



Electrophysiological Mechanisms of Gastrointestinal Arrhythmogenesis: Lessons from the Heart

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Disruptions in the orderly activation and recovery of electrical excitation traveling through the heart and the gastrointestinal (GI) tract can lead to arrhythmogenesis. For example, cardiac arrhythmias predispose to thromboembolic events resulting in cerebrovascular accidents and myocardial infarction, and to sudden cardiac death. By contrast, arrhythmias in the GI tract are usually not life-threatening and much less well characterized. However, they have been implicated in the pathogenesis of a number of GI motility disorders, including gastroparesis, dyspepsia, irritable bowel syndrome, mesenteric ischaemia, Hirschsprung disease, slow transit constipation, all of which are associated with significant morbidity. Both cardiac and gastrointestinal arrhythmias can broadly be divided into non-reentrant and reentrant activity. The aim of this paper is to compare and contrast the mechanisms underlying arrhythmogenesis in both systems to provide insight into the pathogenesis of GI motility disorders and potential molecular targets for future therapy.

Keywords: gastrointestinal electrophysiology, cardiac electrophysiology, electrical excitation, arrhythmia, focal activity, reentry

INTRODUCTION

Abnormalities in the orderly activation and recovery of impulses traveling through the heart and the gastrointestinal (GI) tract can lead to arrhythmogenesis (Tse, 2015; Tse and Yeo, 2015; Tse et al., 2016k). Thus, atrial arrhythmias can cause thromboembolic events resulting in cerebrovascular accidents, whilst ventricular arrhythmias predispose to sudden cardiac death. By contrast, arrhythmias in the GI tract are usually not life-threatening and perhaps this is the reason that they are much less well characterized. However, recent studies have implicated GI arrhythmogenesis with a number of motility disorders, which are associated with significant morbidity. The aim of this article is to compare and contrast the electrophysiological mechanisms of arrhythmogenesis in both systems, drawing analogies to shed light on the GI aspects. This is followed by a discussion on the clinical relevance as exemplified by GI motility disorders and molecular targets for future therapy.

IONIC CONTRIBUTIONS TO ELECTRICAL ACTIVITY

Smooth muscle cells of the GI tract generate slow waves, whereas cardiomyocytes in the heart produce action potentials (APs); both types of electrical activity are dependent upon ionic conductances across the cell membranes. The morphology of these waveforms dependent on the cell type and location in the respective specialized conduction systems. Thus, slow waves by gastric cells are triangular with rapid depolarization and repolarization phases. Slow waves of the small and large intestinal smooth muscle cells have an initial depolarizing phase generated by the pacemaker cells, interstitial cells of Cajal of the myenteric plexus (ICC-MY) (Dickens et al., 1999), and a second phase mediated by ICC within the smooth muscle (ICC-IM) (Bauer et al., 1985; Dickens et al., 2001). Superimposed upon these slow waves are regenerative Ca^{2+} spikes, which only develops when the membrane potential is above a threshold; these spikes are intrinsic to the smooth muscle cells (Lee et al., 1999; Suzuki and Hirst, 1999; Lammers and Slack, 2001). Cardiac APs have a rapid upstroke, rapid repolarization and a plateau phase. The reader is directed to these articles here for a review of the ionic currents mediating GI slow waves and cardiac APs (Lammers et al., 2009; Tse et al., 2016c). Both systems show features of restitution, where the duration of electrical activity shortens in response to higher pacing rates. Thus, slow waves in the gastric antrum normally discharges at a frequency of 1–2 cycles per minute (cpm) (Bauer et al., 1985; Publicover and Sanders, 1986). Upon a higher rate of extrinsic stimulation, it can exhibit waves at 7 cpm (Sarna and Daniel, 1973). This can be explained by restitution mechanisms that result from shortening or abolishing the plateau phase (Publicover and Sanders, 1986). Similarly, cardiac restitution is responsible for normal shortening of APD observed in response to faster heart rates, and is thought to be an adaptive mechanism for preserving diastole at these rates.

ARRHYTHMOGENIC MECHANISMS

Both cardiac and gastrointestinal arrhythmias can be classified into non-reentrant and reentrant mechanisms (Table 1).

