The pacemaker functions of visceral interstitial cells of Cajal

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Abstract: Interstitial cells of Cajal (ICCs) are located in most parts of the digestive system. Although they have been found over 100 years, their functions began to be unravelled only recently. ICCs are considered as pacemaker cells which elicit spontaneous rhythmic electric activity termed “basic electrical rhythm” or “slow waves” in gastrointestinal tract. Moreover, they also mediate neurotransmission from neurons to smooth muscle in gastrointestinal tract. ICC-like cells also exist in other visceral smooth muscles, such as urinary tract, genital system and vascular smooth muscle. In this paper we review the progress of research about the functions of visceral ICCs.

Key words: interstitial cells of Cajal; pacemaker cells; neurotransmission

1 Introduction

Most visceral smooth muscles, especially the smooth muscle in gastrointestinal (GI) tract, display spontaneous rhythmic contractions in the absence of neuronal or hormonal stimulation, which is associated with their physiological functions. When the electrical activity of the smooth muscles (in either circular or longitudinal layer) is recorded, spontaneous rhythmic waves are observed. These electric activities are termed “basic electrical rhythm” or “slow waves”. Slow waves are of great functional importance because they determine the rate and timing of activity of the muscles in GI system, and their impairment is likely to cause various motility disorders.

In 1893, Cajal discovered the cells in the myenteric plexus region of rabbits and described them as “interstitial neurons” [1]. These cells formed a network of cell bodies and fine processes in the region between the longitudinal and circular muscle layers. As these cells resided near both the neurons and muscles, Cajal suggested that they might be involved in the regulation of muscle activity. The search for the pacemaker mechanism started at the beginning of the 20th century, but for many years progress in this field has been slow. Recent studies have demonstrated that these cells are the pacemakers of GI system and also have other important roles. Interstitial cells of Cajal (ICCs) generate
slow waves and conduct them into adjacent smooth muscle cells to induce spontaneous contractions\textsuperscript{[2-4]}. ICCs can be classified into two types at least based on their distributions and functions: (1) Intermuscular ICC (ICC-MY), located between the circular and longitudinal muscle layers at the level of the myenteric plexus, acting as a pacemaker\textsuperscript{[4,5]}; (2) Intramuscular ICC (ICC-IM), distributed within muscle bundles of the circular muscle layer in close association with nerve varicosities, shown to mediate neurotransmission. Moreover, ICC-IM distributed within the deep muscularis plexus region of the small intestine is called ICC-DMP\textsuperscript{[5,6]}. By using the same methods used to study ICCs in GI tract, researchers have obtained more and more evidence that ICCs are distributed in most visceral organs which have spontaneous rhythmic contractions. For example, ICC-like cells were found in lamina propria region and on the boundary of smooth muscle bundles in the urinary tract, occasionally within the smooth muscle layers\textsuperscript{[7-10]} (Fig. 1). In the genital system, the distribution of ICC-like cells is similar to that in the urinary tract\textsuperscript{[11-14]}. In the organs described above, ICC-like cells are always associated with adjacent smooth muscle cells and neurons, so ICC-like cells are becoming more and more interesting for people to study.

2 Function of pacemakers

ICC\textsuperscript{s} are unique cells that generate electrical pacemaker

![Fig. 1. Morphology of ICCs in rabbit urethra (Adopted from Sergeant et al.\textsuperscript{[23]}). Inset a, b, c and f show morphology of ICCs; Inset c and g show morphology of smooth muscle cells. Left panel, phase contrast micrographs; Right panel, electron micrographs.](image-url)
activity in GI smooth muscles. Many previous studies have attempted to characterize the conductance responsible for pacemaker current and slow waves in GI tract, but the precise mechanism of electrical rhythmicity is still debated. It has been demonstrated that ICCs are pacemakers in GI tract using neutralizing antibody to block the development of ICCs and the 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[3,15,16]. In the stomach and small bowel[17,18], two kinds of electrical activities, pacemaker potentials and slow waves with similar frequencies, were recorded by using microelectrode technique. 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 are passively propagated to the smooth muscle cells to generate slow waves. All these results demonstrate that ICC-MY is the pacemaker triggering spontaneous activities in GI tract. The most direct evidence to support this hypothesis is that both freshly isolated and cultured ICCs can generate spontaneous rhythmic electrical activity the same as that recorded in intact tissues.

