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Research Article

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Modulation of Esophageal Peristalsis by Vagal Efferent Stimulation in Opossum

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ABSTRACT Experiments were performed on anesthetized opossums to study the influence of vagal efferent stimulation on peristalsis in the esophageal smooth muscle using various stimulus parameters. Current intensity, pulse duration, frequency, and train duration were varied systematically. Electrical and mechanical activities were recorded simultaneously at 5, 3, and 1 cm above the lower esophageal sphincter (LES). Vagal efferent stimulation produced a spike burst and contraction with a latency after the termination of the stimulus. This latency varied at different sites with the same stimulus parameters. For example, a stimulus of 5 mA, 0.5 ms, 10 Hz, and 1-s train produced latencies for the electrical response of 1.48 ± 0.04 , 2.2 ± 0.12 , and 3.5 ± 0.09 s ($\pm$ SEM) at 5, 3, and 1 cm above LES, respectively. The differences in latency were statistically significant ($P < 0.01$). The latency of response at any one site also changed with different stimulus parameters; e.g. at 1 cm above LES, the latency of electrical response at 10 Hz was 3.5 ± 0.09 s, but at 20 Hz the latency was 2.01 ± 0.06 s when current intensity, pulse, and train duration remained at 5 mA, 0.5 ms, and 1 s. This decrease in latency with increasing frequency was statistically significant ($P < 0.01$). By changing stimulus parameters, antiperistalsis or peristalsis with different speeds of propagation could be induced. Antiperistalsis or simultaneous responses occurred near threshold stimulus parameters. Suprathreshold stimuli produced peristaltic responses. Speed of peristalsis in the distal esophagus was 1.82 ± 0.08 cm/s with swallowing, which was not different from 1.98 ± 0.14 cm/s ($P > 0.05$) with vagal stimulation of 5 mA, 0.5 ms, 10 Hz, and 1-s train. These studies suggest that: (a) peristalsis in the smooth muscle part of the esophagus can be explained entirely on the basis of peripheral mechanisms, and (b) the central nervous system may modulate the occurrence, polarity, and speed of propagation by modifying the intensity and frequency of vagal activation.

INTRODUCTION

Swallowing produces an aborally propagating peristaltic wave. Peristalsis in the striated muscle part of the esophagus appears to be due to central sequencing in the brain stem (1–3). The mechanism that produces this orderly response in the esophageal smooth muscle is not fully understood. It may also lie in the central nervous system, as in the case of the striated muscle part of the esophagus (1–4), or it may lie in the neuromuscular apparatus of the esophagus (2, 3, 5–9). Peristalsis may also result from a combination of both central and peripheral mechanisms (2).

Roman and Tieffenbach (4) presented evidence for central sequencing of peristalsis in the esophageal smooth muscle. Peristalsis produced by electrical stimulation of decentralized vagal efferents, however, argues against this hypothesis (2, 3). Weisbrodt and Christensen (7) observed a regional latency gradient in the latency of the off-response (rebound contraction) in isolated strips of the esophageal circular muscle. They (7) suggested that the regional latency gradient could explain peristalsislike propagation in the esophageal smooth muscle. However, the velocity of peristalsis as calculated from the latency of the off-response is faster than that found in swallow-induced responses (2, 10).

Dodds et al. (11) reported that vagal stimulation may produce two types of responses: A- and B-waves. The A-waves occur during the early period of stimulation, whereas B-waves (equivalent of off-responses) occur after termination of the stimulation. The speed of peristalsis of A-waves was similar to that of swallow-induced contractions, whereas that of B-waves was similar to that observed *in vitro*. They suggested that A- rather than B-waves represent peristalsis observed with swallowing. However, these two types of responses can be recognized only with long duration stimulations that do not mimic physiological circumstances.

We report here that vagal efferent stimulation with different stimulus parameters, e.g. frequency, current

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intensity, pulse duration, and train duration, can modify polarity and the speed of peristalsis (off-contractions) in the smooth muscle part of the esophagus. The results of these studies may explain the genesis of peristaltic, antiperistaltic, or simultaneous contractions in the esophagus.

METHODS

Apparatus. The method for recording electrical and mechanical activity has been described (12). Briefly, electrical activity was recorded with bipolar Ag-AgCl electrodes and pressures were monitored with a four-lumen catheter assembly pinned in the lower esophageal sphincter (LES)¹ (13). The electrical and mechanical data were graphed on a Beckman R711 dynograph (Beckman Instruments, Inc., Palo Alto, Calif.) and stored simultaneously on a Hewlett-Packard FM tape recorder (model 3968A, Hewlett-Packard Co., Palo Alto, Calif.). Stimulus was delivered by a Grass S-88 stimulator through a stimulus isolation unit (SIU 5). Filters for low and high frequency cut-off were set at 0.16 and 100 Hz, respectively.

