near the cardia (Alvarez 1922). It was not until 1977, when a multi-electrode study was able to locate the pacemaker in the mid-corpus on the greater curvature and provide a refined description of the spread of slow wave activity in the stomach (Hinder & Kelly 1977).

The most comprehensive high-resolution mapping study of the human conduction system was conducted in patients with no known gastric physiology abnormalities (they were undergoing pancreatic, oesophageal or liver resection surgery) (O'Grady, Du, Cheng, et al. 2010). In these studies, flexible arrays containing up to 192 electrodes were placed on the exposed serosa. In concordance with previous studies, slow wave activity originated from a pacemaker region at the mid/upper corpus on the greater curvature. From this pacemaker region, a band of activity rapidly formed and propagated in an organised fashion towards the distal antrum. No dysrhythmic or uncoordinated activity was observed. As summarised in

Figure 3 and in Table 1, the average slow wave frequency was consistent through the stomach at 2.83 ± 0.35 cpm. A high amplitude, high velocity transition zone was localised to the distal antrum where both the amplitude and velocity doubled within a zone of approximately 10 mm. This zone is believed to correlate to a zone of “simultaneous contraction” as also observed by cinegraphy studies (Carlson et al. 1966).

Of great clinical interest is an understanding of the mechanisms underlying gastric motility disorders and their association with slow wave dysrhythmias. Although dysrhythmias had previously been reported in humans, the limited number of recording electrodes restricted their methods to frequency based analysis (Stoddard et al. 1981). In this study, dysrhythmias were characterised by increases in the slow wave frequency, amplitude and wave morphology. The highest antral slow wave frequency for all subjects ranged between 4.5–8.3 cpm, with the mean maximum frequency being 2.32 times higher than the baseline frequency. When high-resolution mapping techniques were applied to gastroparesis patients, prior to undergoing Enterra Therapy (Medtronic, Minneapolis, MN, USA) implantation, complex spatial dysrhythmias were observed in 11 of the 12 patients (O’Grady, Angeli, et al. 2012). The study revealed new categories of abnormal human slow-wave activity in the form of abnormal initiation and abnormal conduction. These events often occurred at the normal slow wave frequency of 3 cpm, meaning that such activity could easily be missed by recordings that lack appropriate spatial resolution (Buist et al. 2006).

6. Current Challenges & Future Directions

The observations in the GI tract first reported by Walter Alvarez only followed the demonstration by Augustus Waller of the human electrocardiograms by approximately 30 years (Alvarez 1922; Waller 1887). Although electrophysiological recordings now play an integral part in clinical electrocardiography, the use of similar knowledge in clinical practice remains severely limited. However, a range of recent technical advances have reinvigorated interest in this research field.

Experimental Challenges

Obtaining reliable extracellular recordings of gastrointestinal smooth muscle can be challenging. This is in part, due to our limited understanding of the electrical activity in the gastrointestinal tract, and difficulty in obtaining access to the musculature itself. Carefully controlling factors such as temperature and humidity are necessary to obtain reliable recordings. Even recently, the validity of extra-cellular recordings have been questioned and subsequently the frequency of slow wave events challenged (Bayguinov et al. 2011; Rhee et al. 2011). However, the claims have yet to be substantiated by other researchers, and the discrepancies of these results compared with historical and current knowledge appear to be attributed to limitations from the experimental setup, analysis techniques and differences between in-vivo and in-vitro setups (Angeli et al. 2013; Sarna 2013; Paskaranandavadi et al. 2013). (O’Grady et al. 2013) provides an excellent review of the practical considerations for reliable in-vivo based extra-cellular recordings.

Challenges in Slow Wave Recording Techniques

The use of high-resolution mapping techniques provides a vast amount of spatial information about the propagation patterns of the slow wave activity that traditional low-resolution techniques were unable to provide. However, their relative invasive nature means the serosa of the stomach must be exposed, typically via laparotomy. This significantly limits the clinical utility of such methods. One solution is the use of a laparoscopic electrode platform which can be inserted via a 5 mm trocar during laparoscopic surgery and map from a restricted area (4 electrodes covering $\sim 12 \text{ mm}^2$) (O'Grady, Du, et al. 2009). Although only a limited field of view can be obtained, the direction of the slow wave propagation could be reliably detected.

