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STUDY OF THE MECHANISM UNDERLYING THE DIFFERENCE IN MOTILITY BETWEEN THE LARGE AND SMALL INTESTINE: THE “SINGLE” AND “MULTIPLE” PACEMAKER THEORY

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1. ABSTRACT

The common movement of the small intestine (SI) is peristalsis and of the large intestine (LI) are giant migrating contractions. The mechanism underlying the difference in the type of motility between the SI and LI is yet to be elucidated; the current communication investigated this point. 7 pigs (4 male) were anesthetized, abdomen opened and a balloon-ended catheter was introduced into the right colon through ileotomy. Balloon was filled in increments of 10 ml of saline and the EMG activity of the colonic longitudinal and circular muscle layers was recorded before and after myotomy performed between 2 of the 3 electrodes fixed to the colon. The balloon was then withdrawn, located in the terminal ileum and distended in increments of 2 ml; the ileal EMG activity was registered before and after myotomy done between 2 of the 3 electrodes applied to the ileum. The LI showed slow waves or pacesetter potentials (PPs) and action potentials (APs) which had the same frequency, amplitude and conduction velocity from the 3 electrodes of the same animal. The waves were recorded from the longitudinal and not the circular muscle coat. Upon LI distension, the electric activity increased and was recorded also from the circular muscle. At 40-50 ml distension, the balloon was dispelled to the transverse colon. Electric activity from SI was similar to that of the LI, but was not the same from the 3 electrodes; it diminished aborally. It increased with increasing balloon distension until, at 8-10 ml distension, the balloon moved slowly aborally. Electric waves were recorded proximally but not distally to colonic myotomy, and the balloon moved up to the cut. In the SI, waves were recorded both proximally and distally to the ileal myotomy, and the balloon moved across the cut. The fact that the colonic electric waves displayed the same variables from the 3 electrodes and that they were not recorded distally to the colonic myotomy, would suggest the presence of a “single” colonic pacemaker, probably situated in the cecum. This is in contrast to the hypothesis of the “multiplicity” of the small intestinal pacemakers, which is based on the fact that the electric activity diminished as the waves propagated aborally and on the existence of slow waves distal to the ileal myotomy. The concept of “single” and “multiple” pacemakers explaining the difference in the motility of small from that of large gut needs further studies.

2. INTRODUCTION

The mechanism of gut motility is not yet fully understood. The main gut movements are effected by peristalsis and giant migrating contractions (1). The latter occur only in the large intestine (LI), not in the small one (SI), while peristalsis is the common movement in the small bowel (1-3). The difference in the type of motility between the small and large intestine seems to be related to functional purposes.

The gut possesses electric activity which is considered to play a significant role in gut motility (4-10). Gut motility disorders are always associated with disturbed electric activity (11-14). Recent studies have demonstrated resting electric activity in the longitudinal muscle coat of the gut which was absent in the circular coat (15). Furthermore, it has been suggested that these electric waves are transmitted from the longitudinal to the circular muscle upon colonic distension (15).

The question that needs to be addressed is how the SI moves its contents in peristaltic while the LI in mass migrating contractions. In the peristaltic activity, the food bolus moves step-wise. This is in contrast to the giant migrating contractions by which the luminal contents are transmitted from approximately one half of the colon to the

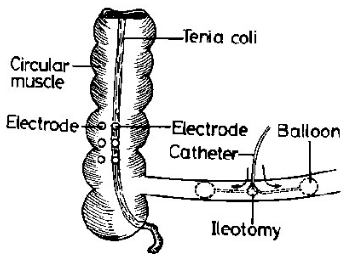

Figure 1. Diagram illustrating the steps of the experiment.

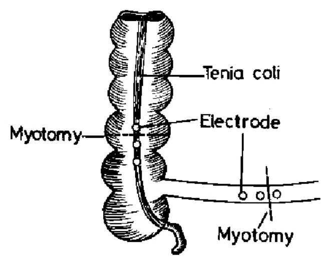

Figure 2. Site of myotomy.

other in one mass contraction. The aim of the current study was to investigate the mechanism underlying the difference in the type of motility between the SI and LI.

3. MATERIAL AND METHODS

3.1. Material

The study comprised 7 pigs (4 male, 3 female) with a mean weight of 53.3±10.4 SD kg (range 45-60). Our Faculty Review Board and Ethics Committee approved the study.