Experimental procedure. Successful studies were performed on seven adult opossums (*Didelphis virginiana*) of either sex weighing between 1.2 and 2.8 kg. The animals were fasted for 16–18 h before the study and were anesthetized with a 40-mg/kg i.p. injection of pentobarbital sodium. The anesthesia was maintained as needed with 5 mg/kg of anesthetic administered intravenously through a cannula in the brachial vein. The animals were strapped supine on an animal board and the femoral vein was cannulated for continuous infusion of physiological saline at a rate of 15–20 ml/h. Respiration was supported with a Harvard respirator (Harvard Apparatus Co., Inc., S. Natick, Mass.) using room air at 20 strokes/min and a tidal volume of 20 cm³/stroke. The body temperature was maintained with a heating pad. The chest cavity was opened by performing a thoracotomy on the left lateral side. The diaphragm was cut at the midline to expose the ventral surface of the esophagus. The electrical and pressure sensors were positioned at 5, 3, and 1 cm above the peak pressure of LES, as described elsewhere (12).

The recordings were begun 30 min after closing the chest cavity. First, a series of swallows was induced by hypopharyngeal stimulation. Then the vagi were identified in the neck and sectioned. The cut peripheral ends of one or both vagi were stimulated with square wave pulses (14).

Threshold stimulus was determined by constructing current intensity-pulse duration and frequency-train duration curves in five animals. For the current intensity-pulse duration curves, pulse duration was fixed at 0.01 ms, and the current intensity was varied in 0.5-mA steps until a small electrical spike burst was detected at all three sites. If no response could be evoked, then the pulse duration was changed to the next higher value where it was held constant. The current intensity was again varied in 0.5-mA steps to evoke a detectable response. This procedure was repeated for various pulse durations up to 10 ms. The pulse duration was varied in 0.01-ms steps up to 0.1 ms, in 0.1-ms steps up to 1.0 ms, and in 1.0-ms steps up to 10 ms. During current intensity and pulse duration manipulations, frequency and train duration were held constant at 10 Hz and 1 s, respectively.

For frequency-train duration curves, the current intensity and pulse duration were held constant at 3 mA and 1 ms, respectively. These values were chosen arbitrarily. Then the frequency was fixed at 1 Hz and the train duration was varied in 0.5-s steps until a small electrical spike burst was detected at all recording sites. If no response could be evoked, then the frequency was changed to the next higher value and the procedure repeated. The frequency was varied in 1-Hz steps up to 10 Hz. Stimuli were also tested at 20 and 40 Hz.

For studying the influence of current intensity on esophageal peristalsis, frequency, pulse, and train duration were held constant at threshold value while the current intensity was increased in 0.5-mA steps. A similar procedure was followed for studying the influence of frequency, pulse, or train duration. An average of 2,320 (2,156–2,620) stimuli were tested in each animal. At the end of the experiment the animal was killed with a lethal dose of the anesthetic.

Data analysis. The latencies were measured from the end of the stimulus train to the onset of the first electrical spike and the onset of upward deflection of the pressure wave form. In two animals, responses also occurred during the early part of the stimulus train (similar to A-waves). In these animals, latencies were measured from the onset of stimulus to the onset of the electrical spike burst and mechanical contraction. There were some differences between the latencies for electrical and mechanical responses (12). For simplicity, however, electrical latencies are described unless otherwise specified. The data were analyzed using two-way analysis of variance with repeated measures and significant interactions were tested by Scheffé's method of multiple comparison test (15). Significance of differences in threshold curves and sensitivity of response at three different sites were tested by chi-square test (15).

RESULTS

Threshold stimulus

Threshold stimulus was defined as that minimal strength stimulus that evoked a detectable electrical spike burst in all three recording sites, i.e., 5, 3, and 1 cm above LES. Sometimes certain stimulus parameters that were less in intensity and duration than the threshold stimulus did not produce an electrical response at all three sites but at only one site. This site was usually the most distal part of the esophagus, namely 1 cm above LES.

Table I shows the influence of increasing the pulse duration on the number of responses evoked at 5, 3, and 1 cm above LES. At 0.1-ms pulse duration (at 5-mA, 10-Hz, and 1-s train), there were no responses observed at 5 cm above LES, whereas 12 responses were observed at 1 cm above LES. However, when the pulse duration was made 0.8 ms, all three sites responded to each stimulus. Chi-square test revealed significant differences between responsiveness of different sites ($P < 0.05$). This data suggests that the distal regions of the esophagus have lower threshold than the proximal parts.

Electrical spike bursts generally were associated with mechanical contraction. At times, however, electrical spike bursts dissociated from contractions

¹ Abbreviation used in this paper: LES, lower esophageal sphincter.

