News Release

Title

Micro-coordination of pacemaker potentials in the intestine of the mouse

Key Points

- By visualizing the data of a dialysis membrane-enforced microelectrode array (MEA), we have tentatively classified three patterns for the micro-coordination of basal electric activity (pacemaker potentials) in the ileum of mice: bumpy, expanding, and migrating.
- The image analysis of a long period of MEA data revealed the existence of considerably large variation in the micro-coordination of pacemaker potentials. For example, an 'expanding' ileal sample showed a large shift of the initiating region, and another sample of 'migrating' dramatically reversed the direction of propagation.
- Image analysis of the micro-coordination pattern of pacemaker potentials and its fluctuation can be used as a sensitive index to estimate the characteristics and functional status of samples. Its application to model animals for various diseases and pharmaceutical studies is anticipated.
- Textbooks of medicine and physiology describe the 'law of the intestine' that is considered to be under the control of the intrinsic nervous system: Stimulation of the content, such as food, causes oral contraction accompanied by anal relaxation in the gastrointestinal tract. Nevertheless, it is pointed out that typical responses occur only in certain conditions. The present study provides visual evidence that pacemaker cells create spatio-temporally coordinated basal electric rhythmicity, that does not conform to the 'law of the intestine'.

Summary

Assoc. Prof. Shinsuke Nakayama and Research Associates (Ms Naoko Iwata, and Chiho Takai) at the Department of Cell Physiology, Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi) demonstrated that micro-coordination of gut pacemaker potentials can be visually classified. This was achieved through collaborative research work, including student research projects (Mr Hirotaka Morishita, First Author).

Functional movement of the gut, such as peristalsis, segmentation, etc. requires sophisticated coordination of micro-regions. Textbooks of medicine and physiology describe the 'law of the intestine' that indicates that the intestine is considered to be under the control of the intrinsic nervous system: Stimulation of the content causes ascending (oral) contraction accompanied by descending (anal) relaxation in the gastrointestinal tract. Nevertheless, a multitude of excitable cellular systems, including network-forming pacemaker cells, are likely to cooperate in coordinated movements of the gut.

In this study, we thus employed a dialysis membrane-enforced micro-electrode array (MEA) technique (Iwata et al. 2017) to measure spontaneous electrical activity in the ileum showing typical pacemaker potentials, and visually analyzed the spatio-temporal coordination

of micro-regions. The micro-coordination of spontaneous field potential oscillations (pacemaker potentials) was tentatively classified into three patterns: 'bumpy', 'expanding' and 'migrating'. In addition, features of micro-coordination fluctuated, and occasionally underwent large changes even in the same sample during a long period of measurements. For example, some samples of 'migrating' patterns showed a reversal of propagating direction.

With further refinement of this classification in future studies, the pattern of micro-electric activity potentially could be used as a sensitive indicator of the functional state of the interstitial cell network and GI tract in physiological and pathological conditions. In addition, the present study presented visual evidence that network-forming pacemaker cells create spatio-temporally coordinated basal electric rhythmicity which does not conform to the 'law of the intestine'. Elucidation of mechanisms underlying the micro-coordination of pacemaker activity may provide researchers with a new therapeutic strategy for various functions related to gut motility.

This study was published in a medical journal "Gastroenterology" in June 2017.

Research Background

Functional movement of the gut, such as peristalsis, segmentation, etc. requires sophisticated coordination of micro-regions. Textbooks of medicine and physiology describe the 'law of the intestine' in which the intestine is considered to be under the control of the intrinsic nervous system and where stimulation of the content, such as food, causes oral contraction accompanied by anal relaxation in the gastrointestinal tract. Nevertheless, it is known that typical responses occur only in certain conditions, suggesting the cooperation of a multitude of excitable cellular systems other than the enteric nervous system. Network-forming pacemaker cells are likely to make a significant contribution to coordinated movements of the gut.

Research Results

In this study, we employed a dialysis-membrane enforced micro-electrode array (MEA) technique (Iwata et al. 2017) to measure spontaneous electrical activity in the ileum showing typical pacemaker potentials, and visually analyzed the spatio-temporal coordination of micro-regions.

