The ACB technique: a biomagentic tool for monitoring gastrointestinal contraction directly from smooth muscle in dogs

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Abstract

The aim of this paper was to verify whether AC biosusceptometry (ACB) is suitable for monitoring gastrointestinal (GI) contraction directly from smooth muscle in dogs, comparing with electrical recordings simultaneously. All experiments were performed in dogs with magnetic markers implanted under the serosa of the right colon and distal stomach, and their movements were recorded by ACB. Monopolar electrodes were implanted close to the magnetic markers and their electric potentials were recorded by electromyography (EMG). The effects of neostigmine, hyoscine butylbromide and meal on gastric and colonic parameters were studied. The ACB signal from the distal stomach was very similar to EMG; in the colonic recordings, however, within the same low-frequency band, ACB and EMG signals were characterized by simultaneity or a widely changeable frequency profile with time. ACB recordings were capable of demonstrating the changes in gastric and colonic motility determined by pharmacological interventions as well as by feeding. Our results reinforce the importance of evaluating the mechanical and electrical components of motility and show a temporal association between them. ACB and EMG are

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complementary for studying motility, with special emphasis on the colon. ACB offers an accurate method for monitoring *in vivo* GI motility.

Introduction

The study of colonic motility *in vivo* in both humans and alert animals is often hampered by methodological limitation (Dinning *et al* 2008, Lentle *et al* 2008). Hence, the association of electrodes with pressure transducers 'strain-gauges' implanted chronically at the same serosal location has been used in several motility studies (Rae *et al* 1998, You and Chey 1984).

Methods based on the detection of magnetic fields originating either from a smooth muscle electrical activity (Bradshaw *et al* 2006) or from a magnetic material existing in the gastrointestinal (GI) segments (Miranda *et al* 1992, Romeiro *et al* 2006) constitute interesting alternatives to the classical methods for *in vivo* GI motility studies.

Biomagnetic methods are potentially noninvasive, devoid of ionizing radiation, and harmless. Alternate current biosusceptometry (ACB), proposed for the first time by Benmair *et al* (1977), is a biomagnetic method that bears additional advantages: is simple, easy to perform and depends on an inexpensive device. ACB has been employed to assess gastric emptying (Miranda *et al* 1992), orocaecal transit time (Oliveira *et al* 1996), esophageal transit time (Daghastanli *et al* 1998) in humans, and gastric contractile activity in humans and dogs (Miranda *et al* 1997, Americo *et al* 2007, Moraes *et al* 2003, Andreis *et al* 2008). In all of these instances, assessment was based on tracking the motions of the ingested ferromagnetic material inside the gut.

This study aims to demonstrate the temporal association, through magnetic markers and electrodes chronically implanted, that ACB is suitable to record contractions directly from GI smooth muscle *in vivo*; also to assess the association of ACB and EMG as tools to monitoring gastrointestinal mechanical and electrical activities in dogs.

Methods

AC biosusceptometer (ACB) fundamentals

An ACB sensor consists of two pairs of coils separated by a fixed distance, where each pair of coils is composed of an excitation coil (outer) and a detection coil (inner), in a first-order gradiometric configuration; one pair works as the reference and the other as the detector probe. The proximity of a magnetic material causes an unbalancing on the magnetic flux in the system, generating a signal which can be recorded. Since the magnetic signal depends on the distance between the sensor and the magnetic material, by changing the relative position of the sensor and magnetic material it causes modulations in the signal recorded by the sensor. A more detailed description of the ACB system has been presented (Cora *et al* 2005). In this study, a multisensor ACB system was employed. It consisted of one pair of excitation coils and seven pairs of detection coils ($\Phi = 3.5$ cm each coil) in a coaxial arrangement; when attached to the dog's abdominal surface, it allows the simultaneous acquisition of magnetic signals on distinct points (Andreis *et al* 2008).