TABLE I
Influence of Pulse Duration on the Number of Electrical
Responses Evoked at 5, 3, and 1 cm above
Lower Esophageal Sphincter

Pulse duration (ms)	Stimuli	Number of responses		
		5 cm	3 cm	1 cm
0.01	25	0	0	12
0.1	25	0	4	12
0.4	25	4	6	18
0.6	25	18	20	25
0.8	25	25	25	25

Other stimulus parameters: 1.5 mA, 1-s train, 10 Hz. Responses are significantly different at each site $\chi^2_{df=2} = 30.94$, $P < 0.005$.

were also observed, as reported earlier (12). Stimuli up to 10-mA and 10-ms pulse duration at lower frequencies of stimulation (≤ 2 Hz) caused a slow change in membrane potential without any associated spikes. These small changes in the membrane potential were not associated with a rise in intraluminal pressure as shown in Fig. 1 or visible contraction of the longitudinal muscle layer.

We determined threshold stimuli by constructing

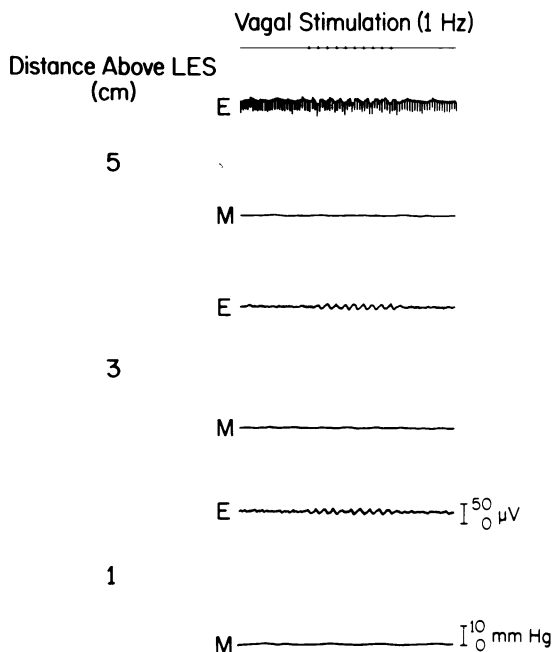


FIGURE 1 Effect of vagal efferent stimulation on the esophagus at 5, 3, and 1 cm above LES. Note that single pulses (5 mA, 0.5 ms) produced a transient hyperpolarization at all three sites. These slow membrane responses were not associated with a detectable spike burst or mechanical contraction. E, electrical activity; M, mechanical activity.

current intensity-pulse duration and frequency-train duration curves.

Current intensity-pulse duration curves. When the frequency of stimulation and train duration were kept constant at 10 Hz and 1 s, respectively, the threshold response occurred at a certain combination of current intensity and pulse duration, as shown in Fig. 2A. Pulse durations of <0.05 ms failed to elicit a response at any current intensity up to 10 mA. Similarly, current intensities <1.5 mA failed to elicit a response at any pulse duration up to 10 ms. Between pulse durations of 0.05 and 1 ms, a longer pulse dura-