Non-reentrant Activity

Non-reentrant activity refers to aberrant initiation due to either enhanced automaticity or triggered activity. Enhanced pacemaker activity in the heart can arise from a depolarizing shift of the maximum diastolic potential, a hyperpolarizing shift of the threshold potential or a faster rate of rise of the spontaneous depolarization (Jalife et al., 2009). In the GI tract, it has been observed in the human stomach (O'Grady et al., 2011, 2012), and the small intestine during inflammation, infection and mitochondrial disease (Der et al., 2000; Scheffer and Smout, 2011; Wu et al., 2013). By contrast, triggered activity refers to activity initiated by the preceding electrical activity (Figure 1). In the heart, it is due to early or delayed afterdepolarization phenomena (EADs and DADs, respectively), which are secondary depolarization events occurring before the subsequent AP (Craneffeld, 1977; January et al., 1991),

which can initiate arrhythmias (Tse, 2015). EADs are typically generated when the repolarization phase of the cardiac AP is prolonged, leading to reactivation of the L-type Ca^{2+} channels (I_{Ca}) (January and Riddle, 1989) or activation of the Na^{+} - Ca^{2+} exchanger (I_{NCX}) secondary to spontaneous Ca^{2+} release from the sarcoplasmic reticulum (Szabo et al., 1994). DADs are associated with Ca^{2+} overload, which activates the following Ca^{2+} -sensitive currents: the non-selective cationic current, I_{NS} , the sodium-calcium exchange current, I_{NCX} , and the calcium-activated chloride current, $I_{\text{Cl,Ca}}$, which together constitute the transient inward current (I_{TI}) (Guinamard et al., 2004). These afterdepolarizations are analogous to “second potentials” that could generate the ectopic beats observed in the GI tract (Qian et al., 2003). However, the mechanism underlying their generation is different. Increased automaticity here is related to increased stretch, enhanced by acetylcholine and inhibited by adrenaline (Daniel and Chapman, 1963). Their ionic contributions are yet to be determined, but could potentially involve Ca^{2+} entry from the extracellular space or Ca^{2+} release from the endoplasmic reticulum (Suzuki and Hirst, 1999; Lammers and Slack, 2001). Premature slow waves, which presumably arise from such secondary potentials, precede and may be a prerequisite for the initiation of tachygastria (Lammers et al., 2008).

Reentry

Reentry is a frequently encountered mechanism and occurs when an impulse fails to extinguish itself and re-excites a region that has recovered from refractoriness. In the heart, it can take place in the presence of an obstacle (circus-type), or in the absence of an obstacle (reflection or phase 2 reentry). Three requirements for circus-type reentry are reduced conduction velocity (CV), unidirectional conduction block and an obstacle around which the AP can circulate. This obstacle can be a permanent anatomical abnormality (anatomical reentry) (Figure 2), but can also involve a functional core of refractory tissue that arises dynamically (functional reentry) (Figure 3; Garrey, 1914).

There are a number of similarities between reentry occurring in the GI tract and the heart: initiation of a premature beat precede reentry, reentry can be non-sustained or sustained. Additionally, anisotropic conduction is important in both systems in reentry (Angeli et al., 2013). However, several differences are observed (Lammers et al., 2008). Firstly, gastric tachyarrhythmia occurs at a much lower frequency of 10–15 cycles per minute, whereas ventricular tachyarrhythmia typically occurs at rates between 100 and 250 beats per minute (bpm). Secondly, unidirectional conduction block is a prerequisite of circus-type reentry (Allessie et al., 1976, 1977; Lammers et al., 1990), but this is not the case in tachygastria as shown by electrograms recorded from the canine stomach using a multi-electrode array (Lammers et al., 2008).

Anatomical Reentry

Circus-type reentry involving an anatomical obstacle was first demonstrated by the ring model using disks made from sub-umbrella tissue of a jellyfish (Mayer, 1906). Mayer made the following observations. The disks were paralyzed when they

