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Network of Gut Pacemaker Cells: Spatio-Temporal Evaluation of Electrical Activity by Use of Microelectrode Array

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1. Introduction

The word 'pacemaker' prompts us to imagine 'heart beats' and also an 'electric cardiogram'. However, spontaneous electrical activity occurs in numerous tissues and organs in the autonomic nervous system, such as in the gastrointestinal and urinary tracts, trachea, uterus, lymph ducts, etc. (Takaki et al, 2010). Recent studies have revealed that special interstitial cells in these tissues and organs act as pacemaker cells. In particular, in the gastrointestinal tract, pacemaker cells surround the myenteric plexus between the circular and longitudinal muscle layers. Since these cells express abundant tyrosine kinase, Kit receptors, on the surface, Kit-immunoreactivity and *kit* cDNA are used as markers for special pacemaker cells. Moreover, these cells are now referred to as interstitial cells of Cajal (ICC) due to their histological features of the network (Maeda et al. 1992; Faussone-Pellegrini and Thuneberg, 1999; Sanders et al. 1999; Rumessen and Vandervinden, 2003; Takaki, 2003).

It is widely accepted that peristaltic movement of the gastrointestinal tract is organized by a network of enteric neurons in the myenteric plexus: Ascending contraction and descending relaxation simultaneously occur to forward luminal contents. It is hypothesized that ICC may also make an essential contribution to the co-ordinated actions of gastrointestinal motility through their network (Nakayama et al. 2006; 2009, see also Fig. 7).

There are an increasing number of papers that report the impairment of ICC in GI motility disorders, for example, in inflammatory bowel diseases (IBD) (Suzuki et al. 2004; Wang et al. 2002; 2007; Kinoshita et al. 2007), diabetic gastroparesis (Camilleri, 2002; Ordög et al. 2000; Vittal et al. 2007), slow transit constipation (He et al. 2000; Lyford et al. 2002; Wedel et al. 2002), Hirschsprung's disease (Vanderwinden et al. 1996), etc. In these studies, the impairment of ICC has been evaluated in histological terms, such as apoptotic changes and reduction of ICC number. However, in some stage of these diseases, GI motility disorders may be caused by functional impairment of ICC preceded by or not linked with histological changes. Therefore, tools for evaluating ICC spatio-temporal activity are now anticipated.

We have thus employed a microelectrode array (MEA) in order to study ICC pacemaker activity. In this chapter, we describe our methods of MEA measurements and provide evidence showing that ICC play crucial roles in propagating electrical activity as well as in pacemaking. In some experiments, we compare ileal muscle preparations of wild-type (WT)

and W/W^v mice as a model to evaluate the impairment of ICC, because it is well known that the latter has a largely reduced population of ICC in the myenteric region due to partial loss-of-function mutation of Kit receptors (Reith, 1990; Ward et al. 2004; Iino et al. 2007).
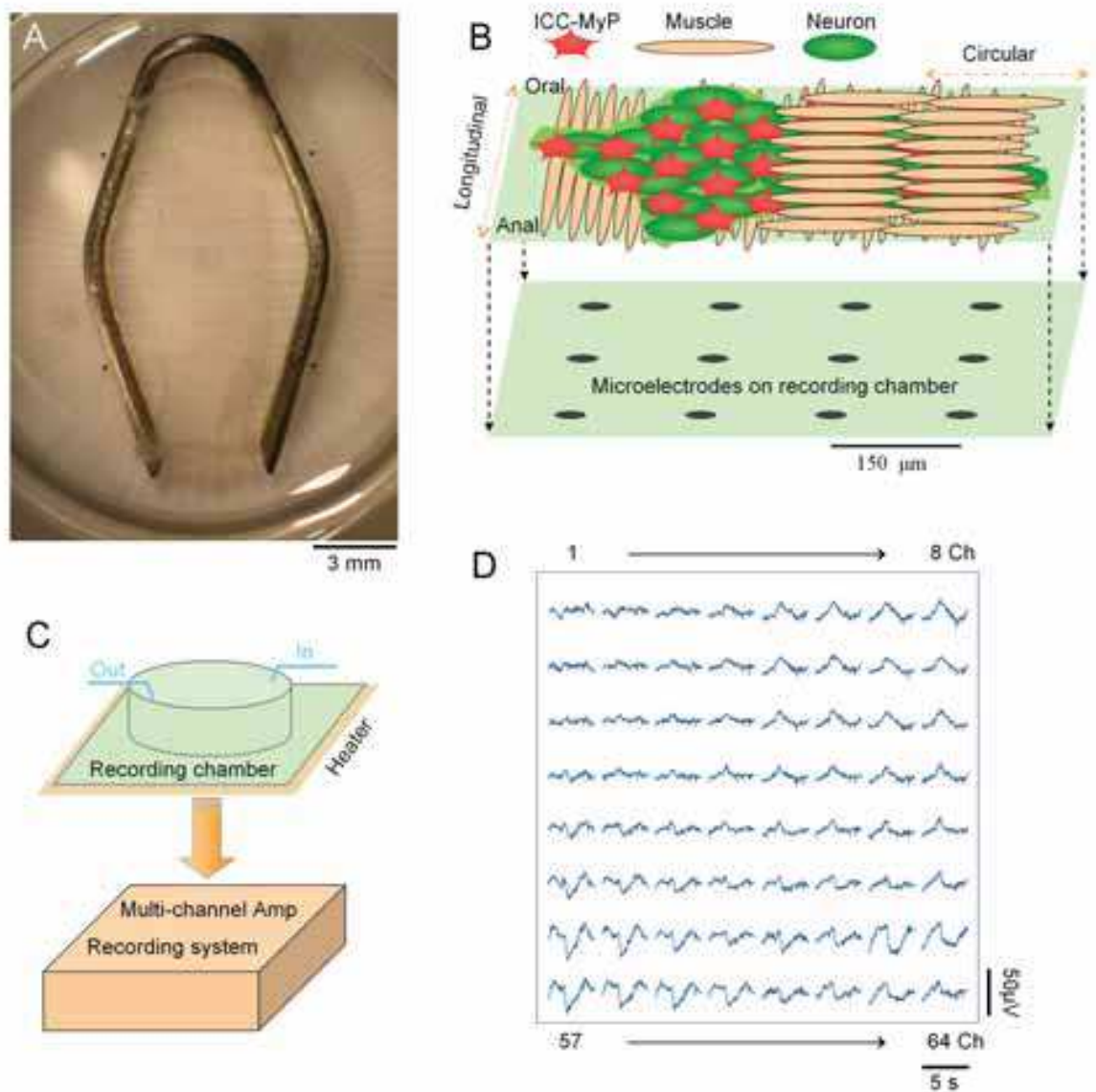