The micro-coordination of spontaneous field potential oscillations (pacemaker potentials) was tentatively classified into three patterns: 'bumpy', 'expanding' and 'migrating' (Figure 1). 1) Samples classified as 'bumpy' showed local electric activity propagating to only limited regions, indicating that electric coupling was poor and spatially confined. 2) In samples of the 'expanding' pattern, spontaneous electric activity was initiated in a small region and subsequently propagated to adjacent regions, with activity persisting for longer in regions near the initiating site. 3) Samples of the 'migrating' pattern showed the formation of an elongated area of activity that propagated approximately orthogonally to its long axis.

The spatio-temporal coordination of pacemaker activity varied throughout continuous measurements. One sample showing an 'expanding' pattern changed the initiating region in

each cycle of activity, while another sample of the 'migrating' pattern occasionally showed dramatic changes such as reversal of propagation direction. These findings indicate that network-forming interstitial cells can organize different patterns of electrical coordination. Furthermore, careful observation of the potential mapping images revealed that light-colored (negative potential) regions followed behind dark-colored (positive potential) regions as the activity migrated over the MEA sensing area. These areas represent the source and sink regions, respectively, of a local circuit current (a volume conductor) for propagating pacemaker activity (Figure 2).

Our research findings were published in an electric medical journal "Gastroenterology" (electronic journal in June 2017).

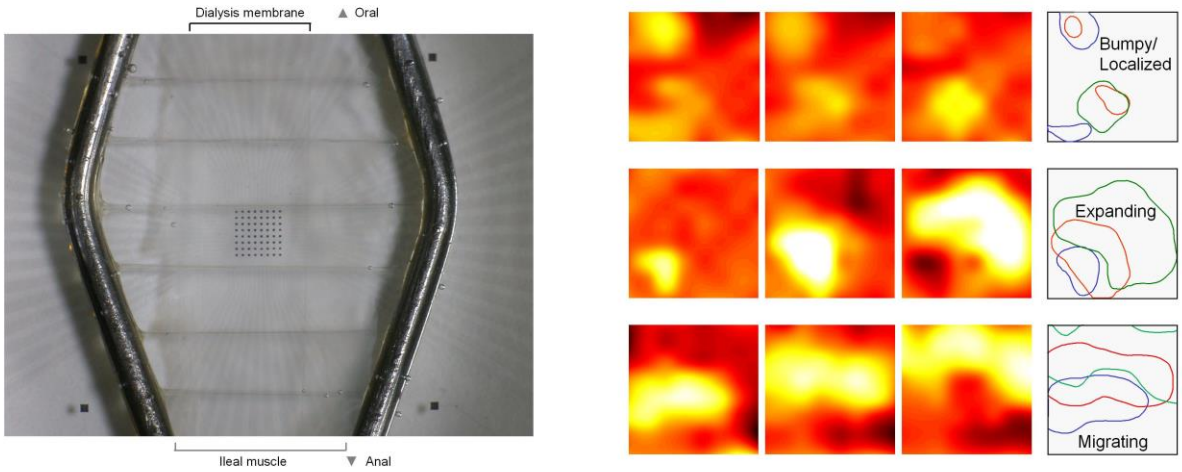

Figure 1. Potential mapping analysis revealed pattern of micro-coordination of pacemaker potentials.
Left panel: Dialysis membrane-enforced MEA technique for recording 8 × 8 field potentials in a micro-region (1 × 1 mm^2) of ileal muscle sample. Right: Three patterns of micro-coordination classified: bumpy, expanding and migrating. Outlines of binarized images are superimposed.