Animal preparation

Seven healthy female beagle dogs (8–14 Kg) were used in the study. Laparotomy was performed under pentobarbital sodium (30 mg kg^{-1}, Abbott Laboratories, Chicago, USA) anesthesia and magnetic markers (pieces of 0.8 g of ferromagnetic material, $MnFe_2O_4$) were implanted under the serosa surface of the right colon by purse-string sutures, 3 cm distal to the ileo-cecal junction. Monopolar electrodes (Ethicon®, Johnson & Johnson, Brussels, Belgium) were implanted on the serosa, close to the colonic magnetic marker. In three dogs, one magnetic marker and one monopolar electrode were also implanted in the distal stomach 3 cm proximal to pylorus. The electrodes were exteriorized by needle puncture through abdomen and fixed in the canine vest. The dogs were allowed to recover for 10 days after surgery and were fasted overnight before each experiment. All experimental and surgical procedures were carried out in accordance with the American Physiological Society's Guiding Principles in the Care and Use of Animals and were approved by the local Animal Ethics Committee (Instituto de Biociências de Botucatu – UNESP). At the completion of the protocols 1, 2 and 3 (see below), the electrodes were removed by direct traction.

Experimental procedures

The multisensor ACB system was fixed to the anterior surface of the abdomen so that detector 6 was placed on the right anterior quadrant point where the signal-to-noise ratio of the signal from the proximal colonic marker was highest (figure 1). At this position, the signal from the gastric magnetic marker was recorded by detector 3 in the animals with implantation in both organs. The detectors coils were attached to lock-in amplifiers systems (Stanford Research System, Sunnyvale, USA) and a continuous magnetic signal recording was started. For electromyography (EMG) recording, the implanted electrode and an external reference electrode attached to the animal's hind leg were connected to an amplifier system (Biopac EGG100C amplifier; set to 1000 gain, low-pass filter at 1 Hz, high-pass filter at 0.005 Hz). Respiratory frequency was monitored simultaneously by a pressure transducer sensor positioned in the nasal cavity. All signals were acquired at the sampling rate of 20 Hz/channel, digitized using a multi-channel recorder (MP100 System; Biopac Inc., Santa Barbara, USA) and stored as ASCII. Experimental set-ups described above have been employed in all the experiment protocols.

Protocol of experiment 1. Three animals with magnetic markers and electrodes implanted in the distal stomach were anesthetized (pentobarbital, 30 mg kg^{-1}) and kept supine in a gutter-type table. Four 30 min-long recordings from the stomach were obtained from each animal without any stimulus.

Protocol of experiment 2. All animals were anesthetized (pentobarbital, 30 mg kg^{-1}) and kept supine in a gutter-type table. ACB and EMG recordings were started and 15 min later neostigmine methylsulfate (Prostigmine®, 0.5 mg ml^{-1}; Roche, Madrid, Spain) 0.5 mg was given intravenously. Twelve minutes later, hyoscine n-butylbromide (Buscopan®, 20 mg ml^{-1}; Boehringer Ingelheim, Ingelheim, Germany) 20 mg was administered and the records continued for at least 12 min.

Protocol of experiment 3. All dogs were trained to lay supine quietly on the gutter-type table. On the day of experiment, the multisensor ACB system was fixed to the anterior surface of the abdomen as previously described, and ACB and EMG recordings were obtained for 30 min. Then, the dogs were fed with a 350 Kcal test meal (100 g of chopped beef; Pedigree® – Mars Inc., Vernon, USA); thereafter, 30 min-long magnetic and electric recordings were obtained.
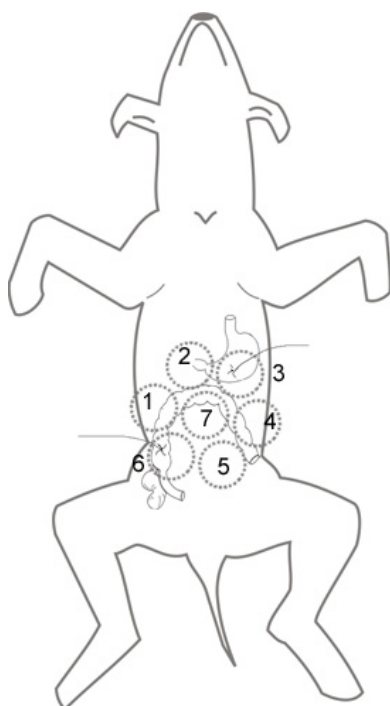
Figure 1. Diagram showing the positioning of the multisensor ACB system (open circles) on the abdominal surface of the dog. Solid lines represent electrode lead wires emerging from the abdominal wall.