Fig. 1. MEA system to measure gut pacemaker electrical activity (modified from Fig. 1, Nakayama et al. 2009). As an example, an MEA recording from ileal musculature is shown. It is known that network-forming ICC in the myenteric plexus (ICC-MyP) generate pacemaker potentials in the ileum.

2. Microelectrode array measurements

In order to analyze spatio-temporal properties of gut pacemaker cells, we employed an MEA system (Nakayama et al. 2006; 2009), which was previously used for brain slice and explant preparations (Shimono *et al.* 2000; Nakamura *et al.* 2002). Musculature preparations

isolated from animals were mounted in a recording chamber with an 8 x 8 planar MEA (Fig. 1). The chamber was kept warm and continuously perfused with physiological solutions. Gut pacemaker electrical activity was recorded at 64 channels simultaneously.

2.1 Animals

The animals used were treated in accordance with the Animal Experimental Guides of Nagoya University Graduate School of Medicine. Guinea-pigs, and WT (BALB/c) and W/W^v mice were used. The gastrointestinal tract was quickly excised. The mucosa was removed with fine scissors in the stomach, and with fine forceps in the ileum. Small segments of the whole-muscle layer containing the myenteric plexus were dissected and mounted in a recording chamber. The musculature preparations were held down under the strings of a slice anchor (SDH series, Harvard Apparatus Japan, Tokyo, Japan), and were superfused with modified Krebs solution (normal extracellular solution) at a constant rate of 2 ml/min, and placed on a heater kept at 35°C.

2.2 Electrical recordings

In this MEA system 8 x 8 planar electrodes (150 or 300 μm in polar distance) were connected to a 64-channel amplifier (MED 64 System, Alpha Med Science, Osaka, Japan). Electrical potentials at 64 channels were recorded simultaneously at a sampling rate of 20 kHz, after low-pass filtering at 10 kHz. Also, a high-pass filter (HPF) of 0.1 Hz was applied to stabilise the baseline drift of the DC potential (Brock & Cunnane, 1987). The low impedance of microelectrodes (<10 kΩ, at 1 kHz) and a HPF of 0.1 Hz enabled us to follow slow electrical oscillations of gut pacemaker activity (Nakayama et al. 2006; 2009).

2.3 Solutions and drugs

The composition of the "normal" extracellular solution, a modified Krebs solution, was (in mmol/L): NaCl, 125; KCl, 5.9; $MgCl_2$ 1.2; $CaCl_2$ 2.4; glucose 11; Tris-HEPES, 11.8 (pH 7.4). Nifedipine and tetrodotoxin (TTX) were purchased from Sigma (St Louis, MO, USA).

Gut musculature preparations contain three major cell types which generate electrical activity: smooth muscle cells, neurons and ICC. It is well known that TTX suppresses neural activity by blocking voltage-gated Na^+ channels. In gut smooth muscle, contractility and excitability largely depend on Ca^{2+}-influx via L-type voltage-gated Ca^{2+} channels. Dihydropyridine (DHP) Ca^{2+} antagonists e.g. nifedipine and nicardipine, which selectively block L-type Ca^{2+} channels, nearly completely suppress spontaneous contractile and electrical activities in gut smooth muscle (Nakayama et al. 2007). On the other hand, ICC pacemaking also requires extracellular Ca^{2+}, but DHP Ca^{2+} antagonists have little effect on ICC electrical activity (Dickens et al. 1999; Huang et al. 1999), probably because L-type Ca^{2+} channels are not major Ca^{2+} influx pathways in ICC.

In MEA measurements of gut pacemaker activity, the extracellular solution contained nifedipine (1 μmol/L) in order to suppress smooth muscle electrical activity, and to reduce electrical artefacts due to muscle contractions. In addition, the extracellular solution always contained TTX (500 nmol/L) in order to rule out electrical signals from enteric neurons and neural modulation of ICC activity (linked with neurotransmitter release by action potentials in neurons). MEA measurements started ~30 min after superfusing with the extracellular solution containing nifedipine and TTX.

2.4 Data analysis

Arrayed data of field potentials were normally thinned by a 1000-fold time domain, thereby the sampling interval was increased to 50 ms. This sampling frequency was enough to follow gut pacemaking electrical activity. Cross-correlation, power spectrum, and digital filtering of spontaneous electrical potentials were performed using commercial add-in software (Kyowa Electronic Instruments, Tokyo, Japan). Two-dimensional field potential images were constructed by calculating values at the desired location via spline interpolation, using the MATLAB software package (Mathworks: Natick, MA, USA)(Shimono et al. 2000; Nakayama et al. 2009).