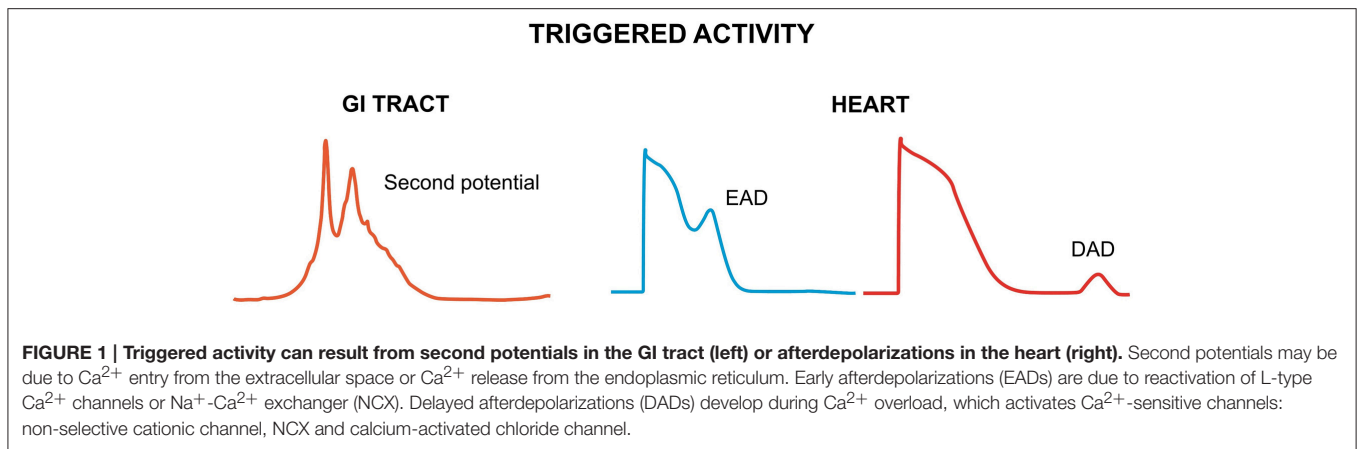
TABLE 1 | Arrhythmogenic mechanisms in the GI and cardiovascular systems can be divided into non-reentrant and reentrant activity.

Classification	Mechanism	Sub-types	Clinical relevance	References
Non-reentrant	Enhanced pacemaker activity	–	GI: Gastroparesis, intestinal infection, inflammation and mitochondrial dysfunction	Der et al., 2000; O'Grady et al., 2011, 2012; Scheffer and Smout, 2011; Wu et al., 2013
		–	Cardiac: increased sympathetic tone, hypovolaemia, ischaemia, electrolyte disturbances	Jalife et al., 2009; Tse, 2015
	Triggered activity	Second potentials (GI)	Tachygastric	Daniel and Chapman, 1963; Suzuki and Hirst, 1999; Lammers and Slack, 2001; Qian et al., 2003; Lammers et al., 2008
		Early afterdepolarizations (cardiac)	Long QT syndromes, heart failure	Weiss et al., 2010; Maruyama et al., 2011
	Delayed afterdepolarizations (cardiac)	Ca ²⁺ overload Catecholaminergic polymorphic ventricular tachycardia (CPVT), heart failure	Priori et al., 2001; Nam et al., 2005	
Reentrant	Obstacle	Anatomical (GI and cardiac)	GI: circumferential reentry Cardiac: AV nodal reentrant tachycardia, AV reentrant tachycardia and pre-excitation syndromes, post-myocardial infarction, fibrosis in cardiomyopathies, myocarditis, cardio-metabolic disorders	Sinha et al., 2002; Angeli et al., 2013 Wong et al., 2013; Vassiliou et al., 2014; Baksi et al., 2015; Tse et al., 2015a,b; Tse et al., 2016a
		Functional (GI and cardiac)	GI: double-loop Cardiac: spiral and scroll wave, figure-of-eight, torsade de pointes	Gullikson et al., 1980; Stoddard et al., 1981; Kim et al., 1987; Lammers et al., 2012; Angeli et al., 2013 Allessie et al., 1973, 1975, 1976, 1977, 1989; Smeets et al., 1986; Rensma et al., 1988
		Reflection (cardiac)	Ischaemia	Antzelevitch et al., 1980; Antzelevitch and Moe, 1981; Rozanski et al., 1984; Lukas and Antzelevitch, 1989; Auerbach et al., 2011; Tung, 2011
	No obstacle	Phase 2 (cardiac)	Ischaemia, Ca ²⁺ overload, Brugada syndrome	Kuo et al., 1983; Di Diego and Antzelevitch, 1993; Lukas and Antzelevitch, 1996; Shimizu et al., 2005

