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ELECTROPHYSIOLOGIC IDENTIFICATION OF THE LOCATION OF THE COLONIC PACEMAKERS. A HUMAN STUDY

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1. ABSTRACT

Colonic inertia, total or segmental, is a known cause of constipation, yet its etiology is poorly understood and its treatment not satisfactory. Although the colonic electric activity has been studied by many investigators, the colonic pacemakers that are assumed to generate the electric waves, are scarcely addressed and their location, to our knowledge, has not been determined. The current communication investigates the possible sites of the colonic pacemakers, aiming at a better understanding of the mechanism of colonic motility and its disorders, notably colonic inertia. The tests were performed during the repair of huge incisional hernia in 12 subjects (mean age 37.7 ± 10.2 years, 7 women). Monopolar silver-silver chloride electrodes were applied to the terminal ileum (TI) and cecum (C), and to the ascending (AC), transverse (TC), descending (DC) and sigmoid colon (SC); they were fixed by electrode gel to the ileal and colonic serosa. The electric activity of each of the TI, C, AC, TC, DC and SC was recorded. Electric waves in the form of slow waves or pacesetter potentials and action potentials were recorded from the TI and colon. Differences in the frequency, amplitude and conduction velocity of the waves occurred between the TI and the various segments of the colon. The change in the wave variables between the TI and C occurred at the ileocecal junction, between the C and AC at the cecocolonic junction, the AC and TC at the mid third of the TC and the DC and SC at the colosigmoid junction. The colonic electric waves are suggested to be generated by at least 4 pacemakers, which are presumably located at the ileocecal junction, the cecocolonic junction, the mid third of TC and at the colosigmoid junction. The electric waves appear to be responsible for conducting the colonic motor activity. We postulate that disordered colonic pacemakers may produce segmental or total colonic inertia, a proposition that needs further investigation.

2. INTRODUCTION

The motor physiology of the colon has attracted the attention of many investigators. The principle functions of the colon comprise water and electrolyte absorption from the chyme as well as storage of fecal matter until it is

Table 1. The frequency, amplitude and conduction velocity of the pacesetter potentials as recorded from the terminal ileum, cecum, and the ascending, transverse, descending and sigmoid colon

Site	Frequency (cycle/min)		Amplitude (mV)		Conduction velocity (cm/sec)	
	Mean	Range	Mean	Range	Mean	Range
Terminal ileum	3.8 ± 1.4	3 – 5	0.8 ± 0.1	0.7 – 0.9	3.7 ± 0.5	3.2 – 4.2
Cecum	3.3 ± 0.6	3 – 4	0.8 ± 0.3	0.7 – 1.1	3.8 ± 0.8	3.2 – 5.1
AC & right ½ TC	4.2 ± 1.1	3 – 5	0.9 ± 0.2	0.7 – 1.2	4.2 ± 0.4	3.5 – 4.6
Left ½ TC & DC	4.8 ± 0.8	3 – 5	1.1 ± 0.4	0.9 – 1.3	4.7 ± 0.6	4.1– 5.6
Sigmoid Colon	5.6 ± 0.7	4 – 6	1.1 ± 0.4	0.8 – 1.4	5.2 ± 0.9	4.2 – 6.1

Values represent the mean ± standard deviation (SD), AC = ascending colon, TC = transverse colon , DC = descending colon

expelled (1). The colonic motility is organized specifically to serve these functions.

The colon possesses electric activity in the form of slow waves or pacesetter potentials (PPs) and fast activity spikes or action potentials (APs) (2-7). The APs are coupled with elevation of the colonic pressure. The electromechanical activity of the colon increases with colonic distension (6,7). The electric waves appear to be responsible for the colonic motility (2-7). The source of these waves is not exactly known. Previous studies have shown that they are transmitted through smooth muscles of the gut and are partially controlled by the intrinsic and extrinsic colonic innervation (8,9).