Numerical data are expressed as means±S.D. Significant differences were evaluated by unpaired t-tests.

3. Gut pacemaker activity

3.1 Stomach ICC activity

The stomach is divided into the fundus, corpus, antrum and pylorus. Typical pacemaker potentials are relatively easily observed in the gastric antrum of guinea-pigs, therefore we used musculature preparations in this part of the stomach. It is known that network-forming ICC in the myenteric plexus (ICC-MyP) of the antral muscle act as primary pacemaker cells, while intramuscular ICC (ICC-IM) in the circular muscle amplify the pacemaker electrical activity (Dickens et al. 1999; Hirst & Ward, 2003).

Musculature preparations were placed with the circular muscle layer down, and fixed in a recording chamber with an array of 8 x 8 MEA with 300 μm in interpolar distance. The recording area was ~4mm². Figure 2 shows an example of field potential recordings in the guinea-pig stomach, by use of the MEA. In Aa, a muscle preparation was under superfusion with a "normal" (modified Krebs) extracellular solution. The upper and lower ends correspond to the anal and oral ends of the gastric antrum, respectively, while the left and right correspond to the lesser and greater curvature ends. This set of MEA recordings is plotted with the same scale of amplitude, indicating the existence of a gradient in the field potential amplitude.

In Fig. 2B, the amplitude (y-axis) of MEA recording was expanded to more clearly display spontaneous electrical activity recorded in each planar electrode, indicating that the occurrence of spontaneous electrical activity was well synchronised over the electrode array area. Essentially, the synchoronicity of electrical activities was similar in all antral muscle preparations tested.

As described in Section 2.3, DHP Ca²⁺ channel antagonists can be used to isolate ICC pacemaker electrical activity by suppressing smooth muscle contractility and excitability. As shown in Fig. 2Ab, nifedipine, a DHP Ca²⁺ antagonist had little effect on the frequency of spontaneous electrical activity, and also did not significantly alter the shape of the field potential in the majority of recording channels. Also, additional application of TTX had little or no further effect on these field potential recordings (Fig. 2Ac). These results indicated that ICC make a predominant contribution to the generation of spontaneous electric activity in the stomach musculature.

The shape of the spontaneous electrical activity (≈ ICC pacemaker activity) in the stomach musculature varied greatly, but usually consisted of an initial, fast negative potential (red arrow in Fig. 2D) followed by a slowly decaying component (green double arrow).
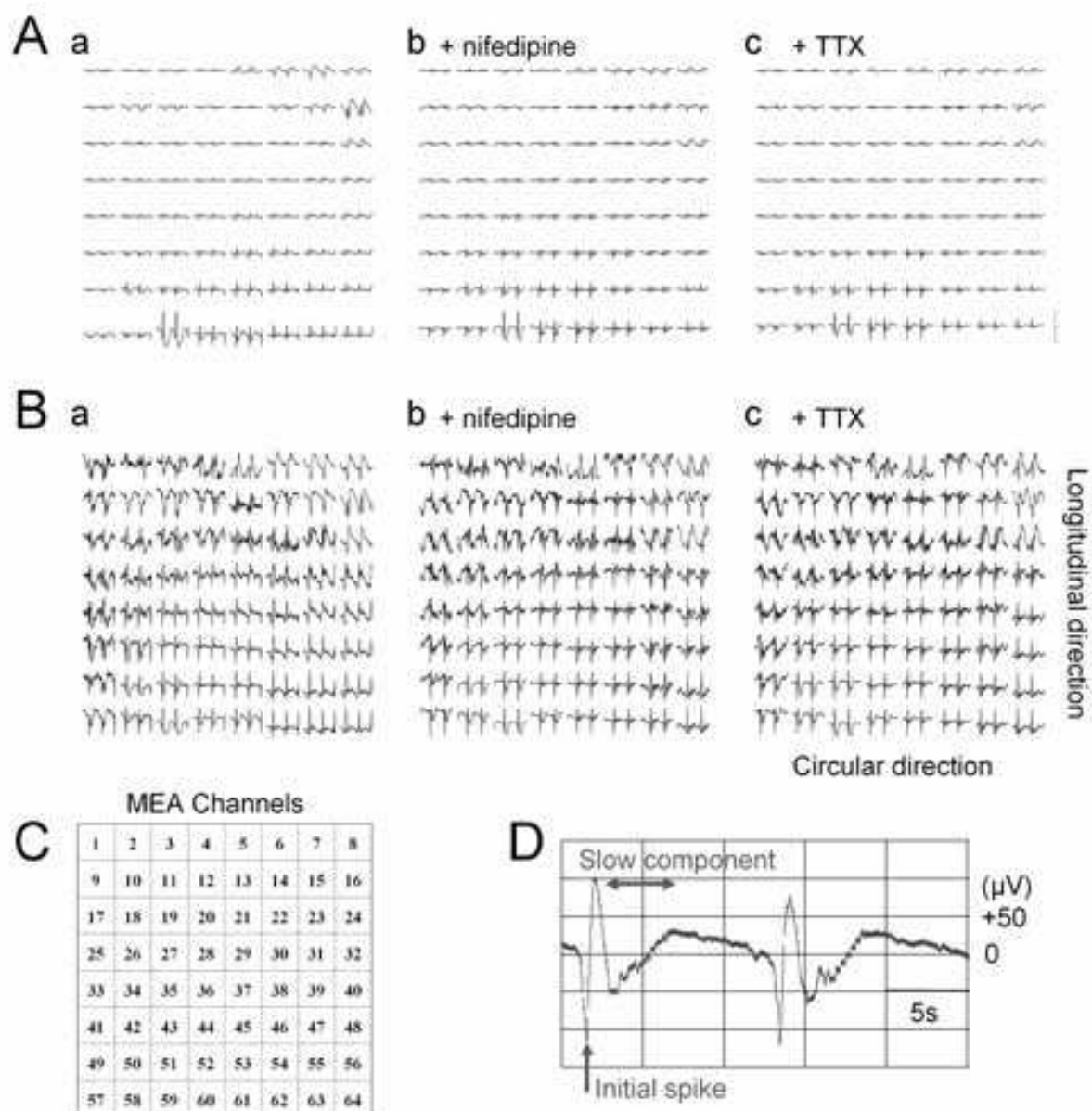
Fig. 2. An example of the distribution of spontaneous electrical activities in a stomach muscle preparation recorded using an 8 x 8 MEA with a polar distance of 300 μm (Modified from Figs. 1 and 3, Nakayama et al. 2006). Each trace in A shows the normalised field potential with a y-range of ±150 μV (scale bar). In B, the y-range was adjusted to more clearly show the shape of spontaneous electrical activity at each recording channel. The channel number of the arrayed electrodes is shown in C. Panel D shows an expanded typical pacemaker activity with initial spike followed by a slow component.

