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Advances in Research on Pacemaking Function of Interstitial Cell of Cajal in Gastrointestinal Tract

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1. Introduction

Most visceral smooth muscles, especially gastrointestinal (GI) smooth muscle, display spontaneous rhythmic contractions in the absence of neuronal or hormonal stimulation, which are associated with their physiological functions. The contractile behavior of gastrointestinal (GI) smooth muscles depends to a considerable extent on the intrinsic electrical activities of the muscles. This is particularly true of the phasic portions of the GI tract where cyclic depolarizations and repolarizations, referred to as slow waves, determine contractile frequency and maintain the phasic nature of contractions. Slow waves are of great functional importance because they determine the rate and timing of GI smooth muscle activity, and their impairment is likely to cause various motility disorders.

GI smooth muscles exhibit a wide range of electrical behaviors (Szurszewski, 1987), and understanding the mechanisms of these events has been the goal of physiologists for more than half a century. Electrical activity can vary from slow changes in membrane potential, to hyperpolarization and depolarization responses to neurotransmitters, to oscillatory slow wave activity, to fast Ca^{2+} action potentials. All this behavior can be recorded during impalements of a single smooth muscle cell, which suggests that a plethora of ionic conductances and regulatory mechanisms are at play in GI muscles. Such diversity is almost unprecedented in other excitable cells. Diversity, the small size of smooth muscle cells, and the structural complexities of GI muscles have slowed progress toward understanding the ionic basis for electrical rhythmicity. The electrical output of GI muscles is a product of contributions from two electrically coupled cell types, smooth muscle cells and interstitial cells of Cajal (ICC) (Sanders,1996). These cells have distinct electrical missions and express different types of ionic conductances to accomplish those tasks. ICC generate slow waves and conduct them into adjacent smooth muscle cells to generate spontaneous contractions (Sanders, 1996; Thuneberg et al, 1982; Huizinga et al, 1995; Koh et al, 1998; Sanders et al, 1999). Smooth muscle cells respond to the depolarization/repolarization cycle imposed by ICC.

Regulatory input from nerves, hormones, and paracrine substances are superimposed upon the ongoing myogenic activity. Responses to biologically active substances result from modulations of ionic conductances that are already active and going through dynamic changes in open probability during the slow wave cycle and from activation of new

conductances that do not participate in basal electrical activity (Sanders et al, 1999). The conductances affected by regulatory substances could be expressed in either smooth muscle cells or ICC. Finally, the conductance of both cell types mutually affects the electrical behavior of the total syncytium.

2. Morphological and physiological properties of ICC in gastrointestinal tract

Morphological studies have shown that each of the pacemaker regions in the GI tract contains ICC (Dickens et al, 1999; Suzuki et al, 1986; Burns et al, 1996; Thuneberg, 1982). To anatomists, the morphological features of ICC suggested that ICC may serve as pacemaker cells (Thuneberg, 1982; Faussone Pellegrini et al, 1997). Two types of ICC are found in the guinea-pig gastric antrum, namely ICC-MY and ICC-IM (Burns et al., 1997). Both ICC-MY and ICC-IM express Kit receptors on their cell membrane and can be identified by ACK2 (neutralizing Kit antibody) (Torihashi et al., 1995; Komuro et al., 1996; Burns et al., 1997). ICC-MY which lie in the plane of the myenteric plexus between the circular and longitudinal muscle layers (Sanders et al, 2006) have triangular or irregularly shaped cell bodies with multiple processes which interconnect to form a dense network with other ICC-MY (Burns et al., 1997; Dickens et al., 1999). There are also ICC in the small intestine near the submucosal surface of the circular muscle layer in close association with the nerve terminals in the deep muscular plexus (DMP) which cells are called ICC-DMP (Sanders et al,1999; Ward and Sanders, 2006). Pacemaker cells in the colon along the submucosal surface of the circular muscle layer are referred to as ICC-SM. The gastric antrum and pylorus also have populations of ICC-SM (Horiguchi, 2001; Ward, 1998), but the physiological roles of these ICC have not been described. There are important differences in the organization of electrical pacemaker activity between the small and large intestine. In the small bowel, electrical slow waves are generated by ICC-MY; slow waves in the colon, in contrast to the small intestine, originate in ICC-SMs and actively propagate along the submucosal surface into the circular muscle (Lee et al, 2009).

Intracellular recordings made from the guinea-pig gastric antrum revealed a rhythmic generation of pacemaker potentials with a fast rising phase followed by plateau components, slow waves with triangular form and square shaped follower potentials, each from ICC-MY, circular and longitudinal smooth muscle, respectively (Dickens et al., 1999). The amplitude and maximum rate of rise (dV/dtmax) of pacemaker potentials are larger than those of either slow waves or follower potentials, while the frequency and duration of pacemaker potentials and potentials recorded from smooth muscle cells are similar (Dickens et al., 1999, 2000; Hirst and Edwards, 2001; Kito and Suzuki, 2003). Simultaneous recordings of the electrical responses from ICC-MY and smooth muscle cells show that pacemaker potentials appear prior to slow waves or follower potentials, suggesting that the signals are generated in ICC-MY and are propagated to smooth muscle cells, possibly through gap junctions (Dickens et al., 1999; Hirst and Edwards, 2001). Thus, the potentials produced in the smooth muscle cells are largely passive, as an electrotonic potential of the pacemaker potentials. The difference between the active and passive properties of the potential is apparent when the membrane is hyperpolarized by a group of chemicals which open ATP-sensitive K+-channels (K-channel openers), in that the amplitude of the pacemaker potentials is increased while that of the slow waves is decreased. The latter is due to inhibition of the first component, probably because the decrease of input resistance induced by hyperpolarization decreases the amplitude of the passive electrical responses (Kito and

Suzuki, 2003). On rare occasions, discharges of membrane noise (unitary potentials) are generated during the interval between pacemaker potentials (Hirst and Edwards, 2001; Kito et al., 2002). The frequency of the generation of unitary potentials increases with time after the cessation of the pacemaker potentials, suggesting that depolarization of the membrane due to summation of unitary potentials then triggers pacemaker potentials (Hirst and Edwards, 2001; Kito et al., 2002). Pacemaker potentials recorded from ICC-MY in the mouse gastric antrum also showed properties similar to those of the guinea-pig stomach (Hirst et al., 2002). Immuno-histochemical studies have shown that the density of ICC-MY is highest in the greater curvature, while the population is reduced successively towards the lesser curvature and that they are either absent or distributed very sparsely in the lesser curvature (Hirst et al., 2002).