Before induction of anesthesia, all animals were sedated with an intramuscular injection of atropine (0.01 mg/kg), acepromazine (1 mg/kg) and ketamine (5mg/kg). After endotracheal intubation, the animals were allowed to breathe spontaneously, and anesthesia was maintained with 5% halothane -95% oxygen by inhalation.

The abdomen was opened through a midline incision and the ileocecal junction was identified. At a distance of 10 cm proximal to the junction, a 0.5 cm opening in the ileum was performed through which a balloon-ended 6 F catheter was inserted and manipulated to enter into the cecum (Figure 1). The balloon (London Rubber Industries Ltd., London, UK) was 2 cm in diameter. The ileotomy was sutured around the catheter using a purse-string suture of 3/0 chromic catgut. The catheter was connected to a strain gauge pressure transducer (Statham 230 B, Oxnard, CA). The balloon was filled with normal saline in increments of 10 ml up to a volume that initiated mass contraction of the right colon and balloon movement.

3.2. EMG recording

During balloon filling, the EMG activity of the circular and longitudinal muscle fibers of the colon was recorded by means of monopolar silver-silver chloride electrodes (Smith Kline Beckman, Los Angles, 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 by electrode gel to the serosa of the proximal part of the ascending colon. Three electrodes were applied over the tenia coli and another 3 over the circular muscle coat between 2 tenia coli (Figure 1). The distance between one electrode and the next was 2-3 cm. The electrodes were attached to a metal cannula containing a 6-pin socket. The insulated wire leads were attached to the pins in the cannula and connected to a Brush Mark 200 rectilinear pen recorder. The electric activity including frequency, amplitude and velocity of conduction of the waves was recorded from the 6 electrodes.

The electric activity of the LI upon incremental balloon distension was recorded until a giant migrating contraction would occur. The balloon was then emptied, withdrawn from the LI and manipulated to be located in the small intestinal segment proximal to the ileotomy by approximately 20 cm. This was done without pulling the balloon out of the ileotomy. The balloon was filled with normal saline in increments of 2 ml up to the volume at which the balloon started to move. The EMG activity of SI at rest and on balloon filling was recorded by means of 3 silver-silver chloride electrodes applied to the gut wall with 2-3 cm distance between each 2 electrodes; the electrodes were similar to those applied to the colon.

3.3. Colonic myotomy

To see the effect of colonic myotomy on electric wave transmission and balloon movement, a myotomy was performed between the first and second electrode applied to the tenia coli (Figure 2). The colonic wall was divided down to, but not including, the mucosa. The electric activity was recorded proximally and distally to the myotomy before and after balloon distension in increments of 10 ml.

The balloon catheter was then withdrawn from the colon and located into the SI. Myotomy was performed between the first and second electrode fixed to the SI. The electric activity was recorded proximally and distally to the cut before and after balloon distension in increments of 2 ml.

To ensure reproducibility of the results, the aforementioned recordings were repeated at least twice in the individual animal and the mean values were 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

No adverse effects were encountered during or after performance of the tests, and all the animals were evaluated. The mean resting pressure of the SI was 7.8±1.1 cm H_2O (range 6-9) and of the LI 7.2±1.1 cm H_2O (range 5-8).

The LI showed slow waves or PPs recorded from the electrodes overlying the tenia coli; no waves were recorded from electrodes applied to the circular muscle fibers. The PPs had a triphasic configuration with a small

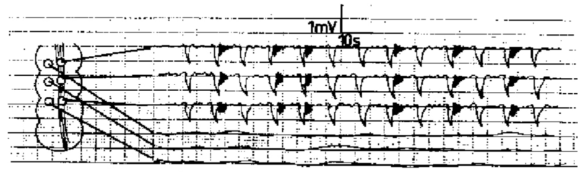

Figure 3. Pacesetter and action potentials recorded from the 3 electrodes applied to the colonic longitudinal muscle layer. No waves were recorded from the electrodes applied to the circular muscle layer. The waves had the same frequency, amplitude and conduction velocity from the 3 electrodes.