Data analysis

All raw signals were analyzed in MatLab (Mathworks, Inc., Natick, USA) by visual inspection and by using bi-directional Butterworth band-pass filters by fast Fourier transform (FFT) and running spectrum analysis (RSA) (Reddy *et al* 1987). Electrical (EMG) and mechanical (ACB) signals from the stomach were analyzed using band-pass filters with a cut-off frequency at 0.03–0.15 Hz (1.8–9.0 cpm). In the colon, ACB and EMG recordings were quantified in frequency using a band-pass filter between 0.005 and 0.05 Hz (0.3–3.0 cpm).

Temporal cross-correlation (R) analysis was used to determine correlation between ACB and EMG gastric signals for experiment 1 described above. The nonparametric Spearman rank correlation test (r) was used to determine correlation between ACB and EMG frequencies.

Area under contraction (AUC) was calculated for the stomach and colon for experiments 2 and 3 employing the same filters described above. A comparison of all evaluated periods was performed for both techniques.

The statistical significance of differences between ACB and EMG signal amplitudes and frequencies before and after stimuli was determined with the paired Student's *t*-test. Differences were considered statistically significant at $P \leqslant 0.05$. The data are presented as mean $\pm$ SE (standard error).

Results

Figure 2(A) illustrates ACB and EMG recordings from the distal stomach in an anesthetized animal. A strong temporal correlation between mechanical (ACB) and electrical (EMG)
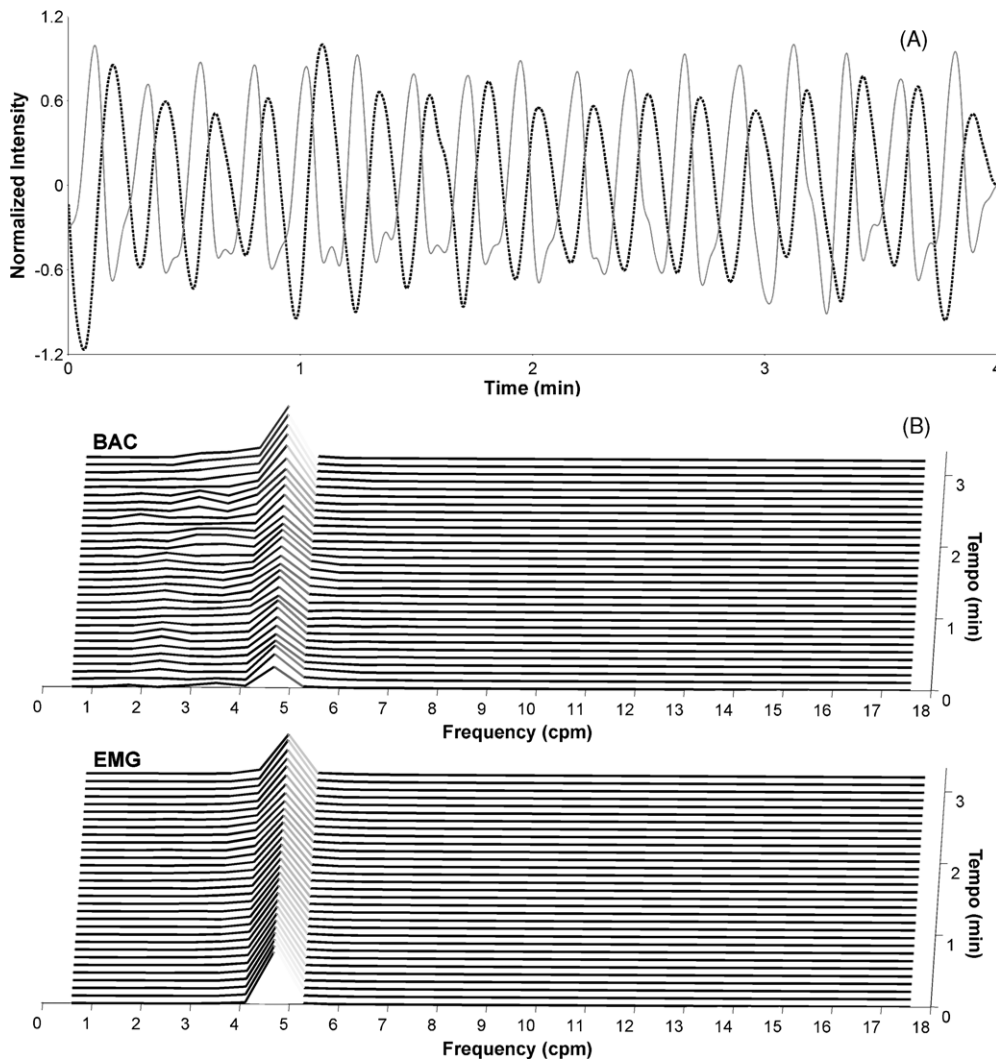
Figure 2. (A) Typical EMG (gray solid line) and ACB (black dashed line) recordings from the distal stomach. (B) Running spectrum analysis showing the high similarity between ACB and EMG recordings, with coincident peak values. Phase-difference in electrical activity following a contraction can be noticed.