It is postulated that the electric waves of the gut are generated from the interstitial cells of Cajal (ICC) (10-15). These cells are located at the level of the myenteric plexus, in the deep muscular plexus and within the circular muscle layer itself (10-15). They are considered to be generators of spontaneous pacemaker activity in the smooth muscle layers of the gut (16-18) and are also involved in neurotransmission (8,9,15). These cells pace the gastrointestinal phasic activity and are considered as the pacemaker cells in the gastrointestinal muscles. They mediate or transduce inputs from enteric motor nerves to the smooth muscle syncytium (8,9,15).

In preceding studies we could determine the site of the pacemaker initiating the rectal motor activity as being located in the rectosigmoid junction (19,20). We defined the pacing parameters required for rectal evacuation of normal and constipated subjects (21). Rectal pacing was then performed in patients with constipation caused by rectal inertia and it succeeded in effecting evacuation (22).

Colonic inertia, total or segmental, is a known cause of constipation, but its etiology is poorly understood and its treatment not satisfactory (23-25). Although the colonic electric activity has been studied by many investigators (2-7), the colonic pacemakers that are assumed to generate these waves have not been sufficiently addressed. To our knowledge the location of these colonic pacemakers has not yet been determined. In this communication, we investigated the potential sites of the colonic pacemakers. Their recognition is suggested to assist in better understanding of the mechanism of colonic motility and its disorders, notably colonic inertia.

3. MATERIAL AND METHODS

3.1. Subjects

The study comprised 12 subjects with a mean age of 37.7±10.2 SD years (range 26–48). 7 were women and 5 men. They were selected from patients who were due for repair of huge incisional hernias after cesarian section in 6 of the women and after midline abdominal incision for cholecystectomy in the remaining 6 patients. An informed consent was given specifically for doing the pacemaker investigation. Laboratory work as well as colonoscopy and barium enema studies were normal. Our Faculty Review Board and Ethics Committee approved the study.

3.2. Methods

The tests were carried out while the patients were under general anesthesia during the operation for incisional hernia repair. The whole colon could be exposed through the incision performed for the hernia repair. The electric activity of the colon was recorded by means of monopolar silver-silver chloride electrodes (Smith Kline Beckman, Los Angeles, CA). Each electrode had a diameter of 0.8 mm and was covered by an insulating vinyl sheath sparing its tip. The electrodes were serially fixed to the colon. For the distribution of the electrodes, we had to determine the length of each of C, AC, TC, DC and SC. The mean length of C was 5.2 ± 1.2 cm (range 4 – 6), of AC 14.9 ± 2.3 SD cm (range 12-18) of TC 38.6 ± 4.8 SD cm (range 33 – 44), of DC 26.3±1.3 SD cm (range 23–28) and of SC 37.4 ± 4.9 SD cm (range 32-43). The electric activity of the TI was recorded by 2 electrodes separated by 2 cm. The two electrodes applied to the C were separated by 3-4 cm. For the rest of the colon, the electrodes were placed with a distance of 5 cm from each other (Figure 1). They were fixed to the colonic serosa by electrode gel, attached to a metal cannula containing pin sockets and connected to a Brush Mark 200 rectilinear pen recorder. The electric activity including the frequency, amplitude and velocity of conduction of the waves was recorded.

To ensure reproducibility, the aforementioned recordings were repeated at least twice in the individual subject and the mean value was calculated. The results were analyzed statistically using the Student's t test, and values were given as the mean ± standard deviation (SD). Differences assumed significance at $p<0.05$.

4. RESULTS AND DISCUSSION

All the subjects were evaluated with no adverse side effects related to the tests. Electric waves were recorded from all the electrodes applied to the TI and colon. PPs were registered as monophasic waves with a large negative deflection (Figure 2). APs were

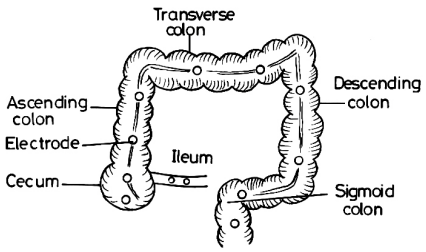

Figure 1. Sites of the electrodes applied to the terminal ileum and colon

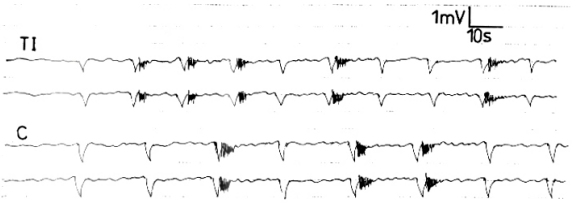

Figure 2. Electric activity recorded from the 2 electrodes applied to each of the terminal ileum (TI) and cecum (C) showing difference in the frequency, amplitude and conduction velocity between the ileal and cecal electric waves.