3.2 Reversible propagation

ICC pacemaking field potentials were well synchronized over the recording area; however, phase differences were clearly observed between some of the recording channels. Figure 3A shows an example in which the pacemaker potentials propagate from the oral to anal end. The field potential traces (a-c) were recorded in Ch. 25, 27, and 29, respectively. The initial

spike (down-stroke) in trace (a) was followed by those in (b) and (c). The field potential images (d) show excitation (yellow area) running from the right to the left, indicating the oral to anal propagation.
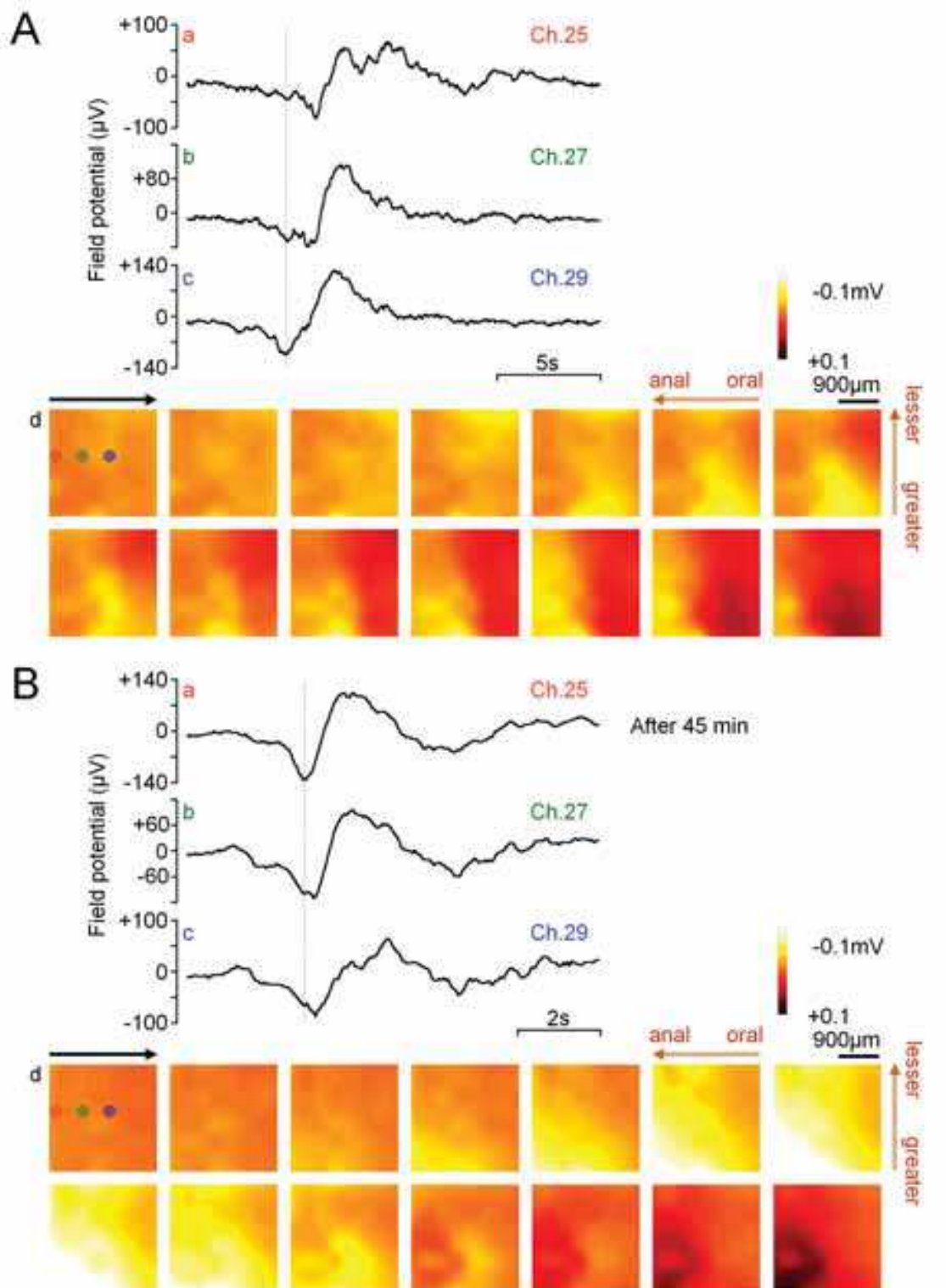

Fig. 3. An example of reversed ICC pacemaker activity (Modified from Fig. 8, Nakayama et al. 2006).