Additionally, colon and stomach have ICC intermixed with smooth muscle fibers. These intramuscular ICC are referred to as ICC-IM which are critical for inputs from enteric motor neurons (Ward and Sanders, 2006; Horiguchi, 2001). In contrast to ICC-MY, the ICC-IM are spindle shaped cells with bipolar processes that run parallel to the direction of the smooth muscle cells (Burns et al., 1997; Dickens et al., 2001; Hirst et al., 2002). In isolated bundles of the circular smooth muscle layer of the mouse gastric antrum, transmural nerve stimulation evokes two types of inhibitory junction potentials (IJP), both fast-IJP and slow-IJP, with a following depolarizing excitatory junction potential (EJP)(Suzuki et al., 2003). Since atropine and Nω-nitro-L-arginine (nitroarginine) inhibit the EJP and slow-IJP, respectively, it is likely that the former is generated in response to released acetylcholine and the latter is generated by the release of nitric oxide (Suzuki et al., 2003). On the other hand, the EJP and slow-IJP are absent in the antrum region of *W/WV* mice which lack ICC-IM. Therefore, ICC-IM may be transducing both cholinergic and nitrergic nerve signals to circular smooth muscle cells in the mouse gastric antrum (Suzuki et al., 2003). Similar results are also obtained in smooth muscle isolated from the fundus region of *W/WV* mutant mice and *steel* mutant mice (Burns et al., 1996; Beckett et al., 2002). In the small intestine, ICC-IM are replaced by a dense network of ICC located at the level of deep muscular plexus; ICC-DMP are intimately associated with the enteric nerve terminals (Torihashi, et al, 1993). The enteric nerve terminals appear to form synapses preferentially with ICC-DMP rather than the smooth muscle cells (Wang et al, 1999). In an ultrastructure study, it was found that ICC-DMP were innervated by both cholinergic and nitrergic nerves and were the only cells to possess specialized synapse-like junctions with nerve varicosities and gap junction contacts with the smooth muscle cells (Wang et al, 2003; Ward and Sanders, 2006). The functional role of ICC-DMP is difficult to prove since they persist in the small intestine of W/Wv and Sl/Sld mutants. However, the loss of ICC-DMP by blocking Kit was shown to cause loss of cholinergic and nitrergic neural responses (Ward et al, 2006), suggesting that in the small intestine, ICC-DMP play a critical role in the cholinergic and nitrergic neurotransmission.

2.1 Pacemaking activity in ICC

ICC are unique cells that generate electrical pacemaker activity in gastrointestinal (GI) smooth muscles. Many previous studies have attempted to characterize the conductances responsible for pacemaker current and slow waves in the GI tract, but the precise mechanism of electrical rhythmicity is still debated. ICC are pacemaker cells in the small bowel, and therefore this cell type must express the mechanism responsible for slow wave activity. Koh et al (1998) early demonstrated that isolated ICC cultured for 1~3 days from

the murine small intestine were rhythmically active, producing regular slow wave depolarizations with waveforms and properties similar to slow waves in intact tissues. The spontaneous activity of ICC was inhibited by reduced extracellular Na^+, gadolinium, and reduced extracellular Ca^{2+}. Voltage clamp studies showed rhythmic inward currents that were probably responsible for the slow wave activity. The subsequent experiments also indicated that both the whole-cell currents and single-channel currents reversed at 0 mV when the equilibrium potentials of all ions present were far from 0 mV(Koh et al, 2002). The recordings from on-cell patches revealed oscillations in unitary currents at the frequency of pacemaker currents in ICC. Voltage-clamping cells to -60 mV did not change the oscillatory activity of channels in on-cell patches. Depolarizing cells with high external K+ caused loss of resolvable single-channel currents, but the oscillatory single-channel currents were restored when the patches were stepped to negative potentials. This conductance may contribute to the pacemaker current and generation of electrical slow waves in GI muscles. ICC have been studied after chemical isolation and under culture conditions, but concerns that these methods affect the intrinsic properties have hindered progress in our understanding of ICC. To overcome this problem, Wang et al (2008) developed a method to obtain electrophysiological recordings from ICC in situ. The critical feature is the ability to make high resistance seals onto cells that are embedded within tissue to obtain patch clamp recordings. Their results showed a prominent presence of a chloride channel, one of the proposed ICC pacemaker channels.

Microelectrode arrays (MEAs) are useful in spatiotemporal studies of pacemaker activity in the gut. Previously, MEA analysis was used to investigate neuronal activity in brain slices that generate action potentials with a high rate of increase. To record electrical slow waves originating from ICC in musculature preparations, microelectrodes with low impedance (<10 kU at 1 kHz) have been recently employed. In the guinea pig stomach (Nakayama et al., 2006), such a high-performance MEA system has revealed spontaneous electrical activity synchronised with resolving phase shifts over a range of several hundred micrometers. The electrical activity frequently propagates from the oral to the anal direction, even in the presence of tetrodotoxin (TTX). These observations indicate that the ICC-MY network also contributes to coordinated actions of gut motility and probably enables smooth contractions. In the small intestine of wild-type mice (Nakayama et al., 2009), the propagation of ICC electrical activity is also measurable over an area of 1 mm^2, although oral-to-anal and anal-to-oral propagations are both observed. In contrast, in W/Wv mice with a largely reduced population of ICC-MY in the small intestine, electrical activity is significantly smaller and fluctuates with no clear propagating direction.