were separated from their sense organs. They do not pulsate in seawater, but did so when ring-like cuts were made from the tissue. Upon mechanical stimulation, the disks then showed “rhythmical pulsations so regular and sustained as to recall the movement of clockwork.” Later, Mines used a ring-like preparation of the tortoise heart, demonstrating that it was possible to initiate circus-type re-entry by electrical stimulation (Mines, 1913). He noted that when an excitation wave has a high CV and a long duration, the whole circuit would be excited at the same time, causing the excitation to die out. By contrast, when the wave has slow CV and a short ERP, the tissue ahead of the excitation wave would recover from refractoriness and can therefore be re-excited, resulting in circus-type re-entry. Mines predicted “a circulating excitation of this type may be responsible for some cases of paroxysmal tachycardia as observed clinically.” He was the first to formulate the three criteria for circus-type reentry mentioned above. It was later recognized that conduction of the excitation must be sufficiently slow to allow the tissue

ahead in the circuit to recover from refractoriness so that it can be re-excited. It is useful to describe this excitation as a propagating wave (Weiss et al., 2005), with a wavefront that represents action potential depolarization, and a tail that represents repolarization (Weiss et al., 2000) with the assumption that APD is equal to the effective refractory period (ERP) (Tse et al., 2016i). The length of this excitation wave (λ) is given by $CV \times ERP$ (Wiener and Rosenblueth, 1946), and must be smaller than the length of the circuit in order for re-entry to be successful. Thus, reduced and increased λ is associated with greater and lesser likelihood of circus-type reentry, respectively (Smeets et al., 1986; Vaidya et al., 1999; Osadchii and Olesen, 2009; Osadchii et al., 2009, 2010; Osadchii, 2010, 2012a,b, 2014a,b, 2016; Tse et al., 2012, 2016b,c,d,e,f,g,h,j; Tse and Yan, 2016; Tse, 2016a,b,c).

Anatomical reentry is relevant in different types of tachyarrhythmias, such as AV nodal reentrant tachycardia, AV reentrant tachycardia and pre-excitation syndromes including Wolff-Parkinson-White Syndrome. It can be also



the mechanism underlying atrial and ventricular tachycardia, where the AP wave circulates around a fixed fibrotic scar, such as post-myocardial infarction (Sinha et al., 2002). Moreover, micro-reentry around areas of fibrosis, which is observed in conditions such as cardiomyopathies, myocarditis and cardio-metabolic disorders of hypertension and diabetes mellitus (Wong et al., 2013; Vassiliou et al., 2014; Baksi et al., 2015; Tse et al., 2015a,b, 2016a). Anatomical reentry involving a fixed pathway has also been observed in the small intestine: re-entrant activity propagating around the circumference has been termed circumferential reentry (Angeli et al., 2013), which is analogous to the anatomical reentry (Allessie et al., 1977). In both cases, this is a fixed circuit whose length is determined by the perimeter of the anatomical obstacle, with an excitable gap between the depolarization wavefront and the repolarization tail. The revolution time is inversely proportional to the CV.

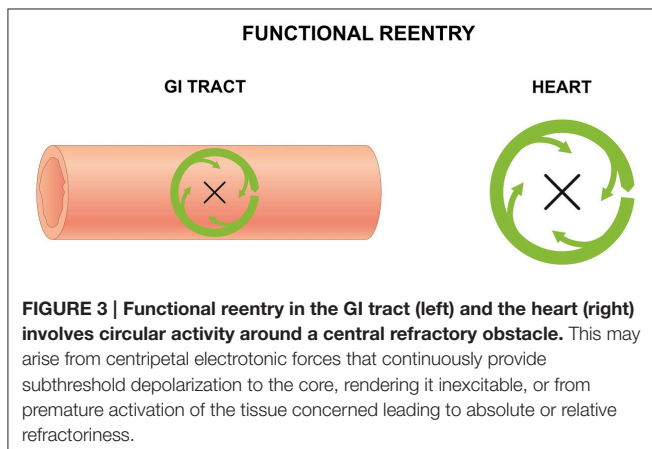
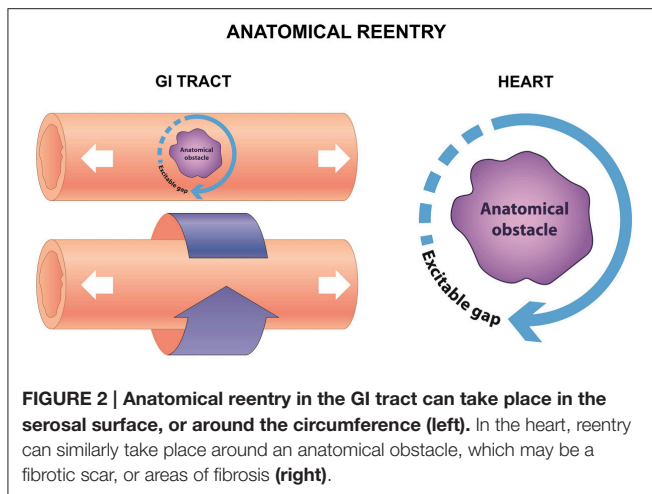
Functional Reentry