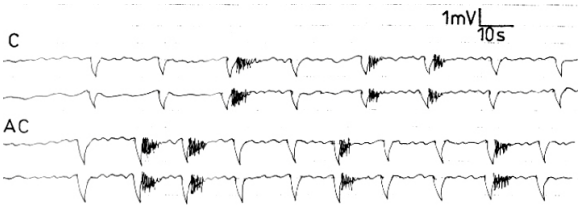

Figure 3. Electric activity recorded from the 2 electrodes applied to each of the cecum (C) and ascending colon (AC) showing difference in the frequency, amplitude and conduction velocity between the cecal and AC electric waves.

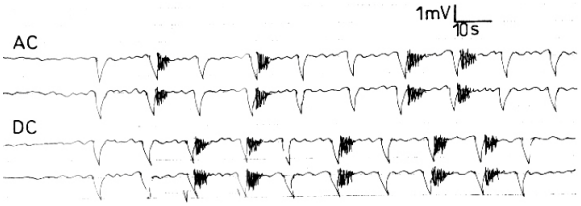

Figure 4. Electric activity recorded from the 2 electrodes applied to each of the ascending (AC) and right half of transverse colon (TC) showing difference in the frequency, amplitude and conduction velocity from those recorded from left half of TC and descending colon (DC).

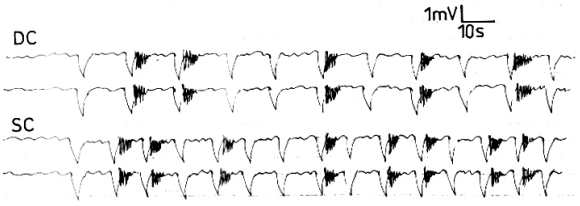

Figure 5. Electric activity recorded from the 2 electrodes applied to each of the descending (DC) and sigmoid colon (SC) showing difference in the frequency, amplitude and conduction velocity between the DC and SC electric waves.

superimposed on, or followed randomly, the PPs. They occurred as negative deflections and did not accompany each PP. The PPs and APs showed the same frequency, amplitude and conduction velocity from the electrodes applied to each of the TI, C, AC, TC, DC and SC. The values are exhibited in table 1. Differences of these wave variables were detected between the studied parts of the colon (Figure 2–5). The change in the wave variables between the TI and C occurred at the ileocecal junction (Figure 2), between the C and AC at the cecocolonic junction (Figure 3), between the right colon (AC and right half of TC) and left colon (left half of TC and DC) at the mid third of the TC (Figure 4), and between the DC and SC at the colosigmoid junction (Figure 5).

The site of change of the wave variables between the different parts of the colon was determined by changing the position of the electrodes over the part to be examined. For example, in the mid third of the TC we found that the wave variables recorded from AC were different from those recorded from the TC. We changed the position of the electrodes in this area moving them closer to each other, and registered the waves. We continued approximating the electrodes of the AC to those of the TC until the site of change of the wave variables between the 2 electrodes could be localized to a distance of 1 to 3 cm. By this maneuver we could define approximately the area where the change of wave variables from one colon segment to the other started.

The sites of change of the wave variables were eventually determined as follows: between the TI and C within the 1–2 cm (mean 1.6±0.6) of the ileocecal junction, between the C and AC within the 1.5–2 cm (mean 1.7±0.3) of the cecocolonic junction, between the AC and TC within the 2–3 cm (mean 2.3±0.9) of the mid third of the TC, and between the DC and SC within the 2–3 cm (mean 2.6±0.9) of the colosigmoid junction.

The aforementioned results were reproducible with no significant difference when the test was repeated in the individual subject.