It has been demonstrated that ICCs are pacemakers in the gastrointestinal tract using neutralizing antibody to block the development of ICCs and animals with gene mutation. ICC-MY in these animals were decreased dramatically or devoid, meanwhile slow waves and associated spontaneous activities were also inhibited significantly (Huizinga et al, 1995; Maeda et al, 1992; Torihashi et al, 1995). In the stomach and small bowel (Dickens et al., 1999; Kito et al, 2003), two kinds of electrical activities with similar frequencies were recorded by using microelectrode technique: pacemaker potentials and slow waves. Pacemaker potentials were proved to be generated by ICC-MY, while slow waves were generated by smooth muscle cells. Compared to slow waves, pacemaker potentials display greater amplitude and longer duration and usually precede slow waves. Pacemaker potentials generated by ICC-MY were passively propagated to the smooth muscle cells to

generate slow waves. All these results demonstrate that ICC-MY is the pacemaker trigging spontaneous activities in gastrointestinal tract. The most direct evidences to support this hypothesis are that both freshly isolated and cultured ICCs generate spontaneous rhythmic electrical activity as it is recorded in intact tissues.

3. Mechanisms Involved in generation of ICC pacemaker currents

3.1 Intracellular calcium activities

It has been still controversial about the mechanism of generating pacemaker currents by far, but the role of intracellular calcium in the generation has been widely proved (Nakayama et al., 2007). Simultaneous recordings of intracellular calcium and electrical activity in ICCs revealed that intracellular calcium oscillations in ICCs were synchronized with slow waves, which indicates the close relationship between the intracellular calcium oscillations and the pacemaker activities of ICCs (Liu et al, 2005a; Liu et al, 2005b). Similar activities were also observed in ICCs of murine stomach and rabbit urethra (Johnston et al, 2005). Moreover, the evidence which 1,2-bis (2-aminophenoxy) ethane- N,N,N′,N′-tetraacetic acid acetoxymethyl ester (BAPTA-AM), an intracellular calcium chelator inhibited both pacemaker potentials and slow waves of murine intestine demonstrates the crucial role of intracellular calcium in the generation of pacemaker activities in ICCs (Kito et al, 2003). The major pacemaker current is presumed to be generated by Ca^{2+}-activated ion channels. Specifically, intracellular Ca^{2+} ($[Ca^{2+}]i$) oscillations periodicallyactivate plasmalemmal Ca^{2+}-activated ion channels such as Ca^{2+}-activated Cl^- channels (Dickens et al., 1999; Huizinga et al., 2002; Tokutomi et al., 1995) and/or non-selective cation channels (Goto et al., 2004; Koh et al., 1998; Kim et al., 2002; Thomsen et al., 1998; Walker et al., 2002); however, it remains unclear which Ca^{2+}-activated ion channels make a predominant contribution.

Generally, intracellular calcium level are controled by calcium influx from extracellular circumstances and calcium release or uptake by calcium stores and mitochondrion. It was demonstrated that extracellular calium influx is important for the pacemaker activities of ICCs because both removal of extracellular calcium and replacement of extracellular calcium with equimolar Mn^{2+} abolished intracellular calcium oscillations and spontaneous electrical activities (Koh et al, 1998; Sergeant et al, 2000; Torihashi et al, 2002; Johnston et al, 2005). Unlike cardiac pacemaker cells that utilize voltage-gated ion channels to produce spontaneous rhythmicity, intracellular Ca^{2+} dynamics play a crucial role in ICC-MY pacemaking (Torihashi et al., 2002; Yamazawa and Iino, 2002). However, it is very interesting that L-type calcium channels blocker, for example, nicardipine did not affect to slow waves, intracellular calcium oscillations and spontaneous electrical activities of ICCs (Dickens et al., 1999; Torihashi et al, 2002; Johnston et al, 2005; Liu et al, 2005a), but both Ni^{2+} and mibefradil inhibited the upstroke component of pacemaker potentials (Kito et al, 2003). These phenomenon strongly suggest that L-type calcium channels are not involved in the pacemaker activities but a voltage-dependent dihydropyridine-resistant calcium channel may be involved in the pacemaker activity.

Intracellular calcium oscillations induced by calcium release or uptake by calcium stores and mitochondrion is very important factor for generation of pacemaker currents in ICCs. Sanders et al (Sanders et al, 2006) suggest that 'pacemaker unit' comprised of inositol1,4,5,-trisphosphate (IP_3)-operated calcium stores, adjacent mitochondrion and ion channels in the plasma membrane is the basic structure to generate pacemaker currents. The generation of pacemaker currents is initiated by calcium released from IP_3-operated calcium stores and

intracellular high calcium induce calcium uptake by nearby mitochondrion. Calcium oscillations activate ion channels in the plasma membrane to generate pacemaker currents. In this process, calcium handling between calcium stores and adjacent mitochondria is considered as an important premise (Ward et al, 2000). Many studies have shown that thapsigargin and cyclopiazonic acid (CPA), inhibitors of calcium pump in the calcium stores, inhibited slow waves, calcium oscillations and pacemaker currents of ICCs (Torihashi et al, 2002; Ward et al, 2000; Hashitani et al, 2007). The results suggest that calcium store play an important role in the pacemaker activities. It is a common view that IP_3-operated calcium stores are involved in the pacemaker activities (Liu et al, 2005a; Ward et al, 2000), but the role of ryanodine receptor-operated calcium stores in the pacemaker activities have been still debatable. Ward et al (2000) found that ryanodine, an inhibitor of ryanodine receptor, had no significant effect on the pacemaker currents in ICCs, and Malysz et al (2001) also found that ryanodine had no significant effect on the frequency of slow waves. These results indicate that ryanodine receptor-operated calcium release may not be involved in the pacemaker activities in ICCs. However, Aoyama et al (2004) and Liu et al (2005b) reported that ryanodine abolished intracellular calcium oscillations in ICCs of murine intestine and stomach, respectively, and the expression of ryanodine receptor type3 has been confirmed by using RT-PCR technique. These result suggest that both IP_3-operated calcium stores and ryanodine-operated calcium stores are important for the pacemaker activities. In the rabbit urethra ryanodine-operated calcium stores are considered to be prominent in the pacemaker activities in ICCs. The studies demonstrated that ryanodine abolished the intracellular calcium oscillations and pacemaker currents in ICCs from rabbit urethra, whereas 2-APB, an inhibitor of IP_3 receptor, partially but not completely inhibited the amplitude of the intracellular calcium oscillations (Johnston et al, 2005). Moreover, the calcium uptake by mitochondrion is also important for ICCs pacemaker activities in both gastrointestinal tract and urethra, because disruption of the mitochondiral membrane potential with the electron transport chain inhibitors rotenone and antimycin A and mitochondrial uncoupler carbonyl cyanide p-(trifluoromethoxy) phenylhydrazone (FCCP) and carbonyl cyanide m-chlorophenylhydrazone (CCCP) abolished both intracellular calcium oscillations and pacemaker currents in ICCs (Ward et al, 2000).