For functional reentry without an anatomical obstacle, seminal experiments in rabbit atrial preparations provided its direct evidence in support of Garrey's prediction. Allessie applied electrical stimulation at the center of the atrial preparation and found that electrical activation elicited by regular stimuli spread normally throughout the atrial tissue (Allessie et al., 1973). Contrastingly, premature stimuli elicited electrical activity that only propagated in the direction of shortened ERPs and at a reduced CV. Spatial dispersion in the refractory periods (Allessie et al., 1976) was responsible for unidirectional block of the premature AP (Allessie et al., 1975). To explain the lack of activity in this core, it was proposed that center of the circle was held above threshold by the electrotonic influences of the depolarization wavefront propagating centripetally, which rendered it inexcitable. The AP would continue to revolve around this functional core of refractory tissue. Subsequent experiments utilizing transmembrane potential recordings led to the development of the leading circle model (Allessie et al., 1977). The circuit is defined entirely by the electrophysiological properties of the tissue. The smallest circuit permitting successful re-entry, called the leading circle, is one in which the circulating wavefront can just re-excite the tissue ahead that is still in

its relative refractory period. A variation of functional reentry termed spiral wave reentry was described later (Krinsky, 1966). A spiral wave is a two-dimensional wave of excitation emitted by a self-organizing source of functional reentrant activity, termed a rotor. The three-dimensional equivalent of a spiral wave is a scroll wave.

Spiral waves were described earlier in the Belousov-Zhabotinsky chemical reaction, in which cerium catalyzes the malonic acid oxidation by bromate (Belousov, 1958; Zaikin and Zhabotinsky, 1970). The ratio of cerium (IV) to cerium (III) undergoes repeated temporal oscillations, producing spiral waves with alternating colors (Müller et al., 1985; Epstein, 2006). Later, spiral waves were reproduced in theoretical models of cardiac tissue (Moe et al., 1964; Courtemanche and Winfree, 1991; Leon et al., 1994) and demonstrated in thin slices of epicardial muscle using a potentiometric dye, whose spectral properties are altered by voltage (Salzberg et al., 1973). Previous experiments have demonstrated an excitable phase singularity, although it remains non-excited and can act as a functional obstacle around which the spiral wave can travel (Ikeda et al., 1996). Spiral waves are not fixed in space but can drift (Pertsov et al., 1993). This is accompanied by a Doppler effect, in which the frequency of excitation at a given measurement site depends on its location relative to the drifting spiral wave (Davidenko et al., 1992). Therefore, the sites anterior to the wave are excited faster than those posterior to the wave. Such a mechanism may underlie torsade de pointes (Dessertenne, 1966), whereby two widely separated foci discharging at different frequencies were suggested to underlie periodic torsion of the QRS axis.

Functional reentry in the GI tract can have analogous mechanisms (Gullikson et al., 1980; Stoddard et al., 1981; Kim et al., 1987; Lammers et al., 2012; Angeli et al., 2013). In the stomach, functional reentry can take a circular route (O'Grady et al., 2011) or have a double loop morphology, consisting of two wavefronts traveling in opposite directions (Lammers et al., 2008). The latter is similar to the cardiac figure-of-eight reentry generated by two counter-rotating spiral waves separated by a small distance (El-Sherif et al., 1981). Functional reentry has also been observed in the small intestine (Lammers et al., 2012; Angeli et al., 2013), which is analogous to Allessie's leading circle



model of reentrant tachycardia in the atria with the following similarities (Allessie et al., 1977). Firstly, the length of the circuit is determined by electrophysiological rather than anatomical characteristics. Secondly, the dimensions of the circuits are variable rather than fixed. Thirdly, the depolarization front and the repolarization tail are in close proximity to each other, and so there is only a partially excitable gap between the two. Fourthly, the center of the circuit contains excitable rather than inexcitable tissue, which would permit termination of the reentrant tachycardia if an impulse shorts the circuit by crossing the circle. Finally, the time for one rotation is inversely proportional to the RP of the tissue rather than to the CV of the wave. As pointed out, these circuits can meander along the tissue and are more unstable than anatomical reentrant circuits (Lammers, 2013). This supports previous modeling studies suggesting that self-sustaining spiral waves can be generated in anisotropic smooth muscle syncytium in the intestines (Miftahof, 2005).