As described above, most ICCs are associated with adjacent smooth muscle cells via gap junctions or other junctions. Although the function of these junctions is not sure[19,20], it helps to study the function of ICCs in these organs. It has been recognized that ICCs of urethra also act as pacemakers as it is observed in GI tract by far. Smooth muscles of urethra display spontaneous rhythmic contraction, which is associated with spontaneous transient depolarization and large rhythmic slow waves. The spontaneous activities may be resulted from the opening of calcium-activated chloride channels which were regulated by intracellular calcium released from calcium stores[21,22]. The origin of the spontaneous activities was unclear until it was demonstrated that ICCs were also distributed in urethra. It has been reported that single ICC from the rabbit urethra could generate spontaneous electrical activity similar to that recorded in the whole tissue, but the smooth muscle cell could not. Meanwhile more and more evidence indicated that calcium-activated chloride channels responsible for the generation of slow waves were expressed greatly in ICCs, however, the expression in smooth muscle cells was little[21,22]. Consequently, ICCs in urethra are considered as pacemakers as they are in GI tract. The most direct evidence to support this hypothesis is that spontaneous inward currents similar to pacemaker currents recorded in ICCs of GI tract were also recorded in urethra ICCs by using patch clamp technique[23].

It was reported that imatinib, an inhibitor of c-Kit protein which is crucial for the development of ICCs, decreased the frequency of human uterus contractions in a dose-dependent manner, and the contractions were abolished when the concentration of imatinib was 80 µmol/L[24]. In the murine uterus, the mutation of the gene c-kit or the inhibition of c-Kit protein decreased the contraction of longitudinal smooth muscles, but did not affect the contraction of circular smooth muscles[12]. The studies also demonstrated that single ICC could not generate spontaneous depolarization and inward currents, but the smooth muscle cell in rat uterus could[11]. So it is still unclear whether ICCs act as pacemakers or not in uterus. Spontaneous intracellular calcium transients were recorded in the corporal smooth muscle meshwork of the guinea pig penis and this activity originated from the boundary of muscle bundles where ICCs were located and spread throughout the meshwork[25]. Although all these results indicated that ICCs may be pacemakers in the corporal tissues, no direct evidence was shown to support this hypothesis. In the guinea pig prostate, a kind of electrical activity, named pacemaker potential later, was recorded with intracellular microelectrodes[26]. It is suggested that this spontaneous activity may be generated by ICCs, but still no direct evidence is shown to support this hypothesis.

However, not all ICCs act as pacemakers in the tissues with spontaneous rhythmicity. A kind of cells named ‘atypical’ smooth muscle cells were reported to be located in the pelvicalyceal junction and proximal renal pelvis of guinea pig, as well as murine proximal renal pelvis. The morphology of this kind of cells is between the smooth muscle cells and ICCs, characterized by relatively little amounts of contractile fibrils and many narrow processes[27]. Pacemaker potentials and spontaneous transient depolarizations were recorded in the preparations including these cells[27]. Consequently, the ‘atypical’ smooth muscle cells are considered as pacemaker cells in these tissues, while ICCs play a supportive role and can take over pacemaking in the absence of the pacemaker drive.

3 Mechanisms responsible for pacemaker activities

3.1 Intracellular calcium activities
It has been still controversial about the mechanism of generating pacemaker currents by far, but the role of intracel-
ular calcium in the generation has been widely proved\cite{28}. Torihashi et al.\cite{29} observed spontaneous intracellular calcium oscillations in cultured ICCs clusters isolated from mouse small intestine. 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. Similar activities were also observed in ICCs of murine stomach and rabbit urethra\cite{30,32}.

Moreover, the evidence that an intracellular calcium chelator, 1,2-bis(2-aminophenoxy) ethane- N,N,N',N'-tetraacetic acid acetoxyethyl ester (BAPTA-AM), 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\cite{18}.

Generally speaking, intracellular calcium level is controlled by calcium influx from extracellular circumstances and calcium release, or uptake by calcium stores and mitochondrion. It is demonstrated that calcium 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\cite{4,20,29,32}. It is very interesting that L-type calcium channels blocker, for example nicardipine, did not affect slow waves, intracellular calcium oscillations and spontaneous electrical activities of ICCs\cite{20,29,30,32}. However, both Ni\(^{2+}\) and mibefradil inhibited the upstroke component of pacemaker potentials\cite{18}. These phenomena strongly suggest that a voltage-dependent and dihydropyridine-resistant calcium channel rather than L-type calcium channel may be involved in the pacemaker activity.