Since intracellular calcium is a very important factor for pacemaking activity so what kind of channel is activated by intracellular calcium? There are still divergence of views about pacemaker channels and now two kinds of ionic channels are recognized as the candidates for pacemaker channels.

3.2 Non-selective cation channels

Many studies suggested that intracellular calcium level or calcium oscillation is the premise in the generation of ICCs pacemaker currents. However, it is still debatable which phase of calcium oscillations contribute to elicit pacemaker currents in ICCs. Consequently, it is a very important question which kind of channel is responsible for pacemaker currents and the pacemaker channels are sensitive to low caclium or high calcium. Koh et al (1998; 2002) found that pacemaker currents generated by cultured intestinal ICCs from murine could be abolished by removal of Na^+ in external solution. In succession, buffering intracellular calcium by BAPTA-AM induced persistent inward currents, which could be blocked by replacement of Na^+ in external media with equimolar $NMDG^+$. The open probability of the channels responsible for generating pacemaker currents was increased by the decrease of intracellular calcium using different configurations of patch clamp techniques. These results

indicate that a calcium-inhibited non-selective cation channel is responsible for the generation of pacemaker currents in intestinal ICCs from murine. The current—voltage relationship showed that the spontaneous currents reversed at about +17 mV. These observations are consistent with the involvement of a non-selective cation current in the generation of slow waves, but do not rule out contributions from other conductances or transporters. Moreover, the conductance of single-channel was 13pS, and this channel could be strongly activated by calmodulin inhibitors in on-cell and excised patches. The channels were strongly activated by the calmodulin inhibitors calmidazolium and W-7 in on-cell and excised patches, and calmidazolium and W-7 also activated a persistent inward current under whole-cell conditions. Murine ICC express Ca^{2+}-inhibited, non-selective cation channels that are periodically activated at the same frequency as pacemaker currents (Koh et al, 2002).

Recently the electrophysiologic and pharmacologic study also demonstrated the evidences of non-selective cation channel (NSCC) is involved in generation of pacemaker currents in murine intestinal ICC. The application of flufenamic acid, a non-selective cation channel blocker, but not niflumic acid, abolished the generation of pacemaker currents induced by DA-9701. Then pretreatment with a Ca^{2+}-free solution and thapsigargin, a Ca^{2+}-ATPase inhibitor in the endoplasmic reticulum, abolished the generation of pacemaker currents. In addition, the tonic inward currents were inhibited by U-73122, an active phospholipase C inhibitor, but not by GDP-β-S, which permanently binds G-binding proteins. Furthermore, the protein kinase C inhibitors, chelerythrine and calphostin C, did not block the DA-9701-induced pacemaker currents. These results suggest that DA-9701 might affect gastrointestinal motility by the modulation of pacemaker activity in the ICC, and the activation is associated with the non-selective cationic channels via external Ca^{2+} influx, phospholipase C activation, and Ca^{2+} release from internal storage in a G proteinindependent and protein kinase C-independent manner (Choi et al 2009). The cells studied were identified by RT-PCR using cell-specific primers that included Myh11 (smooth muscle cells), Kit (ICC) and Uchl1 (enteric neurons) following electrophysiolgical recordings. Distinct ionic conductances were observed in Kit-positive cells. One group of ICC expressed a basal non-selective cation conductance that was inhibited by an increase in $[Ca^{2+}]i$ in a calmodulin (CaM)-dependent manner (Takeda et al, 2008).

NSCC in both populations of ICC appear to be regulated by a Ca^{2+}–CaM-dependent process providing an insight into the cellular mechanisms underlying the generation of pacemaker activity and unitary/regenerative potentials. Since their discovery, a number of investigators have suggested that transient receptor potential (TRP) channels are the molecular candidates of NSCC. TRPC 1–7 (Tang et al., 2001; Clapham, 2003; Zhu, 2005), TRPV1 (Numazaki et al. 2003; Rosenbaum *et al.* 2004), V4 (Strotmann et al. 2003) and V6 (Niemeyer et al. 2001; Lambers et al. 2004), along with TRPM2 (Tong et al. 2006) and M4 (Nilius et al. 2005) have been shown to bind with CaM and are positively (facilitated) and negatively (inhibited) regulated in a Ca^{2+}–CaM-dependent manner. The Ca^{2+}–CaM regulation of the NSCC observed in the present study suggests that TRP channels may be involved in the Ca^{2+}–CaM-inhibited or -activated conductances expressed in gastric ICC. It has been suggested that TRPM7 encodes for the NSCC responsible for pacemaker activity in acutely cultured ICC from the small intestine (Kim et al. 2005). At the C-terminus, TRPM7 contains an *a*-kinase domain (chaK1), which negatively regulates channel activity when $[Mg^{2+}]i$ increases (Schmitz et al. 2003). At physiological concentrations of Ca^{2+}, only Mg^{2+} and not other divalents can directly modulate TRPM7/ChaK1 kinase (Ryazanova et al.