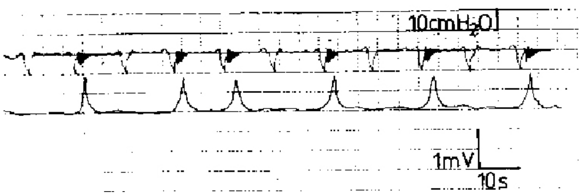

Figure 4. Electric activity (PPs and APs, upper tracing) and colonic pressure (lower tracing) showing pressure rise with APs and not with PPs.

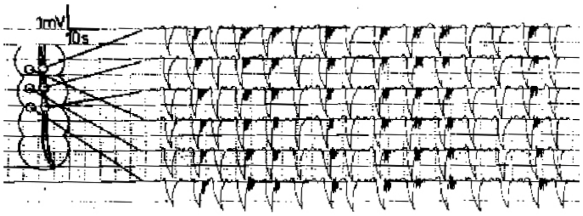

Figure 5. Electric activity upon colonic balloon distension with 30 ml of saline showing increase in the frequency, amplitude and conduction velocity of the electric waves from the longitudinal muscle fibers as well as recording of electric waves from the circular fibers.

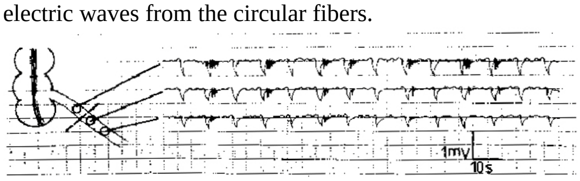

Figure 6. Pacesetter and action potentials recorded from the 3 electrodes applied to the wall of the terminal ileum. The frequency, amplitude and conduction velocity diminished as the waves propagated aborally.

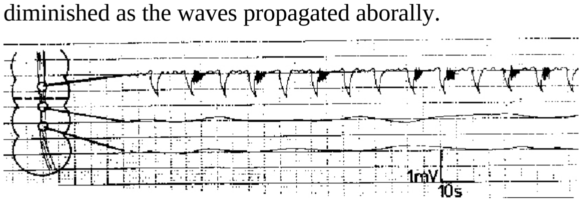

Figure 7. Myotomy of the colonic wall. Electric waves were recorded from the electrodes applied proximally but not distally to the myotomy.

positive, a large negative and another small positive deflection (Figure 3). Bursts of fast activity spikes or action potentials (APs) were superimposed or followed the PPs randomly. They were associated with a rise of the intracolonic pressure to a mean of 17.6±3.8 cm H_2O (range 15-21) (Figure 4). The PPs and APs registered the same frequency, amplitude and conduction velocity from the 3 electrodes of the same animal, even after the distance between each 2 electrodes was increased. The mean frequency was 4.8±1.1 cycle / min (cpm, range 3.8-6.2), amplitude 0.48±0.06 mV (range 0.42-0.70) and conduction velocity 4.9±1.1cm/s (range 4.1-6.6). The PPs were not associated with an increase in the colonic pressure.

Upon colonic distension, the electric waves showed increase in frequency, amplitude and conduction velocity and were recorded not only from the longitudinal but also the circular layer (Figure 5). At a distending volume of 40-50 ml, the balloon was dispelled to the proximal transverse colon.

The SI showed also resting electric activity in the form of PPs and APs (Figure 6). The PPs were triphasic like those of the LI. They had a mean frequency of 7.2±1.1 cpm (range 6-9), amplitude 0.42±0.05 mV (range 0.35-0.54) and conduction velocity 4.2±1.1 cm/s (range 3.6-5.8). The values of these variables were not the same from the 3 electrodes. They diminished as the waves propagated aborally from one electrode to the other (Figure 6).

The electric activity increased upon balloon filling with 2 ml of saline and continued to increase with increasing balloon filling until, at 8 – 10 ml distension, the balloon moved slowly aborally until it passed through the ileo-cecal junction to the cecum where it ceased to move. The balloon, lying in the cecum, was distended with saline in increments of 10 ml. At a mean of 40 – 50 ml, the right colon contracted, pushing the balloon to the proximal part of the transverse colon.

4.1. Effect of myotomy on electric activity and balloon expulsion

In the LI, the electric activity was recorded proximally but not distally to the myotomy (Figure 7). When the balloon was distended with the volume which had produced balloon movement before myotomy, it advanced up to, and stopped short of, the cut and did not proceed beyond the myotomy.

In the SI, electric waves were recorded both proximally and distally to the myotomy (Figure 8). The balloon, distended with the saline volume that initiated pre-myotomy movement, traversed the myotomy in the same manner as before myotomy.