recordings at the same frequency was found (figure 2(B)). ACB and EMG presented a high correlation at gastric frequency (table 1). A high temporal cross-correlation between the periodicals signals recorded by the two techniques was found ($R = 0.9 \pm 0.1$; $P < 0.05$); a phase-difference around of 4.1 ± 0.1 s was consistently observed (figure 2(A)).

The spectral analysis of typical respiration, ACB and EMG recordings from the colon of two anesthetized animals are presented in figure 3, and reveal that both ACB and EMG periodic signals occurred within distinct frequency bands. The spectra of the ACB recordings revealed two distinct periodic components: one, clearly related to respiration, within the range of 10.0–16.0 cpm, and another within a distinctly lower frequency range (0.7–2.0 cpm), whereas
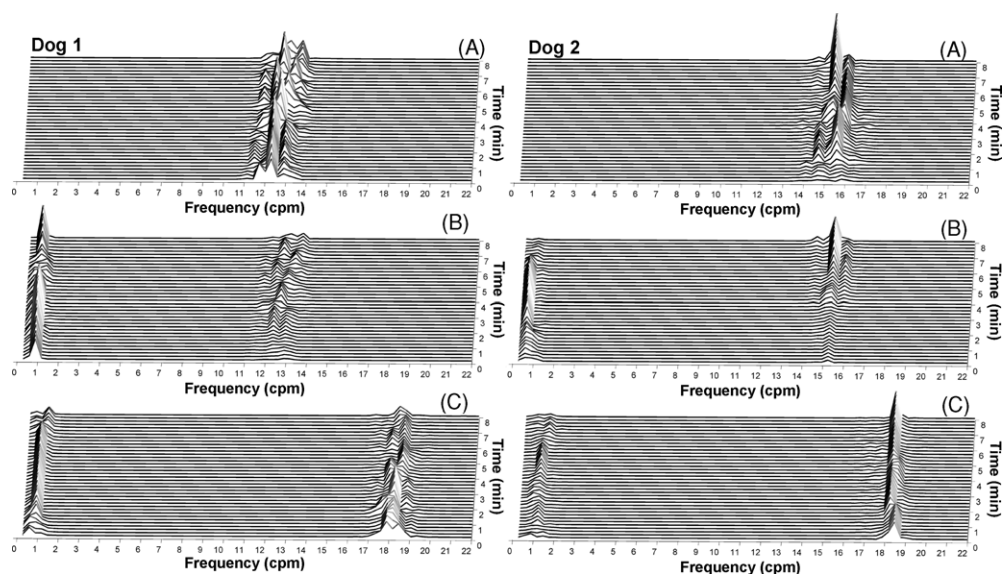
Figure 3. Running spectrum analysis of respiratory (A), ACB (B) and EMG (C) recordings from the right colon of dog 1 and dog 2 during baseline. A lower frequency range (0.7–2.0 cpm) is recorded by both ACB and EMG whereas a higher frequency band (12.0–19.0 cpm) is recorded only by EMG. Within the same low-frequency band, ACB and EMG signals are characterized by simultaneity (dog 1) or by a widely changeable frequency profile with time (dog 2).

Table 1. Mean gastric frequency (cpm) in dogs obtained by EMG and ACB.