2004). At high concentrations of [Ca^{2+}]i (>100 μm), CaM (5 μm) can inhibit ChaK1 phosphotransferase activity. Binding of CaM to its substrates or competitive inhibition of the *a*-kinase domain by CaM was suggested to inhibit the phosphotransferase activity (Ryazanova et al. 2004). Although the CaM binding sequence on TRPM7 has not been identified, it is known that Ca^{2+}–CaM inhibits ChaK1 and therefore it is possible that Ca^{2+}–CaM could enhance TRPM7 activity. Since pacemaking was activated by a reduction in [Ca^{2+}]i in ICC cultured from the small intestine (Koh et al. 2002), it is unlikely that TRPM7 activity is responsible for this pacemaker activity. A [Ca^{2+}]i-inhibited conductance expressed in one population of ICC was similar to the conductance previously described in cultured ICC from the small intestine. A conductance of this type appears to be responsible for spontaneous pacemaker activity in the small bowel and may serve the same function in the stomach. The properties of this calcium-inhibited non-selective cation channel are in analogy to those of TPRC4 in transient receptor potential (TRP) family, which is also regulated by intracellular calcium and calmodulin, and both channels have similar conductance (13 versus 17 pS) (Sander et al, 2006). The expression of TRPC4 has been confirmed in cultured ICCs clusters of murine intestine (Torihashi et al, 2002) and stomach (Liu et al, 2005a) by using immunohistochemistry and RT-PCR techniques. However, recently study demonstrated that human GI tract generated slow electrical waves and had ICCs which functioned as pacemaker cells an flufenamic acid, a nonselective cation channel blocker, and 2-APB (2-aminoethoxydiphenyl borate) and La^{3+}, TRPM7 channel blockers, inhibited the slow waves. Also, TRPM7 channels were expressed in ICCs in human tissue (Kim et al, 2009). They suggested that the physiological role of TRPM7 channels in ICCs in human GI tract requires more investigation. As a primary molecular candidate for the NSCC responsible for pacemaking activity in ICCs, TRPM7 may be a new target for pharmacological treatment of GI motility disorders.

3.3 Calcium activated chloride channels

Chloride channels have long been considered as just 'background' channels but recently they have been implicated in important physiological and pathophysiological processes related to blood pressure regulation, muscle tone, volume regulation, synaptic transmission, and cellular excitability. Up to now more and more evidences were demonsted that calcium activated chloride channels are responsible for ICCs pacemaker currents. In smooth muscle cells and, presumably, interstitial cells of Cajal (ICC), the Cl^- equilibrium potential is positive to the resting membrane potential, which makes it possible that selective opening of Cl^- channels contributes to cell depolarization (Kito et al, 2003). Many studies have implicated that inward (depolarizing) pacemaker currents were carried by chloride channels in ICC (Kito et al, 2003; Kito et al, 2002; Zhu et al, 2009).

Early study has been presented that Cl^- channels may contribute to the depolarization phase and the plateau phase of rhythmic membrane potential changes (slow waves) in ICC. First, pharmacological data suggested that Cl^- channels play a role in rhythmic inward currents generated by chemically isolated ICC (Tokutomi et al, 1995). As ICC in the urethra resembled ICC in the GI tract it was thought that they may share a common pacemaker mechanism. Under voltage clamp conditions ICC isolated from the rabbit urethra and networks of ICC cultured from the murine small intestine develop spontaneous transient inward currents (STICs) of similar amplitude and time courses (Koh et al, 1998; Sergeant et al, 2000). However, the ionic basis of pacemaker activity in both tissues appears to be fundamentally different. STICs in urethral ICC were inhibited in Ca2+-free medium and by

the traditional chloride channel blockers A-9-C and niflumic acid (Sergeant et al, 2000). Recent study demonstrated that ICCs exhibite a specialized 'slow wave' current, for example, the reversal of tail current analysis showed this current was due to a Cl^- selective conductance in a new transgenic mouse with a bright green fluorescent protein and the ICC express ANO1, a Ca^{2+}-activated Cl^- channel (Zhu et al, 2009). Removal of extracellular Ca^{2+}, replacement of Ca^{2+} with Ba^{2+}, or extracellular Ni^{2+} blocked the slow wave current. Single Ca^{2+}-activated Cl^- channels with a unitary conductance of 7.8 pS were resolved in excised patches of ICC. Slow wave current was associated with transient depolarizations of ICC in current clamp, and these events were blocked by niflumic acid (Zhu et al, 2009). Most recently study proposed that $[Cl^-]i$ is seen to fluctuate in ICC explant clusters, possibly evoked by rhythmic changes in intracellular calcium. The intracellular chloride concentration in ICC fluctuates to keep its equilibrium potential constant (E_{Cl}). The identification of E_{Cl} as positive to the resting membrane potential of ICC indicates that opening of chloride channels will depolarize ICC (Zhu et al, 2010). These findings demonstrate a role for a Ca^{2+}-activated Cl^- conductance in slow wave current in ICC and are consistent with the idea that ANO1 participates in pacemaker activity.

4. Function of neurotransmission

How nerves transmit their signals to regulate activity of smooth muscle is of fundamental importance to autonomic and enteric physiology, clinical medicine and therapeutics. A traditional view of neurotransmission to smooth muscles has been that motor nerve varicosities release neurotransmitters that act on receptors on smooth muscles to cause their contraction or relaxation via electromechanical and phamacomechanical signaling pathways in the smooth muscle. In recent years, an old hypothesis that certain ICC may transduce neural signals to smooth muscle cells has been resurrected. This later hypothesis is based on indirect evidence of closer proximity and presence of synapses between the nerve varicosities and ICCs, gap junctions between ICC and smooth muscles and presence of receptors and signaling pathways for the neurotransmitters and ICCs (Daniel et al, 1984).