The aforementioned results were reproducible with no significant difference when the measurements and recordings were repeated in the same animal.

The current study could shed some light on the mechanism underlying the difference between the contractile activity of the small and that of the large intestine. The increased electric activity upon gut (small or large) distension assumingly denotes increasing motility of the gut up to a certain distending volume which, when reached, would move the balloon. In the SI, the balloon moved slowly and step-by-step, whereas in the colon rapidly and in a one-step mass movement.

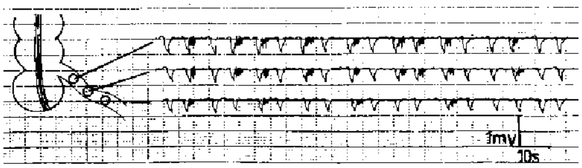

Figure 8. Myotomy of the small intestine. Electric waves were recorded from the electrodes applied proximally and distally to the myotomy.

4.2. The 'single' and 'multiple' pacemaker theory

Large gut myotomy showed that the electric waves were recorded proximally but not distally to the cut and the distended balloon did not move beyond the cut. This presumably indicates that the electric waves proceed aborally. We suggest the existence of a pacemaker proximally to the cut, which is responsible for initiation of electric activity spreading aborally along the colon. Myotomy interrupted the electric waves that presumably arose from a proximal pacemaker. It appears that no pacemakers able to initiate electric activity and balloon movement exist distally to the cut. In contrast to the results of the large gut, SI myotomy did not affect the existence of electric activity distally to the cut. The electric waves were recorded both proximally and distally to the cut and the balloon moved across and distal to the myotomy. Since the electric waves are thought to be initiated by a pacemaker, it is suggested that a pacemaker exists also distally to the cut. Accordingly, we postulate that the SI possesses a "multiplicity" of pacemakers, and that each peristaltic wave is initiated by a pacemaker so that gut interruption does not affect wave initiation or balloon transmission. This is in contrast to the LI in which the electric waves and the balloon movement were interrupted by myotomy, suggesting the absence, distal to the cut, of pacemakers which are believed to initiate the electric activity and pace the motility. We suggest the presence of a "single" pacemaker in the proximal ascending colon, which appears to initiate the electric activity in the right half of the colon.

The hypothesis of the "multiple activity" of the small intestinal pacemakers is based on the fact that the electric activity of the SI diminished in a segmental manner as the waves propagated aborally from one electrode to the other, especially when the electrodes were widely spaced along a big segment of the SI. The electric waves were faster from the proximal than the distal electrode. This sequential drop in the slow wave variables as well as the presence of slow waves distal to the myotomy postulate the possible existence of a series of pacemakers of descending discharge rates located in successive bowel segments proximodistally. Accordingly, it appears from the current study that SI motility is not regulated by a single pacemaker, which occurs in the gastric antrum(16-18), the rectosigmoid junction (19, 20) or possibly the colon.

The pacemaker activity of the gut is believed to be generated by specialized cells called the interstitial cells of Cajal (21). They lie in the gut wall between the submucosa and the circular muscle layer and appear to pace the motile activity of the gut in rate and direction.

The "single" pacemaker theory of the right colon is evidenced in the current study by the fact that the colonic slow waves had the same frequency, amplitude and conduction velocity from the 3 electrodes applied to the colon; they did not show diminution as they propagated aborally, even when the electrodes were widely spaced. This is in addition to the absence of electric waves distally to the colonic myotomy as well as failure of balloon transmission across the cut. It seems that this single colonic pacemaker is located in the proximal part of the right colon, possibly in the cecum, as can be derived from the aboral progress of the waves and their interruption upon myotomy. We believe that this single pacemaker supplies electric waves to the proximal part of the colon (ascending and up to proximal transverse colon) as is evident from the balloon distension test. When the balloon was distended with 40-50 ml of saline, it was dispelled to the right side of the transverse colon.

In conclusion, we suggest that the difference in the mechanism of small or large gut motility depends on the distribution of the pacemakers in the gut wall. While these pacemakers seem to be "multiple" in the SI thus initiating its peristaltic activity, they appear to be "single" in the colon evoking the giant migrating waves. The concept of the single and multiple pacemakers in gut motility needs further studies.

5. ACKNOWLEDGMENT

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