The current study could shed some light on the potential sites of pacemakers in the colon. The electric waves recorded from the colon comprised PPs and APs. Previous studies have shown that APs are always coupled with elevated colonic pressure and are considered to be responsible for producing the colonic motility[2-7]. Meanwhile, the function of the PPs is not exactly known. It was postulated that the PPs may act to pace the APs in terms of direction and frequency (6-9).

Our previous studies have shown that the electric waves, though conducted most likely through the smooth musculature of the gut, appear to be partially under the control of the intrinsic and extrinsic gut innervation (8,9). The source of these waves is not exactly known. It was claimed that they are generated by the interstitial cells of Cajal (10-15) .

4.1. Colonic pacemakers

The current results have shown that the electric wave variables differed from one colonic segment to the

other. These findings most likely denote that the electric waves recorded from each segment of the colon are initiated by a pacemaker and, moreover, that the electric waves registered from the whole of the colon are not evoked by a single pacemaker. The fact that the electric wave variables of the C differed from those of the TI would suggest that the waves of these two gut segments are not evoked by the same pacemaker and that each of the two segments has its own pacemaker.

The AC pacemaker is most likely situated in the AC close to the cecocolonic junction, since the change in the electric wave variables of the AC compared to those of the C occurred in the electrodes close to the 1.5-to-2-cm-area between the C and the AC. The AC waves are believed to proceed aborally to the mid third of the TC where they changed their character, probably indicating that they were evoked by another pacemaker in this area. The waves it produced appeared to proceed through the left part of TC and DC until they reached the SC where a change of the wave variables occurred, denoting the existence of yet another pacemaker at the colosigmoid area. The aboral spread of the electric waves in the colon has been demonstrated in previous studies (6-9).

The current findings suggest the existence of at least 4 colonic pacemakers that evoke electric waves for the different colonic segments. These waves are believed to be responsible for colonic motility. The presence of more than one pacemaker in the colon seems to serve separate functional activity for each colonic segment. Thus, one part of the colon can function and move its contents independently from the other. A single pacemaker, located for example at the C and moving the colonic contents directly to the SC in one mass contraction, would deprive the colonic contents of the functions performed by the different segments of the colon. The fractionation of the passage of colonic contents through the colon, presumably effected by the multiple pacemakers, appears to be beneficial as it allows the different colonic segments to perform their specific function. Furthermore, the pacemaker multiplicity in the colon may preserve the colonic motility in case one or more pacemakers are disordered.

4.2. Colonic inertia and the artificial pacemaker

The presence of more than one pacemaker in the colon might explain the segmental colonic inertia. Intestinal transit studies have demonstrated that colonic inertia may affect the right or left or the whole of the colon (23-25). We assume that right-sided colonic inertia results from a dysfunction of the cecal or AC pacemaker. Likewise, left-sided colonic inertia may be due to dysfunction of the TC pacemaker and SC inertia due to SC pacemaker disorder. In total colonic inertia, most or all colonic pacemakers might be disordered. If we could prove that the colonic inertia is induced by disordered pacemakers and could succeed in detecting the affected one, an artificial pacemaker may resume the colonic motor activity.

A disordered pacemaker may be recognized by applying electrodes at the potential site of the colonic pacemaker and then recording the electric activity. We used this method in the treatment of rectal inertia constipation. The site of the deranged pacemaker was defined at the rectosigmoid junction and an artificial pacemaker was implanted in this area (21,22). Rectal pacing succeeded in producing defecation (22). Further studies are required to investigate the functional status of the colonic pacemakers in colonic inertia and the possibility of applying artificial pacemakers for the treatment of such conditions.

In conclusion, the colonic electric waves are suggested to be generated by at least 4 pacemakers, which are presumably located at the ileocecal junction, the cecocolonic junction, the mid third of TC, and at the colosigmoid junction. The electric waves appear to be responsible for conducting the colonic motor activity. We postulate that disordered colonic pacemakers may produce segmental or total colonic inertia, a proposition that needs further studies.

5. ACKNOWLEDGMENT

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Key Words: Slow waves, Pacesetter potentials, Action potentials, Interstitial cells of Cajal, Constipation, Colonic inertia

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