4.1 Morphologic evidence for ICC-IM mediate neurotransmission

Ultrastructural studies have identified membrane densifications between enteric nerve terminals and ICC-IM in different organs of the GI tracts from several species (Wang et al, 2000; Horiguchi et al, 2003; Sanmarti-Vila et al, 2000). The ultrastructure of these membrane specializations are unlike the nerve-to-nerve synapses that exist in the central nervous system (Kennedy et al, 2000; Aoki et al, 2001; Ruegg et al, 2001) or the structural arrangement of the skeletal neuromuscular junction (Aguado et al, 1999). Even less is known about these proteins that exist between nerve terminals and neuroeffector cells in the GI tract. It has been established that enteric motor nerve terminals in the rat oesophagus and small intestine and in the murine stomach contain members of the *N*-ethylmaleimide-sensitive fusion protein attachment protein receptors or SNAREs that are involved in the release of neurotransmitters from these terminals (Beckett et al, 2005; Sudhof et al, 1996). SNAREs are involved in neurovesicle docking to the presynaptic membrane, fusion of the neurovesicle and release of neurotransmitter in the synaptic cleft. Several of the SNARE proteins that have been identified to date in the murine stomach include synaptotagmin, syntaxin and SNAP-25 (Vannucchi et al, 1997). Each of these proteins has a specific role in the neurotransmitter release process (Lavin et al, 1998). Varicosities containing these

SNARE proteins were only observed in intimate association with ICC-IM and were not observed in close apposition to smooth muscle cells (Vannucchi et al, 1997). These data support the hypothesis that ICC-IM are directly innervated by active sites where neurotransmitter release occurs.

Transcripts for two postsynaptic scaffolding proteins PSD-93 and PSD-95 have been detected by RT-PCR in the murine stomach. Quantitative RT-PCR revealed that expression of PSD-93 and PSD-95 are decreased in the stomachs of W/W^V mutants that lack ICC-IM (Vannucchi et al, 1997). Finally, double-labelling immunohistochemical experiments using antibodies that recognize the PDZ domain of the PSD-95 family members (PSD-95 and PSD-93, and SAP 97) and Kit revealed the expression of PSD proteins on ICC-IM but not neighbouring smooth muscle cells (Vannucchi et al, 1997). These data suggest that ICC-IM express the necessary proteins to form postsynaptic proteins and further support the hypothesis that ICC-IM are directly innervated.

4.2 Functional evidence for ICC-IM mediate neurotransmission

ICCs possess a variety of receptors for neurotransmitters, hormones and paracrine substances, for example, NK1 receptors (Lavin et al, 1998; Epperson et al, 2000), VIP receptors (Patterson et al, 2001) and CCK-A receptors (Ward et al, 2000), and so on. More direct functional evidence for the primary role of ICCs in enteric motor neurotransmission came from experiments performed on the stomachs of W/W^V mutant mice that lack ICC-IM. In the absence of ICC-IM post-junctional neural responses to cholinergic excitatory and nitrergic inhibitory neurotransmission were absent or greatly attenuated within the circular muscle layers of the gastric fundus and antrum (Beckett et al, 2003; Suzuki et al, 2003; Song et al, 2005a). Although post-junctional cholinergic and nitrergic responses are absent or greatly attenuated in W/W^V mutant mice that lack ICC-IM, neural responses still persist. In the gastric antrum of wild-type animals, nerve stimulation evokes a complex series of post-junctional responses, consisting of an initial apamin-sensitive inhibitory junction potential (IJP) and a slower nitrergic IJP; the inhibitory responses are followed by an excitatory response that consists of both atropine-sensitive and at more sustained stimulation frequencies an insensitive excitatory response (Song et al, 2005b). In antrums of W/W^V mice the initial apamin-sensitive component still persists. Sustained stimulation of W/W^V mutant tissues also reveals a non-cholinergic excitatory response that is probably mediated through neurokinins (Iino et al, 2008). It is interesting that these post-junctional responses are still present but the cholinergic and nitrergic responses are absent when ICC-IM is absent.

A lot of studies indicated that soluble guanylate cyclae (sGC) is present in ICC-IM which are closely apposed to nitrergic neurons processes containing neuronal nitric oxide synthase (nNOS) (Iino et al, 2009; Wang et al, 2003). In guinea pig caecum, stimulation of nitrergic neurons or treatment with nitric oxide (NO) enhanced cyclic guanosine 3',5'-monophospate (cGMP) which is a signal molecule in the NO signal pathway in ICC-IM (Wang et al, 2003), but the same phenomenon was not observed in the smooth muscle cells. These results indicate that ICC-IM may be the primary targets for NO released from neurons and mediate nitrergic signal transmission. In the murine antrum, transmural nerve stimulation evoked a fast inhibitory junction potential (IJP) followed by a long lasting inhibitory junction potential (slow-IJP) and a period of excitation. Slow-IJP and the excitatory component could be abolished by an inhibitor of NOS and atropine, respectively, which indicate that these two reactions were mediated by nitrergic and cholinergic neurons, respectively. But in the animals which lack ICC-IM, the nitrergic and cholinergic components were absent (Gillespie

et al, 2004), which indicate the important role of ICC-IM in neurotransmission. It was also showed that ICC-IM were associated with cholinergic neurons containing vesicular acetylcholine transporter (VAChT) in the murine fundus. Fast excitatory junction potentials (EJP) which were blocked by atropine were induced by electrical field stimulation (EFS) in the smooth muscle. The neuronal responses were greatly reduced in the gene-mutation mouse in which ICC-IM were devoid (Beckett et al, 2003). These results suggest that ICC-IM also mediate cholinergic neurotransmission.

5. Pathophysiology of ICC in gastrointestinal tract

ICCs have, in the past 2 decades, been recognised as important elements in the regulation of gastrointestinal motility. Specifically, they have been shown to be critical for the generation and propagation of electrical slow waves that regulate the phasic contractile activity of gastrointestinal smooth muscle, and for mediating neurotransmission from enteric motor neurons to smooth muscle cells. These different functional roles are carried out by different phenotypic classes of ICC that have discrete distributions within the tunica muscularis. In humans, under certain pathophysiological conditions, loss or defects in ICC networks appear to play a role in the generation of certain motility disorders (Vanderwinden et al, 1999; Horisawa et al, 1998). Recent evidence suggests that loss of ICC is associated with numerous gastrointestinal disorders ranging from gastroparesis, pseudoobstruction and idiopathic constipation (Vanderwinden et al, 1999; Sanders et al, 1999; Burns et al, 2007; Rolle et al, 2007; Farrugia et al, 2008). An animal model of ICC loss, the W/WV mouse, has been used extensively to examine functional changes resulting from lesions in ICC (Maeda et al, 1992; Ward et al, 1994;. Huizinga et al, 1995) dense network of ICC in the region of the myenteric plexus (ICC-MY) is disrupted in the small intestine of these mice and ICC-MY are largely absent along the anti-mesenteric aspect. However, scattered remnants of ICC-MY networks can be found in the tunica muscularis of the small intestine (Ward et al, 1994). ICC-IM (which are concentrated in the region of the deep muscular plexus of the mouse and therefore are referred to as ICC-DMP) are preserved in the small bowel of the W/WV mouse (Ward et al, 1994), making this an ideal model to study the consequences of significant loss of the ICC-MY pacemaker network on motility.