An alternative approach involves obtaining electrical recordings from the mucosal surface. Such techniques were briefly mentioned by (Alvarez 1922) where he reports that “some recordings have been made from the intra-gastric electrode ... modifications are still being made ... I will reserve its description for a later paper”. It remains uncertain if these developments were ever published. Subsequently, mucosal recordings from the duodenum were made using an “intraluminal salt-bridge” electrode (Christensen et al. 1964). Following this, a sequence of different mucosal “rubber cup suction” electrodes were described that allowed reliable recordings of gastric slow wave activity (Monges & Salducci 1970; Bellahsene et al. 1985; Couturier et al. 1972). However, each of these systems was only able to record from a localised region of the stomach. To address these shortcomings a multi-channel catheter non-suction based electrode was developed (Familoni et al. 1987). Once positioned appropriately, this system was capable of deploying four electrodes over a distance of 6 cm. Normally, the electrodes would lie flush with the side of the catheter, but with the application of suction they would protrude from the catheter a short distance allowing improved contact with the mucosa. This approach claims to overcome any potential signal degradation caused by suction pulling the mucosa away from the smooth muscle. In addition to frequency, information regarding the direction and velocity of propagation in the antrum could then be obtained.

More recently, endoscopically guided systems have been developed for obtaining measurements from discrete locations on the mucosal wall (Coleski & Hasler 2004). However, again, data can only be obtained from a limited number of electrode sites as the electrodes were either introduced along-side or through the internal channel of the endoscope. Nevertheless, it was possible to detect changes in slow wave parameters such as frequency, power and propagation induced by acute hyperglycaemia (Coleski & Hasler 2009). We await the appropriate technical advances before spatially dense recordings can be reliably obtained from the mucosal surface.

Challenges in Slow Wave Modulation

Electrical stimulation and pacing has been widely applied in various clinical areas to modulate function. These include cardiac pacemakers, implantable defibrillators, deep brain and spinal nerve stimulators. Pacing holds promise as a potential treatment for a number of gastric electrical disorders. The concept of gastric electrical stimulation for the treatment of paralytic ileus was introduced over 50 years ago (Bilgutay et al. 1963). In fact, Keith Kelly

remarked that “we can pace the stomach much in the same way that one can pace the heart. Thus, in the future we may be able to treat abnormalities in human gastric peristalsis caused by disease or operation by gastric pacing.” (Hinder & Kelly 1977).

At the same time, the effect of transections of the stomach or “partial cuts” on the slow wave patterns were investigated (Sarna et al. 1972a). In these studies, transections were made longitudinal or circumferentially and relatively uncoupling of the slow waves in different regions and directions investigated. However, there has been limited work following on from this study.

A variety of studies have shown that it is possible with appropriate stimulation parameters to entrain the underlying slow wave activity. In dogs, studies have shown the ability to change the propagation patterns by “forward pacing” and “backward pacing” in the retrograde direction and also alter the emptying rates of the stomach (Sarna & Daniel 1973; Sarna et al. 1976). Similar studies were also conducted in humans and used to investigate as a potential method for correcting gastric myoelectric disorders (Miedema et al. 1992). More recently, high-resolution “entrainment mapping” technique have shown the ability to determine the area that is entrained or influenced by a given stimulus protocol and the evolution of these areas over time (O’Grady, Du, Lammers, et al. 2010).

Despite a variety of promising research studies, the use of such techniques continues to have limited clinical acceptance (Yin & Chen 2008). High-frequency gastric electrical stimulation via Enterra therapy (Medtronic, Minneapolis, MN) is a relatively new treatment for medically refractory gastroparesis (O’Grady, Egbuji, et al. 2009; McCallum et al. 2013). Although studies have showed improvements in patient symptoms and, in some cases, improved emptying times (O’Grady, Egbuji, et al. 2009; Chu et al. 2012), the quality of these studies is weak, and therefore, the device is only approved for use by the FDA on a humanitarian device exemption basis. Further studies are necessary to determine the mechanisms underlying such devices. The ability to integrate recording and stimulation/pacing technologies into endoscopically implantable device is a fertile area of research in the near future (Deb et al. 2012; Farajidavar et al. 2012).