	EMG	ACB	R
Dog 1	5.7 ± 0.2	5.5 ± 0.2	0.79
Dog 2	4.8 ± 0.2	4.8 ± 0.3	0.96
Dog 3	5.7 ± 0.1	5.7 ± 0.1	0.99

Four recordings were obtained from each dog ($n = 3$). The mean values were determined for each experiment, and from these the mean values were determined for each dog (mean $\pm$ SE). Correlation coefficient (r) at frequency was calculated between techniques for each dog ($p < 0.05$).

the spectrum of the EMG recordings also demonstrated two signal bands: one within a lower frequency range (0.7–2.0 cpm), and another within a higher frequency range (12.0–19.0 cpm). Within the same low-frequency band, ACB and EMG signals are characterized by simultaneity in frequency during time (dog 1) or by a widely changeable frequency profile with time (dog 2).

The amplitudes of signals of both ACB and EMG gastric and colonic recordings were similarly increased by neostigmine and reduced by hyoscine butylbromide in all animals (table 2). The tracings presented in figure 4 illustrate these findings and show that the changes are contemporary in ACB and EMG recordings. Table 2 also shows that the changes due to neostigmine (reduction) and hyoscine (increase) in ACB signal frequency have been parallel to those seen in EMG recordings. The correlation (r) between ACB and EMG frequencies was presented for the stomach and colon (table 2).
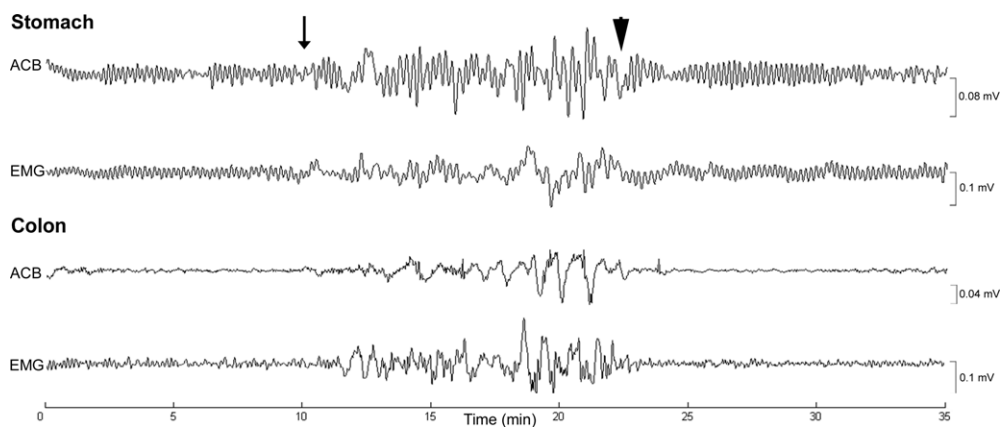
Figure 4. Typical effects of neostigmine (arrow) and hyoscine butylbromide (arrowhead) on ACB and EMG signals recorded simultaneously from the distal stomach and right colon.

Table 2. Effects of neostigmine and hyoscine butylbromide on frequency and amplitude of the signals recorded by ACB and EMG.

	Stomach			Colon		
	Baseline	Neostigmine	Hyoscine butylbromide	Baseline	Neostigmine	Hyoscine butylbromide
AUC (mV s^{-1})						
ACB	0.5 ± 0.1	1.8 ± 0.2^a	0.5 ± 0.1^c	1.4 ± 0.6	6.3 ± 0.7^a	1.5 ± 0.4^c
EMG	2.2 ± 0.7	4.4 ± 1.0	2.8 ± 1.1	2.3 ± 0.5	7.4 ± 1.1^a	1.7 ± 0.3^c
Frequency (cpm)						
ACB	5.0 ± 0.1	4.0 ± 0.1^b	$4.2 \pm 0.1^{d, e}$	1.2 ± 0.1	1.0 ± 0.1^b	1.3 ± 0.2
EMG	5.0 ± 0.1	4.2 ± 0.3^b	4.4 ± 0.1^d	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.2
r	0.99	0.40	0.80	0.82	0.84	0.98

Values are means $\pm$ SE; $n = 7$ for the colon and $n = 3$ for the stomach; (r) is the correlation coefficient for frequency ($p < 0.05$).
[a] $p < 0.01$.
[b] $p < 0.05$ versus baseline.
[c] $p < 0.01$.
[d] $p < 0.05$ versus neostigmine.
[e] $p < 0.05$ versus baseline.