5.1 Pathophysiology of ICC in diabetic gastroparesis

Gastric neuromuscular dysfunction occurs in up to 30–50% of patients after 10 years of type I or II diabetes. Symptoms of diabetic gastropathy can range from mild dyspepsia to recurrent vomiting, abdominal pain and gastroparesis (Mearin et al, 1995; De Block et al, 2006). Neither the pathophysiology of gastroparesis, nor the pathogenesis of patients's symptoms, is well understood; hence, medical therapy is generally not effective. A major symptom of gastroparesis is delayed gastric emptying although there is a poor correlation between symptom severity and the rate of gastric emptying (Koch et al, 2001). Numerous physiological studies have demonstrated that both enteric nerves and ICC play critical roles in gastric peristalsis (Koh et al, 1998; Thomsen et al, 1998; Hirst et al, 2002), a major determinant of gastric emptying (Vittal et al, 2007; Hirst et al, 2006). Another predominant symptom of gastroparesis is vomiting and nausea likely involving vagal afferent innervation (Andrews et al, 2002). ICCs are associated with vagal afferent nerves (Fox et al, 2000) and hence studies into the pathophysiology of ICC associated with gastroparesis may

hold the key to advancing our understanding of the causes of gut motility disorders associated with diabetes. In some patients with severe diabetic gastroparesis, the number of ICC has been shown to be significantly reduced in different parts of gut using immunohistochemistry (He et al, 2001; Nakahara et al, 2002; Forster et al, 2005; Miller et al, 2008). Damage to ICC, pacemakers, and mediators of neuromuscular neurotransmission in the gastrointestinal tract contributes to the pathogenesis of diabetic gastroenteropathy in both patients and animal models. Viktor et al (2005) cultured murine gastric smooth muscle in normoglycemic or hyperglycemic basal media with or without insulin or IGF-I for 1–3 months, the time required for gastroparesis and ICC damage to develop in diabetic mice. Then they assessed ICC expression by c-Kit immunohistochemistry and quantitative analysis of c-kit expression. They found that ICC survived for at least 34 days in unsupplemented normoglycemic media, but their networks, c-kit expression, and slow waves were profoundly reduced after 68 days. These changes could be entirely prevented by insulin or IGF-I supplementation. ICC networks were completely resistant to hyperglycemia for at least 72 days. They suggested that hyperglycemia is unlikely to be responsible for the diabetes-associated depletion of ICC. In contrast, maintenance of ICC requires insulin or IGF-I, which are reduced or ineffective in diabetes. Insulin and IGF-I receptors were detected in smooth-muscle cells and myenteric neurons but not in ICC. The successive study (Horvath et al, 2006) showed that cell-surface expression of SCF was only found in smooth-muscle cells, and ICC depletion in diabetes was accompanied by smooth-muscle atrophy and reduced SCF, whereas neuron-specific gene expression remained unchanged. In organotypic cultures, prevention of ICC loss by insulin or IGF-I was paralleled by rescue of smoothmuscle cells and SCF expression but not of myenteric neurons. Immunoneutralization of endogenous SCF caused ICC depletion closely resembling that elicited by insulin/IGF-I deficiency. The results suggest that reduced insulin/IGF-I signaling in diabetes may lead to ICC depletion and its consequences by causing smooth-muscle atrophy and reduced SCF production. Thus, myopathy may play a more central role in diabetic gastroenteropathies than previously recognized.

ICC are associated with afferent innervation and peristalsis of the stomach suggestive of a key role in the pathophysiology of gastroparesis. Recently study was investigated that changes in the density and ultrastructure of ICC and enteric nerves in the streptozotocin-induced diabetes mellitus (STZ-DM) in Wistar rats using immunohistochemistry and electron microscopy (Wang et al, 2009). In the STZ-DM antrum, a marked reduction was observed in the density of the intramuscular ICC (ICC-IM) and ICC located at the submucosal border of the circular muscle layer of the antrum (ICC-SM). The surviving ICC showed lamellar bodies and partial vacuolation of the cytoplasm content, loss of connections between ICC-IM and nerves; it appeared that injured ICC-IM developed into fibroblast-like ICC. ICC associated with Auerbach's plexus (ICC-AP) in the antrum and ICC in the fundus were not affected significantly except for a loss of connections with nerve structures. Marked reduction in nerve tissue (Protein Gene Product-9.5 positivity) was also restricted to the muscle layers including nitrergic nerves (neuronal nitric oxide synthase positivity). In vivo assessed gastric emptying was markedly reduced in STZ-DM rats. These data demonstrate in the STZ-DM rat stomach a decreased density of ICC limited to the antrum and to ICC-IM and ICC-SM, and structural degeneration in ICC-IM and associated nerves with a special emphasis on loss of synaptic connections, accompanied by a decrease in gastric emptying.

5.2 Pathophysiology of ICC in other gastroenteropathy

The findings outlined above, obtained from laboratory animals, highlight the key roles played by ICCs in the regulation of GI motility, and suggest that alterations in ICC networks in humans also could have an impact on gut motility and/or GI diseases. Indeed, loss of ICCs or disruption of ICC networks has been reported in a wide range of GI diseases, including achalasia, chronic intestinal pseudoobstruction, Hirschsprung disease, inflammatory bowel diseases, slow transit constipation, and others (Vanderwinden et al, 1999; Sanders et al, 2002).