Intracellular calcium oscillations induced by calcium release or uptake by calcium stores and mitochondrion are very important for the generation of pacemaker currents in ICCs. Sanders et al.\cite{33} suggested that ‘pacemaker unit’ comprised of inositol 1,4,5-trisphosphate (IP\(_3\))-operated calcium stores, adjacent mitochondrion and the ion channels in the plasma membrane is the basic structure to generate pacemaker currents (Fig. 2). The generation of pacemaker currents is initiated by calcium released from IP\(_3\)-operated calcium stores, and then intracellular high calcium induces calcium uptake by nearby mitochondria. Calcium oscillations activate ion channels in the plasma membrane to generate pacemaker currents (Fig. 2C). In this process, calcium handling between calcium stores and adjacent mitochondria is considered as an important premise\cite{34} (Fig. 2A, B). 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\cite{29,34,35} (Fig. 2D, E, F). The results suggest that calcium stores play an important role in the pacemaker activities. It is common view that IP\(_3\)-operated calcium stores are involved in the pacemaker activities\cite{30,34}, but the role of ryanodine receptor-operated calcium stores in the pacemaker activities has been still debatable. Ward et al.\cite{36} found that ryanodine, an inhibitor of ryanodine receptor, had no significant effect on the pacemaker currents in ICCs, and Malysz et al.\cite{37} 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.\cite{38} and Liu et al.\cite{39} reported that ryanodine abolished intracellular calcium oscillations in ICCs from murine intestine and stomach, respectively, and the expression of ryanodine receptor type 3 has been confirmed by using RT-PCR technique. These results suggest that both IP\(_3\)-operated calcium stores and ryndine receptor-operated calcium stores are important for the pacemaker activities. However, in the rabbit urethra ryanodine receptor-operated calcium stores are considered to be prominent in the pacemaker activities in ICCs. The studies demonstrated that ryndine 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 intracellular calcium oscillations\cite{32}.

Moreover, the calcium uptake by mitochondrion is also important for ICCs pacemaker activities in both GI tract and urethra, because disruption of the mitochondrial membrane potential with the electron transport chain inhibitors, rotenone, antimycin A, mitochondrial uncoupler carbonyl cyanide p-(trifluoromethoxy) phenylhydrazone (FCCP) and carbonyl cyanide m-chlorophenylhydrazone (CCCP) abolished both intracellular calcium oscillations and pacemaker currents in ICCs\cite{30}.

Since intracellular calcium is very important for pacemaking activity, then which kind of channels activated by intracellular calcium is responsible for the pacemaker currents? There is still a divergence of view about pacemaker channels, and now two kinds of ionic channels are recognized to be the candidates for pacemaker channels.

### 3.2 Non-selective cation channels

Many studies suggested that intracellular calcium level or calcium oscillation was the premise in the generation of ICCs pacemaker currents. However, it is still debatable which phase of calcium oscillations contributes to eliciting
Fig. 2. Mechanism of pacemaker currents carried by non-selective cation channels. Top: Model proposed for pacemaker unit composed of sacroplasmic reticulum (SR), mitochondrion and non-selective cation channels in plasma membrane (Adopted from Sanders et al. [33]). A shows mitochondrial Ca$^{2+}$ oscillations in an ICC, which were inhibited by xestospongin C, an inhibitor of IP$_3$ receptors. B shows effect of xestospongin C on pacemaker currents of ICC. C shows one-to-one relationship between mitochondrial Ca$^{2+}$ oscillations and pacemaker currents in simultaneous recordings of these activities (left) and mitochondrial Ca$^{2+}$ oscillations ahead of pacemaker currents (right). D and E show the effects of FCCP, a mitochondrial uncoupler, on the pacemaker currents and mitochondrial Ca$^{2+}$ oscillations, respectively. F shows the effect of thapsigargin, an inhibitor of Ca$^{2+}$ uptake by SR, on the pacemaker currents. (Reproduced from Ward et al. [34])
pacemaker currents in ICCs. Consequently, it is very important to determine what channel is responsible for pacemaker currents and whether the pacemaker channels are sensitive to low or high calcium. Koh et al.[4,39] found that pacemaker currents generated by cultured intestinal ICCs from mouse could be abolished by the removal of Na⁺ in external solution. In succession, buffering intracellular calcium by BAPTA-AM induced persistent inward currents, which could be blocked by the 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 via 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 mouse. Moreover, the conductance of single-channel was 13 pS, and this channel could be strongly activated by calmodulin inhibitors in on-cell and excised patches[39]. The properties of this calcium-inhibited non-selective cation channel are in analogy to those of transient receptor potential (TRP) C4 in TRP channel family, which is also regulated by intracellular calcium and calmodulin, and both channels have similar conductance (13 versus 17 pS)[33]. The expression of TRPC4 has been confirmed in cultured ICCs clusters of murine intestine[29] and stomach[30] by using immunohistochemistry and RT-PCR techniques.