The field potential traces and images in Fig. 3B were obtained from the same gastric antrum preparation used in A, after approximately 45 min. This preparation was continuously superfused with the same extracellular solution (containing nifedipine). The field potential traces and images clearly show reversed electrical excitation, running from the anal to the oral end.

A phase shift proceeding from the oral end was observed in the majority (15 out of 18) of the stomach preparations. The propagation velocity of the spontaneous electrical activity along the longitudinal muscle ranged from –14.25 to +13.27 mm s^{-1}, but it was around ~1 (or –1) mm s^{-1} in the majority (13 out of 18) of preparations (plus indicates the oral to anal propagation). In 10 antral muscle preparations with the pacemaker phase shift proceeding from the oral end in the initial observation, field potentials were continuously recorded for ~30 min. The direction of propagation was reversed in four out of 10 preparations (Nakayama et al. 2006). Altogether, these results indicate that coupling of ICC pacemaker activity has plasticity and that that an ICC network can even produce reversible propagation of pacemaker potentials in the stomach.

3.3 Ileal ICC activity in wild-type and W/W^v mice

Musculature preparations isolated from the mouse ileum were placed with the longitudinal muscle layer down on an 8 x 8 MEA with a polar distance of 150 μm. The recording area was ~1 mm^2. Ileal musculature preparations contained both circular and longitudinal muscle layers and the myenteric plexus between these muscle layers. In order to suppress smooth muscle and neural activities, the extracellular solution contained nifedipine and TTX, respectively.

In the WT mouse ileum, network-forming ICC-MyP predominantly contribute to the generation of pacemaker potentials. W/W^v mice are known to lack or largely reduce pacemaking ICC-MY in the ileum (Reith, 1990; Ward et al. 1994; Iino et al. 2007). Therefore in the presence of nifedipine and TTX, only little spontaneous electrical activity was anticipated in ileal preparations from W/W^v mice. Figure 4 shows such the difference between WT and W/W^v mice. In WT mice spontaneous electrical potentials occurred regularly, while in W/W^v mice electrical activity was significantly smaller in amplitude and irregular in occurrence.

Power spectra over the recording area (Fig. 5A and B) were constructed from field potentials of all 64 channels for approximately 40 s recorded from the same preparations shown in Fig. 4. The power spectrum of WT mice had a prominent peak corresponding to the frequency of ileal ICC electrical activity, but that of W/W^v mice did not, reflecting an irregular occurrence of small electrical activities. Essentially the same tendencies were observed in other WT (n=28) and in W/W^v (n=27) ileal musculature preparations. In all preparations of WT mice, the spectral peak was normally observed between 9.4-27.0 cpm, thereby, the ratio of spectral power in this frequency range ($Pw_{9.4-27.0cpm}$) was significantly greater in WT mice (74.8±15.9%, n=29) than in W/W^v mice (38.0±15.6%, n=28) (P<0.0001, Fig. 5C).

3.4 Spatio-temporal analysis

Pacemaker potential images were constructed from field potentials measured by MEA. Panels in Fig. 6A show a sequence of field potential images obtained from the same WT mouse ileum preparation in Fig. 4. The top and bottom of each image correspond to the oral and anal ends of the MEA recording region, respectively. In this preparation, initial
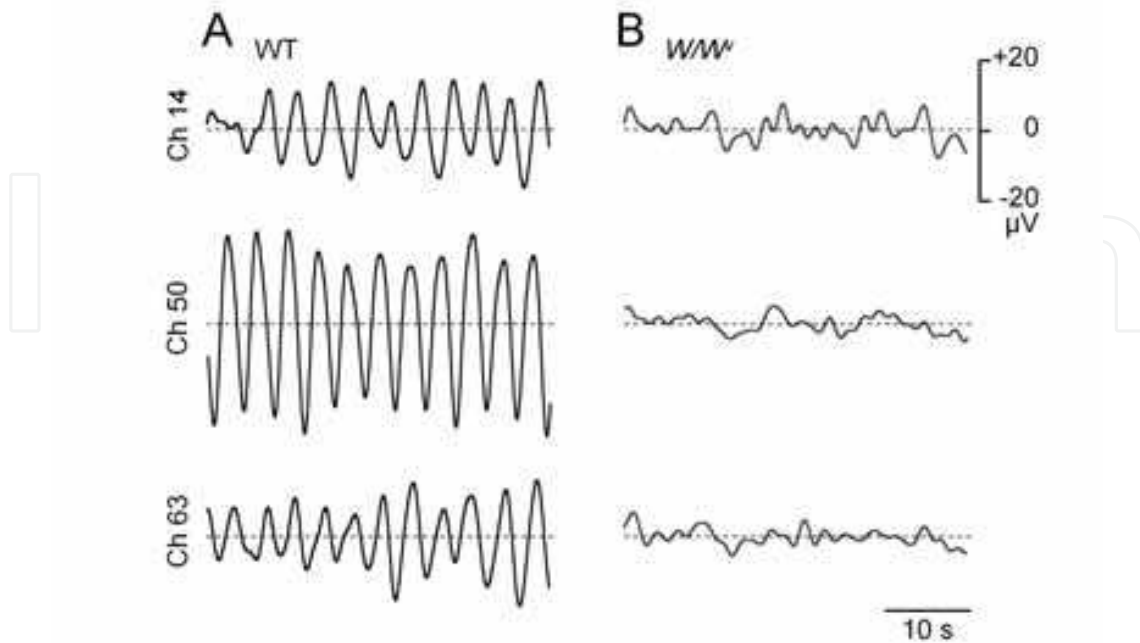
Fig. 4. Examples of field potentials recorded from ileal muscle preparations of WT (A) and
W/W^v mice (B) (Reproduced from Fig. 2, Nakayama et al. 2009). Field potentials were plotted
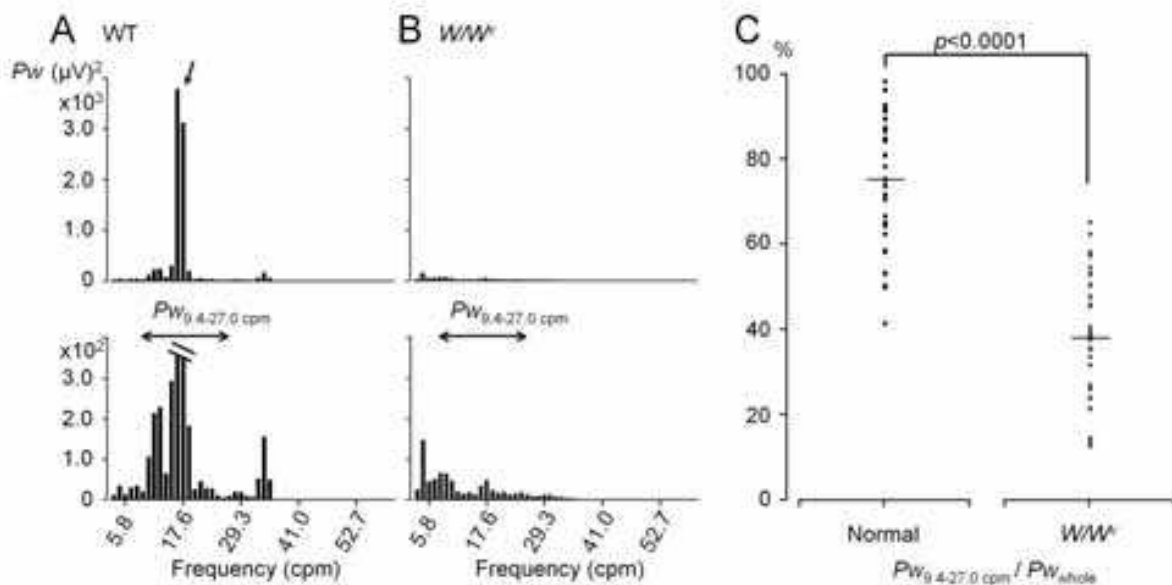after digital band-pass filtering at 0.05-0.5 Hz.