Intestinal obstruction may ensue from mechanical or functional causes and, when complete, it may represent a fatal complication of several gastrointestinal disorders. If partial, the stenosis progressively hinders the flow of ingesta, generating orally distension and thickening of the gut wall. Both motor and absorptivesecretory dysfunctions, along with widespread morphological and neurochemical changes, are reported to occur orally to the point of occlusion (Schuffler et al, 1993; Prommegger et al, 1997). Since ICC generate and propagate electrical slow waves in gastrointestinal muscles, Chang et al (2001) investigated whether the loss of ICC leads to loss of function in partial bowel obstruction. They observed that the populations of ICC decreased oral, but not aboral, to the site of obstruction, two weeks following the onset of a partial obstruction, as well as increased in diameter and hypertrophy of the tunica muscularis, oral to the obstruction site. ICC networks were disrupted oral to the obstruction, and this disruption was accompanied by the loss of electrical slow waves and responses to enteric nerve stimulation. Ultrastructural analysis revealed no evidence of cell death in regions where the lesion in ICC networks was developing. Cells with a morphology intermediate between smooth muscle cells and fibroblasts were found in locations that are typically populated by ICC. However, removal of the obstruction led to the redevelopment of ICC networks and recovery of slow wave activity within 30 days. These data describe the plasticity of ICC networks in response to partial obstruction. Chronic idiopathic intestinal pseudoobstruction (CIIP) has similarities to the neonatal form in that it presents with symptoms suggestive of intestinal obstruction due to abnormalities in intestinal transit, causing significant morbidity and mortality. Several studies have indicated that ICC are decreased or absent in some idiopathic CIIP patients (Jain et al, 2003; Streutker et al, 2003; Isozaki et al, 1997; Yamataka et al, 1998; Feldstein et al, 2003; Faussone-Pellegrini et al, 1999; Tong et al, 2004). There is also a second subgroup of CIIP patients with myocyte changes suggestive of visceral myopathy in whom ICC are absent in the dilated portion of the megaduodenum (Boeckxstaens et al, 2002). CIIP can also occur in the colon and electrophysiological studies show that these patients have absent or decreased slow wave rhythms (Shafik et al, 2003) and absent / decreased ICC are also demonstrable in some cases (Jain et al, 2003; Streutker et al, 2003) the changes in the ICC occur in a subpopulation of cases and are often focal.

Gastrointestinal tract is one of the most susceptible organ systems to ischaemia. Not only mucosal injury but also alterations of the intestinal motility and loss of ICC have been reported in response to ischaemia and reperfusion (I/R) (Shimojima et al, 2006). Most recently study demonstrated that gastric emptying was transiently delayed at 12 h after I/R, but returned to normal by 48 h, and expression of c-Kit protein of the smooth muscle layer was reduced at both 12 and 48 h after I/R. The expression of neuronal nitric oxide synthase (nNOS) protein was also decreased at 12 h after I/R, but was restored to normal by 48 h (Suzuki et al, 2010). These data suggest gastric I/R evokes transient gastroparesis with

delayed gastric emptying, associated with disruption of the ICC network and nNOS-positive neurons.

6. Summary

Most region of the gastrointestinal (GI) tract generate an ongoing discharge of rhythmical electrical activity in the absence of neural or hormonal stimulation. ICCs are the pacemaking cells in gastrointestinal smooth muscles that generate the rhythmic oscillations in membrane potential known as slow waves. The ICC lie in the myenteric region (ICC-MY) are pacemaker cells. Individual ICC-MY form gap junctions with neighbouring ICC-MY forming a network of cells which is in turn electrically coupled to the adjacent muscle layers. Another ICC distributed through the muscle layers (ICC-IM) which similarly form gap junctions with surrounding smooth muscle cells, so presumably forming an electrical syncytium. Calcium release from inositol triphosphate (IP_3) is known to contribute to many important cellular functions, including generation of spontaneous rhythmicity in gastrointestinal motility. However, there are differences and contradictions what kind channel is involved in generation of pacemaker currents. One candidate for pacemaker current is intracellular low calcium-sensitive nonselective cation channels and another is calcium activated chloride channels. These two kinds of candidate channels have supported experimental evidences, respectively. ICC plays an important role in gut motility and absent or disordered ICC networks have been identified in a variety of motility disorders. Many evidences suggest that normal gastrointestinal motility depends on interactions among several cell types occurring within the smooth muscle layers. ICC just like other regulatory cell types, perform specialized functions and should retain their place among the key players. However, in order to explain the ICC pacemaking mechanism many studies are need to do further.

7. Reference

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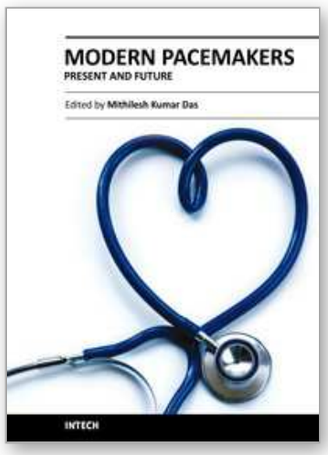

Modern Pacemakers - Present and Future

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The book focuses upon clinical as well as engineering aspects of modern cardiac pacemakers. Modern pacemaker functions, implant techniques, various complications related to implant and complications during follow-up are covered. The issue of interaction between magnetic resonance imaging and pacemakers are well discussed. Chapters are also included discussing the role of pacemakers in congenital and acquired conduction disease. Apart from pacing for bradycardia, the role of pacemakers in cardiac resynchronization therapy has been an important aspect of management of advanced heart failure. The book provides an excellent overview of implantation techniques as well as benefits and limitations of cardiac resynchronization therapy. Pacemaker follow-up with remote monitoring is getting more and more acceptance in clinical practice; therefore, chapters related to various aspects of remote monitoring are also incorporated in the book. The current aspect of cardiac pacemaker physiology and role of cardiac ion channels, as well as the present and future of biopacemakers are included to glimpse into the future management of conductions system diseases. We have also included chapters regarding gut pacemakers as well as pacemaker mechanisms of neural networks. Therefore, the book covers the entire spectrum of modern pacemaker therapy including implant techniques, device related complications, interactions, limitations, and benefits (including the role of pacing role in heart failure), as well as future prospects of cardiac pacing.

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