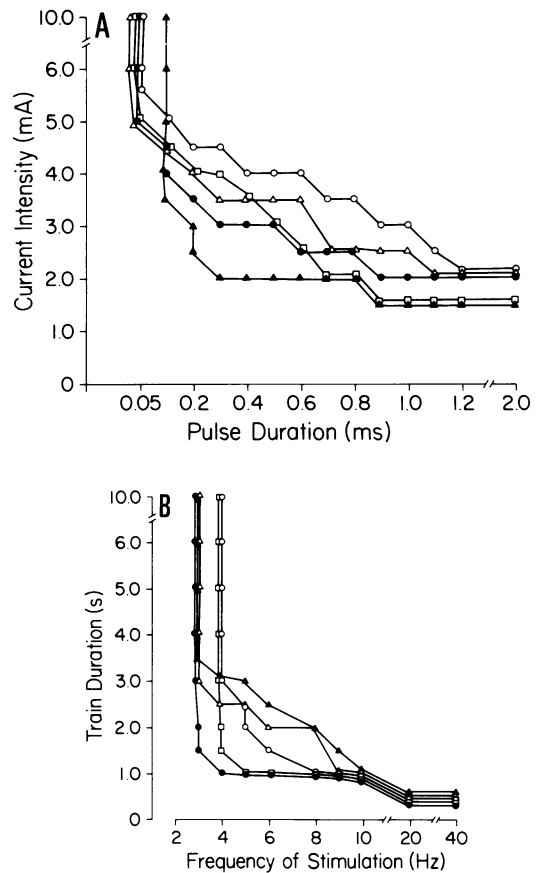


FIGURE 2 (A) Current intensity-pulse duration curves. Train duration and frequency of stimulation were held constant at 1 s and 10 Hz, respectively. Each point represents the threshold value for a combination of stimulus parameters when an electrical response was detected at all three recording sites. Note that threshold curves in all animals are similar in shape and show no significant differences ($\chi^2_{df=2} = 0.40$, $P > 0.05$). (B) Frequency-train duration curves. Current intensity and pulse duration were held constant at 3 mA and 1 ms, respectively. Each point represents the threshold value for a combination of stimulus parameters when an electrical response was detected at all the recording sites. Note that the frequency-train duration curves in all animals are similar in shape and show no significant differences ($\chi^2_{df=2} = 0.61$, $P > 0.05$).

tion required a smaller current intensity to elicit a threshold response.

The current intensity-pulse duration curves for the threshold stimuli varied somewhat in different animals. However, these differences were small and the general shapes of the curves were similar in all animals (Fig. 2A). The difference in threshold curves was not significant ($P > 0.05$). These curves were also made for other stimuli using different frequencies and train durations. The general shapes of the curves were not modified by these manipulations.

Frequency-train duration curves. When current intensity and pulse duration were kept constant at 3 mA and 1 ms, respectively, the threshold response occurred at a certain combination of frequency of stimulation and train duration, as shown in Fig. 2B. This figure shows that a frequency of <3 Hz and a train duration of <0.5 s failed to elicit an electrical spike burst in the esophageal smooth muscle. Higher frequencies required shorter train durations to produce a threshold response. The frequency-train duration curves were different in all animals. However, the general shape of the curves in all animals was similar. Moreover, the small differences between the curves were not statistically significant ($P > 0.05$). The shape of these curves remained unchanged with stimuli of other current intensities or pulse durations.

Latencies of esophageal response at different sites

The latency of spike-burst measured from the end of the stimulus was modified by different parameters of vagal stimulation. Even with the same stimulus the latency was different at different esophageal sites.

Latencies at 5 cm above LES. The latencies measured from the end of the stimulation to the onset of spike burst varied from 0.5 to 3.0 s, depending upon the stimulus parameters. Fig. 3A shows the influence of changing the frequency of stimulation and the current intensity on the latencies when pulse duration and train duration were kept constant at 0.5 ms and 1 s, respectively. This figure shows that increases in frequency of stimulation cause progressive decreases in the latency at all current intensities. However, the latencies were markedly influenced by lower current intensities. For example, at 3 mA the latency at 3 Hz was 2.8 ± 0.12 s, which decreased to 0.72 ± 0.16 s at 20 Hz. At 5 mA the latency at 3 Hz was 1.78 ± 0.04 s, which decreased to 1.2 ± 0.11 s at 20 Hz. This decrease in latency with frequency at 5 mA was significantly less than that observed with 3 mA stimulus ($P < 0.01$). The current intensity-frequency curve for 2 mA was similar to that observed with 3-mA stimulus. However, a pulse duration of at least 1 ms was required to evoke the responses. Changes in other stimulus

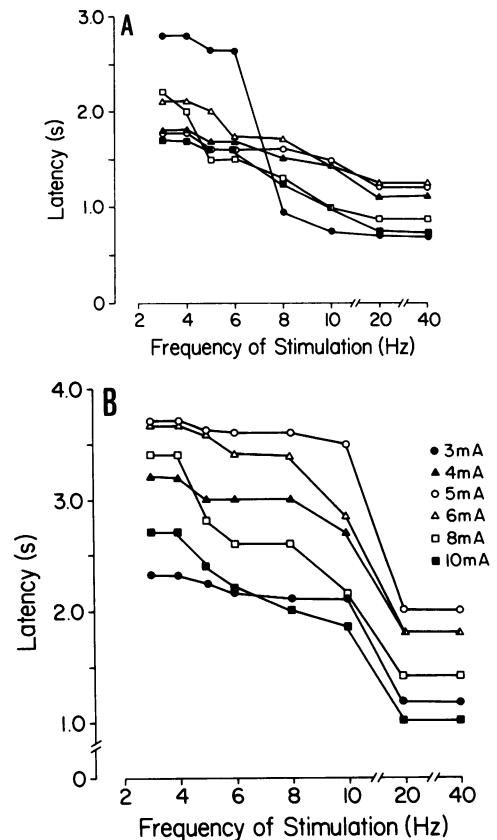


FIGURE 3 Influence of current intensity (mA) and frequency of stimulation (Hz) on the latencies of electrical off-response at 5 cm (A) and 1 cm (B) above LES. Other stimulus parameters (0.5-ms pulse duration and 1-s train) were held constant. Each point is a mean of 25 observations in five animals. Note that the latencies decrease with increasing frequencies. However, at 5 cm above LES the shapes of the curves are more influenced by current intensities as shown by the 3-mA curve (A). At 1 cm above LES the latencies increase with increasing current intensity up to 5 mA and then decrease thereafter with further increase in current strength (B).

parameters, that is pulse duration (0.05–1 ms) and train duration (0.5–5 s), also produced quantitatively similar results.