3.3 Calcium-activated chloride channels
Up to now more and more evidence has demonstrated that calcium-activated chloride channels are responsible for ICCs pacemaker currents. In smooth muscle cells and, presumably, ICCs, Cl⁻ equilibrium potential is positive to the resting membrane potential, which makes it possible that selective opening of Cl⁻ channels contributes to cell depolarization[48]. Many studies have implicated that inward (depolarizing) pacemaker currents were carried by chloride channels in ICCs[18, 40-44]. Early study has presented that Cl⁻ channels may contribute to the depolarization phase and the plateau phase of rhythmic membrane potential changes (slow waves) in ICCs. Pharmacological data have also suggested that Cl⁻ channels play a role in rhythmic inward currents generated by chemically isolated ICCs[49]. As ICCs in the urethra resembled ICCs in the GI tract, it was thought that they may share a common pacemaker mechanism. Under voltage clamp conditions, ICCs isolated from the rabbit urethra and networks of cultured ICCs from the murine small intestine developed spontaneous transient inward currents (STICs) of similar amplitudes and time courses[4,23]. However, the ionic basis of pacemaker activity in both tissues appears to be fundamentally different. STICs in urethral ICCs were inhibited by Ca²⁺ removal and the traditional chloride channel blockers, A-9-C and niflumic acid[23]. Recent study demonstrated that ICCs exhibit a specialized ‘slow wave’ current, and 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 ICCs expressing ANO1, a Ca²⁺-activated Cl⁻ channel[49]. Removal of extracellular Ca²⁺, replacement of Ca²⁺ with Ba²⁺, or extracellular Ni²⁺ blocked the slow wave current. Single Ca²⁺-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 depolarization of ICCs in current clamp, and these events were blocked by niflumic acid[41]. Most recent study proposed that [Cl⁻]i is seen to fluctuate in ICC explant clusters, possibly evoked by rhythmic changes of intracellular calcium. The [Cl⁻]i in ICCs fluctuates to keep its equilibrium potential constant. The identification of ECl as positive to the resting membrane potential of ICC indicates that opening of chloride channels will depolarize ICCs[49]. These findings demonstrate a role for Ca²⁺-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 which act on receptors in smooth muscles to cause their contraction or relaxation via electromechanical and pharmacomechanical signaling pathways in the smooth muscle. In recent years, an old hypothesis that certain interstitial cells of ICCs may transduce neural signals to smooth muscle cells has been resurrected. This later hypothesis is based on indirect evidence that there are closer proximity and presence of synapses between the nerve varicosities and ICCs, gap junctions between ICCs and smooth muscles and the receptors and signaling pathways for the neurotransmitters and ICCs[40].

4.1 Morphologic evidence that ICC-IM mediates neurotransmission
Ultrastructural studies have identified membrane densifications between enteric nerve terminals and ICC-IM in different organs of the GI tracts from several species[47-49].
The ultrastructure of these membrane specializations are unlike the nerve-to-nerve synapses that exist in the central nervous system\(^\text{[50-52]}\) or the structural arrangement of the skeletal neuromuscular junction\(^\text{[53]}\). 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, as well as the marine stomach, contain the members of \(N\)-ethylmaleimide-sensitive fusion protein attachment protein receptors or SNAREs that are involved in the release of neurotransmitters from these terminals\(^\text{[54,55]}\). 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 marine stomach include synaptotagmin, syntaxin and SNAP-25\(^\text{[50]}\). Each of these proteins has a specific role in the neurotransmitter release process\(^\text{[57]}\). 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\(^\text{[50]}\). 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 marine stomach. Quantitative RT-PCR revealed that expression of PSD-93 and PSD-95 are decreased in the stomachs of \(W/W^\text{v}\) mutants that lack ICC-IM\(^\text{[50]}\). Finally, double-labeling immunohistochemical experiments using antibodies that recognize the PDZ domain of the PSD-95 family members (PSD-95, PSD-93 and SAP 97) and Kit revealed the expression of PSD proteins on ICC-IM but not neighboring smooth muscle cells\(^\text{[50]}\). These data suggest that ICC-IM express the necessary proteins to form postsynaptic proteins and further support the hypothesis that ICC-IM is directly innervated.