Fig. 5. Power spectrum analysis (Reproduced from Fig. 3, Nakayama et al. 2009). A-B: Field
potential recordings from the same preparations shown in Fig. 4 were used. C: Summary of
power spectra in WT (n=29) and W/W^v mice (n=28). The ratio of the spectral power (Pw)
between 9.4-27.0 cpm to the whole Pw is plotted. Horizontal lines represent mean values.
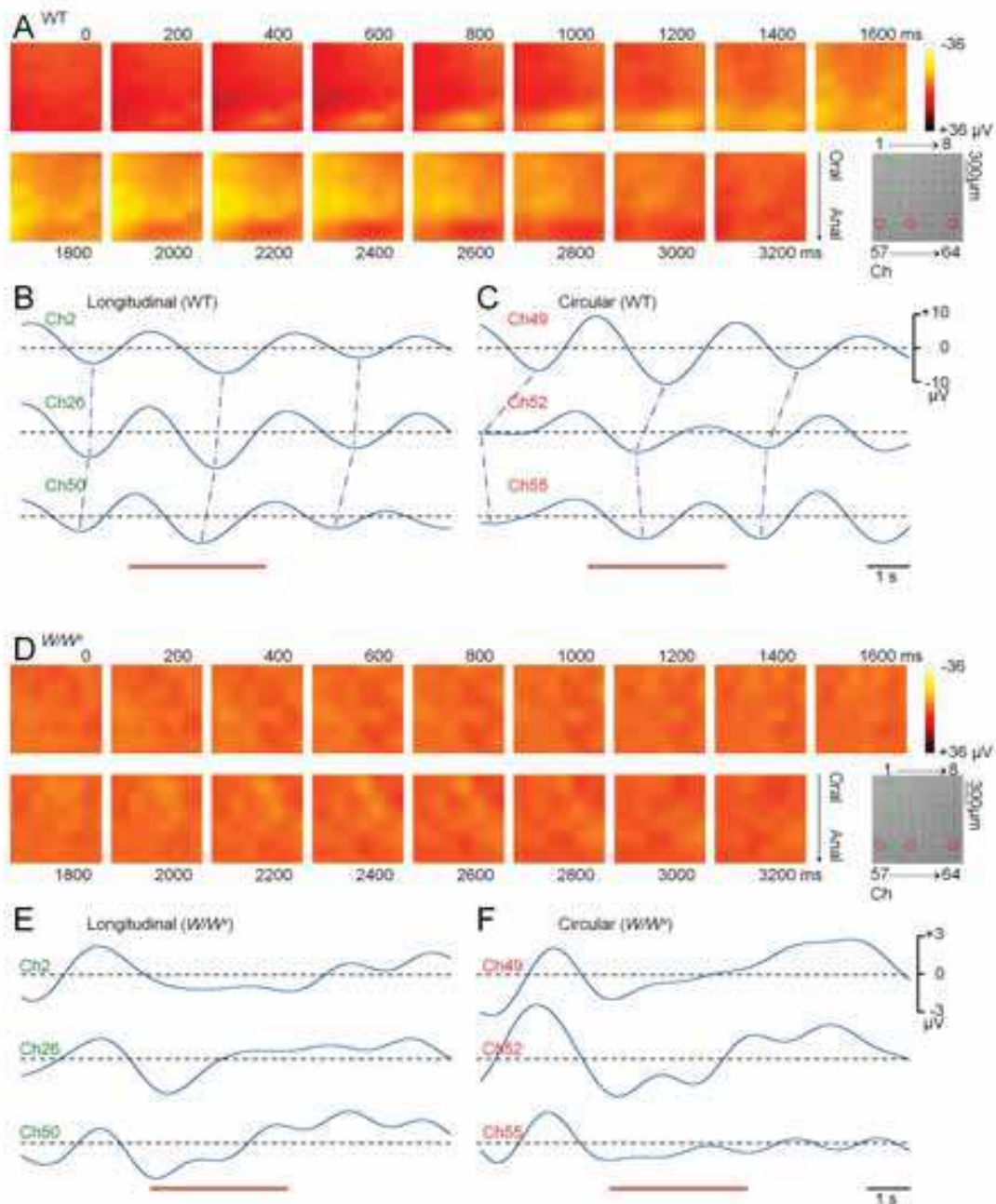
Fig. 6. Spatio-temporal analysis of pacemaker electrical activity in the ileum isolated from WT wild-type (A-C) and *W/W^v* mice (D-F) (Reproduced from Fig. 4, Nakayama et al. 2009). The peaks of electric excitation (down-stroke corresponding to depolarization) are connected by blue dotted lines. The red horizontal lines indicate the period of the potential images acquired.