Latencies at 1 cm above LES. The latencies of electrical spike burst varied from 1 to 4 s as shown in Fig. 3B. The latencies decreased with increasing frequencies of stimulation, at all current intensities. This decrease in latency was statistically significant ($P < 0.01$). The current intensity also exerted a prominent influence on the frequency-response curves. Increase in current intensity first increased and then decreased the latency. The latencies were maximal at 5 mA, and they were lower and close together at 3 and 10 mA.

Latencies at 3 cm above LES. The frequency-response curves were intermediate between those at 5 and 1 cm.

Relative latencies at three different esophageal sites. The relative latencies at the three different esophageal sites are shown in Fig. 4. At 3 mA, 1-ms pulse duration and 1-s train duration, two different patterns of latency gradient were observed, depending upon the frequency of stimulation. At ≥ 8 Hz, the latencies were shortest at 5 cm, intermediate at 3 cm, and longest at 1 cm above the LES. This pattern of latency gradient resulted in peristaltic activity. On the other hand, at ≤ 6 Hz the latency gradients were reversed. The latencies were shortest in the distal and longest in the proximal esophageal sites. These gradients resulted in antiperistaltic or simultaneously occurring responses. An example of antiperistaltic and peristaltic response is shown in Fig. 5. The electrical latencies (Fig. 4A) were shorter than the mechanical latencies (Fig. 4B).

Intrastimulus responses

In two of seven animals long train duration (4 s or longer) stimulus evoked responses that appeared after a certain latency from the onset of the stimulus. These responses have been called A-waves (11). At lower fre-

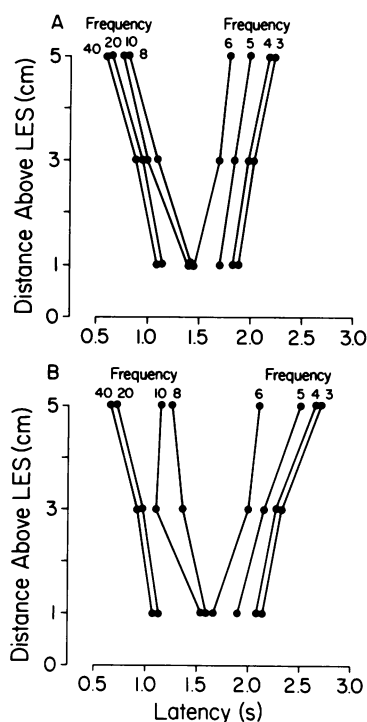


FIGURE 4 Influence of frequency of stimulation on the electrical (A) and mechanical (B) off-response (3 mA, 1 ms, 1-s train) at 5, 3, and 1 cm above LES. Each point is a mean of 25 observations in five animals. Note that at frequencies of ≥ 8 Hz, latencies are smaller at 5 than at 3 or 1 cm above LES. But at a frequency of < 8 Hz, the latencies are longer at 5 than at 5, 3, or 1 cm above LES, resulting in antiperistalsis.

quency of stimulation (≤ 8 Hz when A-waves were present) no off-responses (B-waves) were encountered. However, higher frequencies (≥ 10 Hz) evoked A- as well as B-waves. The A-wave speed of peristalsis increased with an increase in the frequency of stimulation (Table II). For example, at 10 Hz the A-wave speed of peristalsis was 2.32 ± 0.04 and 2.4 ± 0.02 cm/s as calculated from the electrical and mechanical response, respectively. At 20 Hz the corresponding values were 4.01 ± 0.15 and 4.28 ± 0.16 cm/s, respectively. The speed of peristalsis showed little change up to 10 Hz and then suddenly increased at 20 and 40 Hz.

Peristaltic and nonperistaltic responses

Identification of stimulus parameters that cause peristaltic or nonperistaltic responses. The peristaltic responses were always associated with supra-threshold stimuli. Current intensity of ≥ 5 mA, pulse duration of ≥ 2 ms, frequency of ≥ 8 Hz, and train duration of ≥ 6 s were always associated with peristaltic responses irrespective of other stimulus parameters. Lesser stimuli produced either peristaltic or antiperistaltic responses, depending upon the combination of stimulus parameters. Because of the enormous number of permutations and combinations that are possible with four variables, it is not possible to summarize all the stimulus parameters that cause antiperistaltic responses. Fig. 6 shows combinations of current intensity and pulse duration (A) and train duration and frequency of stimulation (B) that elicited antiperistaltic or peristaltic responses in one animal. Note that lower combinations of stimulus parameters elicited an antiperistaltic response shown by the asterisks (*). Suprathreshold stimulus combinations elicited peristaltic responses shown by the solid circles (●). Suprathreshold stimuli produced latency gradients that were smallest in the proximal esophagus and largest in the distal esophagus, thus producing a peristaltic response. Similar observations were made in all five animals tested.