AUTONOMIC MODULATION

Coumel originally proposed a triads of conditions necessary for arrhythmogenesis, which are trigger, substrate and modulating

factors (Coumel et al., 1967, 1978; Coumel, 1993). In both systems, arrhythmias are susceptible to autonomic modulation (Smeets et al., 1986; El-Sherif et al., 1987; Ouyang et al., 2015). In the heart, parasympathomimetic agents such as acetylcholine reduces CV, APD and ERP, thereby decreasing the excitation wavelength to promote reentry (Smeets et al., 1986; Oliveira et al., 2011). In the presence of sympathomimetic agents such as noradrenaline, the Ca^{2+} transient increased (Bers, 2002a,b), and forward activation of NCX, with consequent EADs and triggered activity (Patterson et al., 2006). Sympathetic activation in long QT syndromes and catecholaminergic polymorphic ventricular tachycardia can exacerbate ventricular arrhythmias (Shen and Zipes, 2014). This may be due to increased heterogeneities in repolarization and refractoriness, thereby producing a favorable substrate for reentry. Autonomic dysfunction, particularly affecting vagal nerves, is known to result in GI motility disorders in diabetes mellitus (Feldman and Schiller, 1983). Slow wave arrhythmias in the small intestine mediated by hyperglycaemia is likely the result of higher sympathetic compared to parasympathetic activity (Ouyang et al., 2015). Interestingly, diabetic rats have a higher likelihood of developing functional reentry in the small intestine compared to the control rats (Lammers et al., 2012). The underlying cause is unclear, abnormalities in the enteric nervous system or the smooth muscle itself may be affected but autonomic dysfunction can well play an important role.

CLINICAL RELEVANCE

The question remains, even if arrhythmias occur in the GI tract, are they clinically significant? To answer this, the following evidence should be considered. Gastric tachy- and brady-arrhythmias have been associated with gastroparesis (Bortolotti et al., 1990), in which reduced CV of slow waves has been observed (O'Grady et al., 2012). They also appear to be predictive of dyspeptic symptoms in systemic sclerosis (McNearney et al., 2009). Gastric tachyarrhythmias can be observed following administration of opiate drugs, after anesthesia or post-operatively (Stoddard et al., 1981). Anesthetic agents can act on Ca^{2+} channels directly (Ahn and Karaki, 1988), thereby leading to abnormal slow wave propagation and reentrant arrhythmias. Unexplained nausea and vomiting involves recurrent arrhythmias with abnormal wave propagation and higher frequency in the distal stomach, as demonstrated by gastric serosal electrophysiological study (Abell et al., 2009). Intestinal arrhythmias occur in diabetes mellitus (Lammers et al., 2012; Ouyang et al., 2015) and mesenteric ischemia (Seidel et al., 1999; Irimia and Wikswo, 2008) and may play a role in post-operative ileus, as suggested previously (Angeli et al., 2013).

However, only limited evidence exists on the mechanisms of arrhythmias occurring in these situations, but theoretical considerations suggest reentry playing a key role. Thus, spiral waves are inducible in the myocardium or intestinal smooth muscle because of intrinsic electrical heterogeneities and anisotropic properties (Miftahof, 2005) and their formation

would be made more favorable in the above pathological conditions, which increase tissue heterogeneity and anisotropy (Gizzi et al., 2010). Alternatively, inflammation could result in loss of ICC-MY activity, suggesting that pacemaker activity is impaired (Yanagida et al., 2007; Gizzi et al., 2010). A better understanding of electrophysiology is key to developing effective treatment for these motility disorders. For example, almost all anti-arrhythmic agents in the heart are modulators of ion channels, which can also be targeted in the GI tract.