excitation occurred in the right bottom of MEA near Ch62. Next, the excitation propagated along the circular muscle toward both ends, and then propagated along the longitudinal muscle toward the oral end. Field potential traces in Figs 6B and C show three cycles of spontaneous electrical oscillations recorded in Ch2, 26, and 50 (lined along longitudinal muscle), and Ch49, 52, and 55 (lined along circular muscle), respectively. As shown in Fig. 6A-C, in 29 preparations in WT mice, electrical activities were synchronised, and the propagation velocity of the excitation was ~1.4 mm s^{-1} in both directions. The propagating velocity was, however, changeable.

The sequence of potential images in Fig. 6D and field potential traces in Figs. 6E and F were obtained by applying the same procedures used in Figs. 6A-C, respectively, to the same ileal musculature preparation of W/W^v mice shown in Fig 4. In W/W^v mice, spontaneous electrical activities were smaller in amplitude, were fluctuating, and were not well-synchronized over the recording area (Figs. 6E and F). Furthermore, there was no clear propagating direction observed. Essentially the same results were obtained from other ileal muscle preparations of WT and W/W^v mice.

4. Applications of MEA in gut pacemakers

The mechanisms underling gut spontaneous electrical activity are becoming clearer. Conventional microelectrodes have elucidated that Kit-reactive interstitial cells in the myenteric plexus, i.e. ICC-MyP generate basal pacemaking electrical potentials (Dickens et al. 1999; Kito et al. 2005). Further, there is a growing body of evidence that Ca^{2+} mechanisms provide these cells with fundamental rhythmicity (Nakayama et al. 2007). Namely, intracellular Ca^{2+} release channels and Ca^{2+}-permeable channels in the plasmalemma co-ordinately produce ICC Ca^{2+} oscillations underlying the generation of pacemaker electrical activity (Aoyama et al. 2004; Liu et al. 2005a; b).

Since ICC-MyP are network-forming cells, the next step in the understanding of GI motility and in the treatment of GI dismotility is how these interstitial cells communicate with each other, and how pacemaking electrical activity contributes to coordinated actions of GI motility, i.e. to digest, mix and transport luminal contents. Previously, conventional multiple electrodes have been applied to investigate coordination of motor activity in a rather large distance, e.g. antroduodenal coordination (Wang et al. 2005; Lammers et al. 2005).

Recently, our MEA study successfully demonstrated the propagation of pacemaker potentials generated by an ICC network in a small area (~4 mm²) of the stomach musculature (Nakayama et al. 2006). It is likely that such a phase shift (propagation delay) of pacemaker activity even in a few hundred micrometers enables smooth GI motility. Namely, the contractions of small segments of the gut linked with a linear phase shift in distance would elaborately squeeze luminal contents in a certain direction.

Coupling of pacemaker activity is changeable (plasticity) in the gut. Further, the propagation direction of pacemaker activity is reversible (Fig. 3), in contrast to the enteric neural network. Using this network system, luminal contents stimulate primary afferent neurons, and subsequently co-activate ascending excitatory and descending inhibitory neurons of the myenteric plexus via interneurons, causing ascending contraction and descending relaxation simultaneously (Furness, 2006; Wood, 2006). It is hypothesized that chained reactions of this reflex (i.e. peristaltic reflex) transport luminal contents throughout the gastrointestinal tract. Presumably the ICC network which can produce reversible activity, cooperates with the neural network, resulting in complex gut motility to efficiently digest luminal contents.

MEA has also been applied to investigate spontaneous electrical activity between ileal musculature preparations from WT and W/W^v mice. This comparison provides a model to evaluate impairment of the ICC network, because it is well known that the latter has a largely reduced population of ICC-MyP due to a partial loss-of-function mutation of Kit receptors (Reith, 1990; Ward et al. 2004; Iino et al. 2007). Analyses with power spectrum and potential mapping successfully distinguished electrical properties of these musculature preparations, indicating that network-forming ICC-MyP not only generates pacemaker potentials but also co-ordinates basal electrical activities. Disorders of gut motility based on morphological and/or functional impairments of the ICC network with a range of several hundred micrometers could be uncovered in future extensive studies, including model

animals. As described earlier, there is a considerable body of evidence for the impairment of the ICC network in GI motility disorders. Furthermore, there is also a growing body of evidence that ICC-like interstitial cells are widely distributed outside the GI tract, for example in small vessels, the lymph duct, urinary tract, uterus, and also accessory organs of the GI tract (Huizinga, and Faussone-Pellegrini, 2005; Brading, and McCloskey, 2005; McCloskey et al. 2002; Harhun et al. 2005; Ciontea et al. 2005; Sun et al. 2006). MEA could also be a useful tool to evaluate a wide range of spontaneous rhythmicities and related dismotilities, e.g. unstable urinary bladder in geriatrics.