The speed of peristalsis in the smooth muscle segment of the esophagus was also influenced by the stimulus parameters. A slow speed of peristalsis was achieved with a current intensity of 5 mA, pulse duration of 0.5 ms, a train duration of 1 s, and a frequency of 3–10 Hz. In general, increases in current intensity, pulse duration, frequency, and train duration caused increases in speed of peristalsis (Table III). Also note that these stimulus parameters did not produce antiperistaltic responses.

Esophageal responses to swallowing

Swallows induced by pharyngeal stimulation produced an electrical spike burst and a contraction in the esophageal smooth muscle. This response always

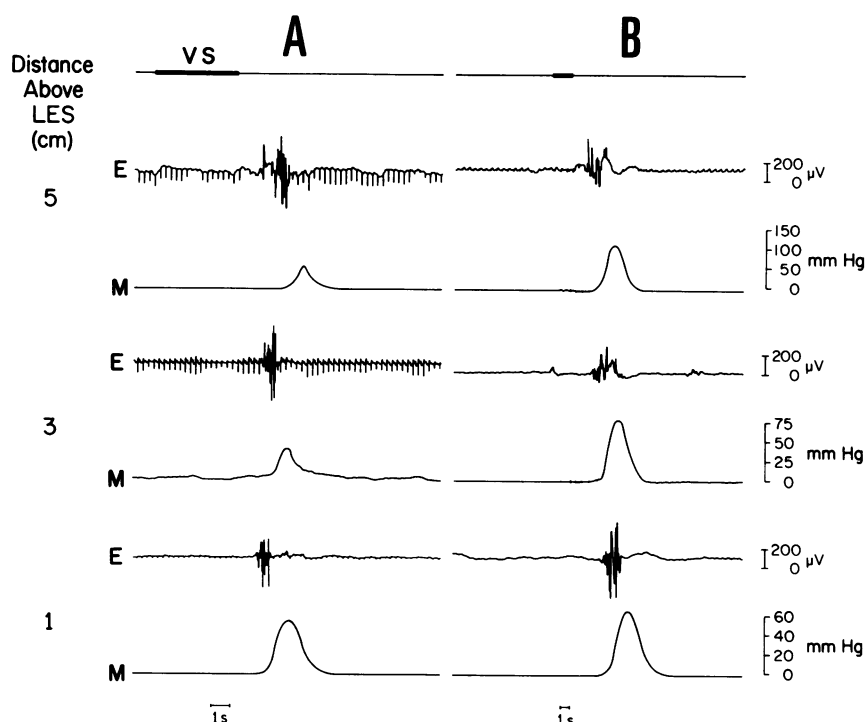


FIGURE 5 Effect of vagal efferent stimulation on the smooth muscle segment of the esophagus. Note that vagal stimulation with 3 mA, 4-s train, 5 Hz and 1-ms pulse durations evoked an anti-peristaltic response (A). However, 5 mA, 0.5-ms pulse, 10 Hz, and 2-s train produced a peristaltic response (B). VS, vagal stimulation; E, electrical activity; M, mechanical activity.

propagated aborally and was peristaltic. The electrical spike burst always preceded the mechanical contraction. The speed of peristalsis as measured from the onset of electrical spike burst and mechanical contraction was 1.82 ± 0.08 cm/s and 2.01 ± 0.12 cm/s, respectively.

DISCUSSION

Electrical stimulation of decentralized vagal efferents in the smooth muscle part of the esophagus causes spike activity and contractions with a certain

latency. The latencies in the different segments of the esophagus are variable and these differences determine the polarity and the speed of propagation of the esophageal response. Our studies show that modifications in the parameters of vagal stimulation can cause: (a) changes in polarity of response, i.e. whether the response is peristaltic or antiperistaltic; and (b) changes in speed of peristalsis. These studies suggest that (a) peristalsis in the smooth muscle part of the esophagus can be explained entirely on the basis of peripheral mechanisms without involving sequential activation of vagal efferents, and (b) the central nervous system may modulate speed and polarity of propagation

TABLE II
Influence of Frequency of Stimulation* on the "A-Wave" Speed of Peristalsis†

Stimulus frequency, Hz	Speed of peristalsis					
	cm/s					
	4	6	8	10	20	40
Mechanical	2.22 ± 0.06	2.28 ± 0.04	2.56 ± 0.01	2.41 ± 0.02	4.28 ± 0.16	5.36 ± 0.12
Electrical	2.17 ± 0.03	2.24 ± 0.02	2.3 ± 0.07	2.32 ± 0.04	4.01 ± 0.15	5.23 ± 0.1

* Other stimulus parameters: 5 mA, 0.5-ms pulse duration and 4-s train duration. Values are $\pm$ SEM.