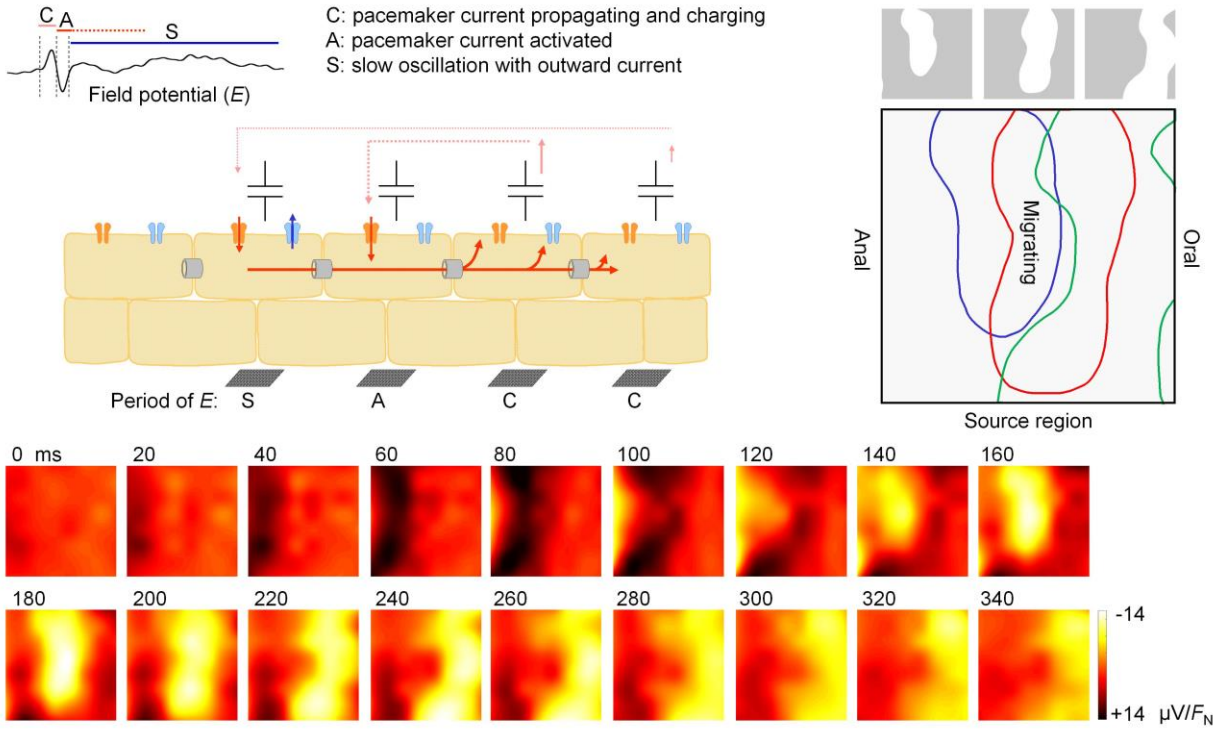

Figure 2. Propagation of pacemaker potentials in the gut. Left top panel: Schematic representation showing propagating pacemaker potential. Bottom: Potential mapping demonstration of pacemaker potentials in 'migrating' pattern. Sink regions (dark-color) precedes pacemaker current source regions (light-color). Right top: Shift of source regions identified by binarizing potential images (160, 200, 240 ms). F_N: normalizing factor of each electrode.

Research Summary and Future Perspective

By visualizing the data of dialysis membrane-enforced MEA, we tentatively classified three patterns for the micro-coordination of basal electric activity (pacemaker potentials) in the ileum of mice: bumpy, expanding, and migrating. With further refinement of this classification in future studies, the pattern of micro-electric activity could potentially be used as a sensitive indicator of the functional state of the interstitial cell network and GI tract in physiological and pathological conditions. Also, the present study provided visual evidence that network-forming pacemaker cells create spatio-temporally coordinated basal electric rhythmicity that does not conform to the 'law of the intestine'. To elucidate mechanisms underlying micro-coordination of pacemaker activity may provide researcher with a new therapeutic strategy of various functions related to gut motility.

Publication

Hirotaka Morishita, Naoko Iwata, Chiho Takai, Naoto Mochizuki, Noriyuki Kaji, Masatoshi Hori, Shunichi Kajioka, Shinsuke Nakayama (2017). Micro-coordination of pacemaker potentials in the intestine of the mouse. *Gastroenterology*.

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