5. Conclusions

MEA has enabled spatio-temporal analysis of gut pacemaker activity in a small area. Network-forming ICC not only generates pacemaker potentials but also co-ordinates basal electrical activities. The propagation velocity of pacemaker potential (i.e. phase shift of ICC electrical activity) is changeable, and even reversible under certain conditions. It is likey that co-contribution of the ICC network and neural network organizes complex gut motility.
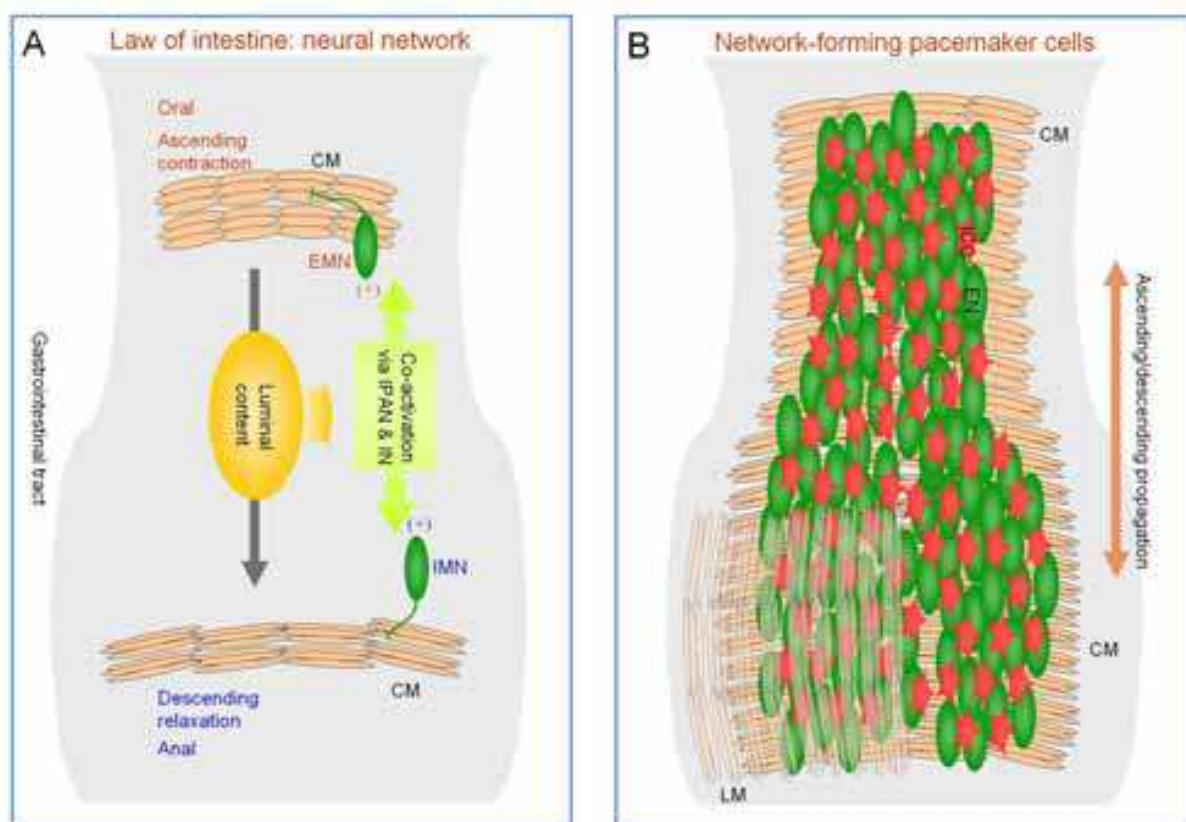

Fig. 7. Schematic diagrams of mechanisms underlying gut motility. A: Generally accepted 'law of intestine' is controlled by neural network. Luminal contents co-activate oral excitatory and anal inhibitory neurons (EMN and IMN) via intrinsic primary afferent neurons (IPAN) and interneurons (IN), thereby produce ascending contraction and descending relaxation simultaneously. B: A new contributor, 'network-forming pacemaker cells'. ICC-MyP surrounding the myenteric plexus between circular and longitudinal muscle layers (CM and LM), propagate as well as generate pacemaker activity. Propagation of pacemaker activity is changeable (plasticity), even reversed under some conditions. ICC network along with intrinsic neural network appears to elaborately control gut motility.

Future extensive studies using MEA will uncover disorders of gut motility based on morphological and/or functional impairments of the ICC network with the range of several hundred micrometers.

6. Acknowledgements

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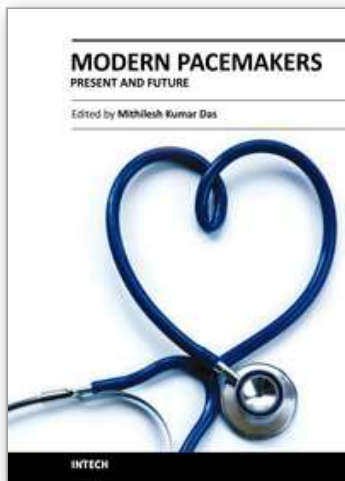
Modern Pacemakers - Present and Future

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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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