† The speed is calculated in the distal 4-cm segment of esophagus from the onset of electrical spike burst and mechanical contraction.

by modifying the intensity and frequency of vagal activation.

Antiperistalsis in the smooth muscle portion of the esophagus with vagal efferent stimulation has not been reported previously. Tieffenbach and Roman (16) reported occasional alpha bursts, which propagated in oral or aboral direction. This activity is quite different from the antiperistaltic responses described here, as the alpha bursts were related to longitudinal muscle activity and were not associated with circular muscle contraction and increases in intraluminal pressure. The present studies have demonstrated antiperistalsis with both electrical as well as mechanical recordings. One of the reasons antiperistalsis has not been reported by other investigators could be that all the previous investigators have used "supramaximal" stimulus parameters, particularly current intensities of ≥ 5 mA (9, 11). We have observed that supramaximal stimulus parameters only elicit peristaltic responses. The antiperistaltic or simultaneously occurring responses were observed near threshold stimuli, particularly at frequencies of stimulation of < 6 Hz and current intensities of ≤ 5 mA. In the transitional stimulus zone, where antiperistaltic responses changed to peristaltic responses, many disorganized responses were seen. These consisted of either simultaneous onset responses at all three sites or simultaneous at two sites and antegrade or retrograde at the other site.

The genesis of antiperistalsis is not known. In retrograde propagated responses the latency of response is longer at the proximal site than the distal site. One possibility is that near threshold stimuli may activate a neural pathway that produces a response that has a greater latency at the proximal than at the distal site. There is no experimental evidence to support this hypothesis. Another explanation is possible. A weaker stimulus may activate the distal esophageal site and the activity then spreads in a retrograde fashion. For this hypothesis to be true, two conditions must be met. Firstly, it should be shown that there are different sensitivities to vagal stimulation of different parts of the esophagus and that the distal esophageal site is more sensitive. Secondly, intramural mechanisms for retrograde propagation must be present. Current studies show that the distal esophageal site is more sensitive to nerve stimulation than the proximal site. It has also been shown that intramural stimulation can cause retrograde propagation of activity in the esophagus (8). Thus, two important criteria underlying the hypothesis of retrograde propulsion appear to have been satisfied. Further studies would be necessary to test this hypothesis.

Simultaneous and disorganized contractions occur in the smooth muscle part of the esophagus in patients with diffuse esophageal spasm. Although antiperistalsis is generally not considered to occur in humans,

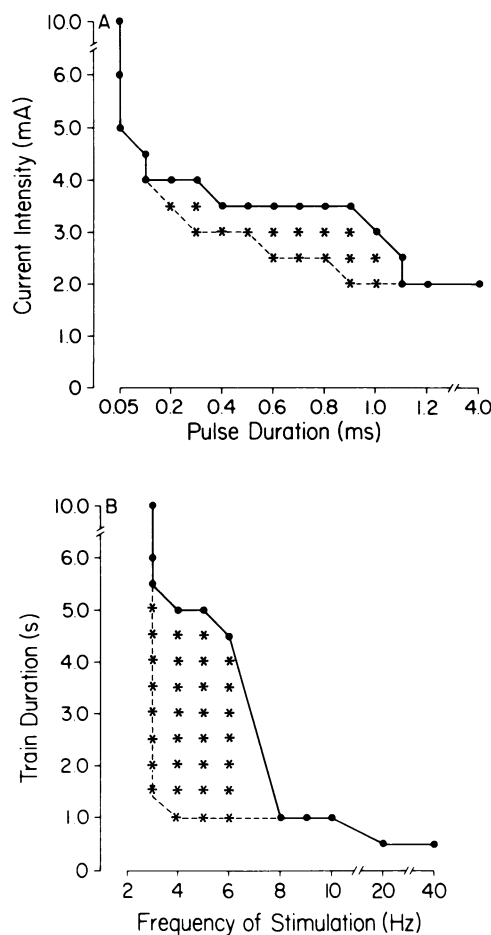


FIGURE 6 Current intensity-pulse duration (A) and frequency-train duration (B) curves for threshold (*-, antiperistaltic or simultaneous nonperistaltic) and suprathreshold (●, peristaltic) response in one animal. Note that lower combinations of stimulus parameters produce antiperistaltic or simultaneously occurring responses and only suprathreshold stimuli produce peristaltic responses.

we have observed antiperistalsis in humans. The pathogenesis of diffuse esophageal spasm is not understood. This study may have some implications in the pathogenesis of nonperistaltic contractions.