Typical colonic recordings obtained from an animal before and after the ingestion of a test meal are shown in figure 5. Frequencies and amplitudes measured during both fasting and postprandial period are displayed in table 3. The frequencies of ACB signals from the distal stomach and right colon were highly correlated with those from EMG during fasting as well as for postprandial period (table 3).

All dogs were regularly checked by a veterinarian and showed no signs or symptoms relating to possible obstruction or to other gastrointestinal malfunctions. Furthermore, a high signal-to-noise ratio was obtained for the right colon magnetic signal in three of the animals followed for at least 6 months after the electrode removal.
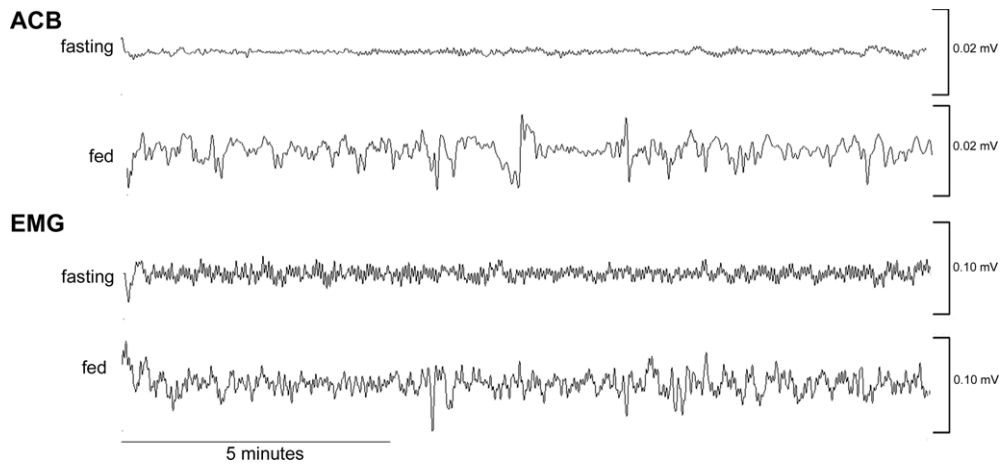
Figure 5. Effects of feeding on ACB and EMG signals recorded simultaneously from the right colon.

Table 3. Effect of feeding on frequency and amplitude of the signals recorded by ACB and EMG.

	Stomach		Colon	
	Fasting	Fed	Fasting	Fed
AUC (mV s^{-1})				
ACB	2.4 ± 0.7	4.0 ± 0.7	2.8 ± 0.8	4.9 ± 1.3
EMG	5.1 ± 2.1	10.0 ± 3.8	2.0 ± 0.7	2.8 ± 0.8[a]
Frequency (cpm)				
ACB	4.3 ± 0.3	5.1 ± 0.4	1.1 ± 0.1	1.2 ± 0.1[a]
EMG	4.9 ± 0.3	5.2 ± 0.2	1.1 ± 0.5	1.3 ± 0.1[a]
r	0.70	0.85	0.95	0.70

Values are means $\pm$ SE; $n = 7$ for colon and $n = 3$ for stomach; (r) is the correlation coefficient for frequency ($p < 0.05$).
[a] $p < 0.05$ versus fasting.

Discussion

In this study, we demonstrate the applicability of a biomagnetic technique for measurement of gastrointestinal motility in anesthetized as well as alert dogs. The implantation of a magnetic marker in the serosa permitted us to record mechanical activity directly through movements of the GI tract wall; in fact, the presence of electrodes close to the magnetic markers allowed evaluating punctually electromechanical activities, an important datum especially for colon.

The frequency spectra of the periodic signals recorded simultaneously from distal stomach by ACB and serosal EMG were virtually identical (figure 2, table 1), and correspond to the well-known narrow frequency spectrum of the canine gastric electrical activity (Kelly *et al* 1969, Xing *et al* 2006). The ACB sensor employed is not dedicated to detecting the magnetic field generated by the gastric electrical activity. Thus, the features of this method per se indicate that the signals recorded by ACB are physiologically meaningful and are in fact generated by the movements of the magnetic markers caused directly by gastric contractions.