Challenges for Mathematical Models

Mathematical models provide an ideal medium to assist with interpretation of experimental recordings and in turn to help guide further experimental studies and test hypotheses. Electrophysiological models of gastrointestinal slow wave activity are substantially less sophisticated than those in the cardiac field. However, there has been rapid progress in recent times (Cheng et al. 2013; Corrias et al. 2013). Below we provide a brief summary, however, the readers also suggested to refer to these reviews for further details (Du et al. 2013; Corrias et al. 2013).

One of the first mathematical models of electrical activity in the small intestine was proposed by Nelson & Becker (Nelsen & Becker 1968). It consisted of a large number of coupled relaxation oscillators. For the next two decades, led primarily by Sarna et al., a variety of studies simulated slow wave activity in the stomach and small intestine using chains of coupled oscillators (Sarna et al. 1971; Sarna et al. 1972b). However, subsequently

the ability of such models to realistically represent slow wave activity were questioned (Publicover & Sanders 1989). More recently, biophysically based cell models that explicitly represent the ICC activity (Corrias & Buist 2008; Lees-Green et al. 2014; Sathar et al. 2014) and smooth muscle activity (Corrias & Buist 2007) have been developed. These cell models have then been used to simulate slow wave activity by integrating into realistic ICC networks (Du, O'Grady, Gibbons, et al. 2010; Gao et al. 2014), stomach models (Cheng et al. 2007; Corrias et al. 2012) and torso models (Du, O'Grady, Cheng, et al. 2010). However, despite these advances, there remains much research to be conducted towards the wide-spread acceptance of mathematical models.

The Outlook

There is a renewed interest in the field of GI motility. The discovery that ICCs are essential for electrical rhythmicity, and consequently, mechanical contractility has been a critical advance to pinpointing the origins of the slow wave activity. There remains much to be discovered about the propagation of the slow wave activity in the stomach, and in smooth muscle organs in general. It is hoped that techniques and knowledge already established in the fields of cardiac and skeletal electrophysiology can be leveraged to accelerate research towards smooth muscle electrophysiology. With continued critical advances in this field, it is envisaged that clinical treatment of a number of functional smooth muscle disorders can be improved.

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Figure 1.

Sketches by Walter Cannon (1871–1945) illustrating the changes in the shape of the stomach during the digestion of a meal. Each panel shows the outline of the stomach of a cat determined by x-ray at 1 hour intervals. Adapted from (Cannon 1911).

Figure 2.
Santiago Ramon y Cajal (1852–1934), a pioneering neuroscientist, in his laboratory.

Figure 3. Schematic of the normal human conduction system. Rapid and high amplitude slow wave activity originates at the pacemaker, rapidly forming bands of activity that propagate distally. The corpus has slow and low amplitude activity, while towards the distal antrum, rapid, high-amplitude activity occurs. The pylorus and fundus are absent of slow wave activity. Adapted from (Cheng et al. 2013).

Table 1

Interspecies variations in gastric slow wave frequency, amplitude and velocity.

Species	Frequency (cpm)	Amplitude (mV)	Velocity (mm s ⁻¹)
Mouse (Dickens et al. 2001)	3.9±0.2		
Rat (Thouvenot et al. 1982)	4.04±1.06		
Guinea Pig (Hirst & Edwards 2006)	5.0		
Cat (Xue et al. 1995)	4.1±0.5		2.2–4.3
Dog (Lammers et al. 2009)	4.9–5.4	0.69–2.02	3.9–15.2
Miniature Pig (Rozé et al. 1976)	4.10±0.04		6.0±0.1
Pig (Egbuji et al. 2010)	3.22±0.23	0.8 – 1.3	6.8–13.3
Human (O'Grady, Du, Cheng, et al. 2010)	2.83±0.35	0.25–0.57	3.0–8.0