Bradyarrhythmias, although not discussed in this review, are also observed in many GI pathologies. Thus, the use of opiate drugs can abolish slow waves or lead to irregular patterns of slow waves, termed amyogenesis and dysmyogenesis, respectively (Sarna and Otterson, 1990). Other causes, where loss of GI pacemaker cells is observed, include achalasia (Chen et al., 2013), gastroparesis (O'Grady et al., 2012), functional dyspepsia (Jung et al., 2012), Hirschsprung disease (Yamataka et al., 1995), and slow transit constipation (Lyford et al., 2002).

Irritable bowel syndrome, a triad of altered bowel habits, bloating and abdominal pain without an organic cause (Sinagra et al., 2016) with either a diarrhea- or constipation- predominant phenotype, is a chronic debilitating relapsing and remitting condition. Loss of ICC-MY (Eshraghian and Eshraghian, 2011), Na⁺ channel mutations (Saito et al., 2009) and altered microbiota profile (Tana et al., 2010; Ng et al., 2013) increasing the intestinal Cl⁻ channel activity have been demonstrated (Chang and Talley, 2010). These changes could lead to impaired initiation of slow wave activity in the intestines. Furthermore, these abnormalities are accompanied by alterations in ICC-MY network and electrophysiological remodeling (Akbarali et al., 2010) caused by chronic inflammation (Der et al., 2000), and could conceivably serve as favorable substrates for reentrant arrhythmogenesis. Interestingly, clinical evidence does not support the notion that autonomic dysfunction plays a role in the symptoms associated with gastrointestinal motility disorders such as chronic dyspepsia or constipation (Vazeou et al., 2004).

Recently, a new syndrome characterized by Chronic Atrial and Intestinal Dysrhythmia, termed CAID syndrome, has been discovered, in which features of both sick sinus syndrome (SSS) (of alternating bradycardia-tachycardia, Chen et al., 2016b) and chronic intestinal pseudo-obstruction (CIPO) are observed (Chetaille et al., 2014). In CAID, mutation in SGOL1, a component of the cohesin complex, was the underlying cause. Both SSS and CIPO are caused by pacemaker dysfunction: SSS can be caused by loss-of-function mutations in the SCN5A gene encoding for the sodium channel, whereas CIPO is caused by loss of the ICC-MY (Feldstein et al., 2003; Struijs et al., 2008). Moreover, atrial fibrillation gut syndrome (AFGS) was used to describe reduced gastrointestinal motility, e.g., gastroparesis, following radiofrequency catheter ablation for atrial fibrillation (Lee and Lee, 2014). This may

arise from vagus nerve injury from electrical injury used for ablation.

FUTURE TREATMENT OPTIONS AND CONCLUDING REMARKS

Improved understanding of the abnormal electrophysiology underlying GI motility disorders can lead to the development of more effective treatment options. In terms of pharmacotherapy, ion channels represent attractive targets. For example, functional constipation or constipation-predominant IBS can be managed by the chloride channel protein 2 agonist, lubiprostone (Camilleri et al., 2006; Andresen et al., 2007), whereas functional diarrhea or diarrhea -predominant IBS can be managed by its inhibitor crofelemer (Manabe et al., 2010; Yeo et al., 2013). For intervention, analogous to cardiac pacing for heart blocks, gastric electrical stimulation can be used in severe cases of gastroparesis (Abrahamsson, 2007). Similarly, colonic electrical stimulation can potentially be used for chronic functional constipation or constipation-predominant IBS (Chen et al., 2016a). Ablation has been used extensively for the management of atrial fibrillation, but its role in gastrointestinal arrhythmogenesis is unclear.

Despite the importance of GI electrophysiology, it is considerably underdeveloped compared to the cardiac electrophysiology, which is a sub-specialty of cardiology (O'Grady et al., 2014). A deeper understanding of the molecular basis and physiological mechanisms underlying GI motility disorders will enable the development of better diagnostic and therapeutic tools and the advancement of this field.

AUTHOR CONTRIBUTIONS

GT: Design of manuscript; drafted and critically revised the manuscript for important intellectual content; preparation of figures. EL: Acquired and interpreted primary research papers; critically revised the manuscript for important intellectual content; preparation of figures. AL: Analyzed and interpreted primary research papers; critically revised the manuscript for important intellectual content. BY: Analyzed and interpreted primary research papers; critically revised the manuscript for important intellectual content. SW: Analyzed and interpreted primary research papers; critically revised the manuscript for important intellectual content.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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