Although the dominant frequencies in magnetic and serosal electrode signals in the right colon share some similarity, it is not so close as that of the stomach. Therefore, it is reasonable to assume that the stomach presents a clear frequency peak, while in the colon it is only possible to describe frequency ranges (figures 2 and 3). There are major differences between the colon and stomach as to spatial and temporal organization of their electromechanical activities (Sarna 1991, Smith *et al* 1987). The electric and mechanical activities are tightly coupled in the distal stomach whereas the colon demonstrates a poor coupling among adjacent smooth muscle (Reddy *et al* 1987) and electrical control events occurring at markedly different frequencies in the circular and longitudinal muscle layers (Huizinga and Daniel 1986). Our findings are consistent with this well-established knowledge. The human colon is covered with a continuous longitudinal muscle coat, thickened in three regions to form the taenia coli whereas in dogs no thickening of longitudinal muscle into bands is present (Huizinga and Daniel 1986). In addition, the thickness of the colon wall is lower than that of the stomach, resulting in a low signal-to-noise ratio for the colonic magnetic signal, which may contribute to impairing the correlation between the colonic signals.

Previous recordings using electrodes and strain-gauges implanted in colon revealed consistent differences between electrical and mechanical activities (Sarna 1986, Huizinga and Daniel 1986). It has been proposed that in the colon occur at least two types of activities in dogs: a lower (0.5–6.0 cpm) electrical and mechanical frequency range and a higher (13–40 cpm) electrical frequency range (Sarna 1991, 1986, El-Sharkawy 1983). Low-frequency events are not always recorded by conventional techniques and are frequently filtered out (Huizinga and Daniel 1986); however, manometric studies demonstrate rhythmic cycles with a frequency of 1 cpm in proximal canine colon (Neri *et al* 1991). Our results seem to be in agreement with previous studies, particularly considering that a lower frequency range (0.7–2.0 cpm) was registered by both techniques and a higher frequency band (12.0–19.0 cpm) was recorded only by EMG (figure 3).

Simultaneous electromyography and ACB revealed similar patterns of motor response to administration of both a cholinesterase blocker and a muscarinic receptor blocker. The time courses of drug effects were particularly similar: both signals demonstrated contemporary increases in magnitude following neostigmine methylsulfate which were promptly interrupted by hyoscine n-butylbromide (figure 4).

Similarly, a sharp increase in both signal amplitudes occurred after test meal ingestion (figure 5). The canine colonic motor response has probably lasted longer, but our experiment ended at this time as evaluating only the immediate response (Scott *et al* 1995, Flourie *et al* 1989, Fioramonti *et al* 1980, Sarna and Lang 1989). It is of note that our data showed that a test meal containing only 350 Kcal, a caloric content lower than those employed by others (Sarna and Lang 1989), was capable of affecting colonic motor activity (table 3).

Also, both drugs and feeding have caused subtle changes of phasic activity frequency, which were similarly detected by the two techniques in the stomach and in the colon (table 2) (Misiewicz *et al* 1966). This study confirms previous findings where frequency was reduced after neostigmine (Moraes *et al* 2003) and increased after meals (Levanon *et al* 1998).

As demonstrated before with electrodes (Donck *et al* 2006), our data showed that it is possible to implant magnetic markers without interfering with normal physiology. ACB signal quality could be obtained more than 6 months after the magnetic markers implantation, indicating that the technique is suitable for repeated and/or for long-lasting motility studies. Another ACB advantage is the possibility of monitoring gastrointestinal motility through ingestion of the magnetic material instead of its implantation (Andreis *et al* 2008).

Our results confirmed that ACB is capable of detecting the gastric or colonic contraction directly from the movements of the gastric or colonic wall, through the magnetic maker fixed,

and support an innovative and promising method toward recording mechanical activity of the stomach and colon in dogs. Simultaneous real-time recordings of ACB and EMG could provide an interesting alternative methodology for examining gastrointestinal motility. Also, both methods have as an advantage the possibility of being used in noninvasive approaches through magnetic tracer ingestion and surface electrodes. In conclusion, the ACB is capable of making a significant contribution to an improved understanding of gastrointestinal motility: it is safe, well tolerated, and performs GI contractility measurements in dogs.

Acknowledgments

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