### 4.2 Functional evidence that ICC-IM mediates neurotransmission

ICCs possess a variety of receptors for neurotransmitters, hormones and paracrine substances, such as NK1 receptors\(^\text{[57,58]}\), VIP receptors\(^\text{[58]}\) and CCK-A receptors\(^\text{[59]}\), and so on. More direct functional evidence for the primary role of ICCs in enteric motor neurotransmission came from the experiments performed on the stomachs of \(W/W^\text{v}\) mutant mice that lack ICC-IM. In the absence of ICC-IM post-junctional neural responses to cholineric excitatory and nitric inhibitory neurotransmission were absent or greatly attenuated within the circular muscle layers of the gastric fundus and antrum\(^\text{[60-62]}\). Although post-junctional cholineric and nitric responses were absent or greatly attenuated in \(W/W^\text{v}\) mutant mice, neural responses still persisted. In the gastric antrum of wild-type animals, nerve stimulation evoked 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 were followed by an excitatory response that consisted of both atropine-sensitive and at more sustained stimulation frequencies an insensitive excitatory response\(^\text{[63]}\). In the gastric antrums of \(W/W^\text{v}\) mice the initial apamin-sensitive component still persisted. Sustained stimulation of \(W/W^\text{v}\) mutant tissues also revealed a non-cholineric excitatory response that was probably mediated through neurokinins\(^\text{[64]}\). In guinea pig caecum, stimulation of nitric neurons or treatment with nitric oxide (NO) enhanced cyclic guanosine 3',5'-monophosphate (cGMP) which is a signal molecule in the NO signal pathway in ICC-IM\(^\text{[65]}\), 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 nitric signal transmission. In the marine antrum, transmural nerve stimulation evoked a fast 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 nitric and cholineric neurons, respectively. But in the animals which lack ICC-IM, the nitric and cholineric components were absent\(^\text{[67]}\), which indicate the important role of ICC-IM in neurotransmission. It was also showed that ICC-IM was associated with cholineric neurons containing vesicular acetylcholine transporter (VACHT) in the marine fundus. Fast excitatory junction potentials (EJP) which could be 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\(^\text{[63]}\). These results suggest that ICC-IM also mediates cholineric neurotransmission.

### 4.3 Evidence that ICC-IM mediates neurotransmission in other viscera

ICCs in other visceral smooth muscles may also mediate
neurotransmission. Double labeling with anti-c-Kit and antinNOS antibodies has shown the close structural relationship between neurons and ICCs in the rabbit urethra[19]. In the mouse and guinea-pig bladder, ICCs incubated with NO donor showed immunopositive for cGMP, and enhanced cGMP generation. Moreover, in the murine bladder, the neurons containing nNOS were closely associated with cGMP immunopositive ICCs[68-70]. In the rat and sheep urethra, both EFS of nitrergic nerves and incubation with NO donor enhanced the immunoactivity of cGMP in c-Kit immunopositive ICCs and relaxed the smooth muscles, and both reactions could be abolished by an inhibitor of NOS[71]. Sergeant et al.[72] also demonstrated that the electrical activity in rabbit urethra was inhibited by NO donors and other activators of the cGMP/PKG pathway, which could be mimicked by the membrane permeant analogue of cGMP, 8-Br-cGMP. These morphological and electrophysiological studies indicate that ICCs play an important role in the visceral nitrergic neurotransmission.

It was reported that ICCs in guinea pig bladder were immunopositive for choline acetyltransferase (ChA T) antibody[72]. Double labeling with anti-c-Kit and anti-VACHT also demonstrated a close structural relationship between ICCs and cholinergic nerves[71]. Moreover, administration of carbachol, an acetylcholine analog, could induce calcium transients in freshly isolated bladder ICCs or ICCs in situ, which was abolished by an M3 receptor antagonist but not affected by M2 receptor antagonist[74,75]. Another study also demonstrated that carbachol augmented the frequency of spontaneous inward currents generated by ICCs in rabbit urethra, which was blocked by atropine[76]. Recent study has confirmed the presence of M3 receptor in bladder ICCs[77]. All these results suggest that ICCs may also mediate cholinergic neurotransmission in visceral smooth muscle.

5 Summary

In conclusion, different kinds of ICCs play different roles in the activities of visceral smooth muscles. ICC-MY acts as pacemaker cell to generate slower waves, while ICC-IM mediates neurotransmission from neurons to smooth muscle cells. In pacemaking mechanism, intracellular calcium oscillation is a very important factor. However, there is a divergence for pacemaker channels, and nonspecific calcium channel and calcium-activated chloride channel are candidates for the channels responsible for pacemaker currents. In organs, ICC-MY and ICC-IM coordinate each other to propel the smooth muscles to contract normally, which helps the organs to fulfill their physiological roles.

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