Mukhopadhyay and Weisbrodt (9) have shown that vagal efferent stimulation at 10 Hz, 0.5 ms, 1–4 s, and supramaximal current intensities (mA) produced esophageal contractions with a speed of peristalsis that was similar to that observed with swallows. We also observed that vagal stimulation at 10 Hz, 0.5 ms, 1 s, and 5 mA produced peristaltic speed both on electrical and mechanical recordings that was similar to that observed with swallows in the same animals. These observations support the view that esophageal peristalsis in the smooth muscle part of the esophagus may be fully explained by a peripheral mechanism

TABLE III
Influence of Stimulus Parameters on the "Off-response" Speed of Peristalsis*

Speed of peristalsis							
	1	2	3	5	6	8	10
Current intensity, mA				cm/s			
Electrical	NR	NR	3.03±0.28	1.98±0.14	2.79±0.09	3.47±0.12	4.7±0.16
Mechanical	NR	NR	3.22±0.26	2.1±0.12	2.85±0.06	3.5±0.28	4.8±0.08
Other stimulus parameters: 0.5-ms pulse duration, frequency: 10 Hz, train: 1 s							
Pulse duration, ms	0.04	0.05	0.1	0.2	0.5	1.0	4.0
Electrical	NR	2.0±0.14	2.1±0.16	2.0±0.13	1.98±0.14	2.8±0.21	3.4±0.12
Mechanical	NR	2.12±0.09	2.24±0.09	2.72±0.06	2.1±0.12	2.94±0.14	3.8±0.11
Other stimulus parameters: 5 mA, 10 Hz, 1-s train							
Frequency, Hz	1	2	3	5	10	20	40
Electrical	SMR	SMR	2.1±0.09	2.0±0.11	1.98±0.14	5.01±0.12	5.0±0.16
Mechanical	NR	NR	2.22±0.09	2.1±0.16	2.1±0.12	5.0±0.18	5.0±0.13
Other stimulus parameters: 5 mA, 0.5 ms, 1-s train							
Train duration, s	0.5	1.0	2	4	6	8	10
Electrical	NR	1.98±0.14	2.0±0.09	2.4±0.12	4.12±0.08	6.85±0.08	6.8±0.11
Mechanical	NR	2.1±0.12	2.12±0.11	2.62±0.09	4.22±0.09	6.85±0.13	6.85±0.15
Other stimulus parameters: 5 mA, 0.5 ms, 10 Hz							

Values are ±SEM, NR, no response, SMR, slow membrane response.

* The speed is calculated in the distal 4-cm segment of the esophagus from the onset of electrical spike burst and mechanical contraction.

involving progressively increasing latency gradient along the esophagus (7).

One of the arguments against this hypothesis is that the speed of peristalsis calculated from differences in latencies in strips of muscle from various levels was 6–7 cm/s, which is much faster than the speed observed with swallowing (2, 7, 10). However, this argument does not take into account the profound influence of stimulus parameters on the latency gradients. The studies reported by Weisbrodt and Christensen (7) were done with 1 ms, 15 Hz, and 0.25 s with "voltage made supramaximal." Our studies show that vagal stimulation with such parameters would also produce a very fast speed of peristalsis. A systematic, in vitro study of the influence of different stimulus parameters on the latency of response in the esophageal body is not available at present.

Dodds et al. (11) suggested that vagal efferent stimulation can activate two different neural pathways. One of the pathways was activated with 1–5-Hz and <0.5-ms pulse duration, which produced slow-speed peristalsis (A-wave) resembling swallow-induced peristalsis. The second pathway was activated by stimuli of 20–50 Hz and >1-ms pulse duration. This produced peristalsis with a faster speed (B-waves) resembling those observed with stimulation of strips in vitro. It is inter-

esting that the strips were also stimulated with stimulus parameters similar to those that elicited B-responses. Our studies show that changes in frequency of stimulation also modified the speed of peristalsis of the A-waves. Moreover, changes in stimulus parameters produced off-contractions with a wide range of speed of peristalsis. Increases in current intensity or pulse duration cause recruitment of additional fibers (spatial summation), whereas increases in frequency or train duration produce more neurotransmitter per fiber (temporal summation). Both spatial and temporal summation produced similar effects. These studies favor the view that changes in speed of peristalsis may be related to changes in the net transmitter released at the synaptic site. It should be noted that the latency curves with different stimulations were neither truly linear nor exponential. The significance of this observation is not clear. However, it may indicate a complex synaptic and neuromuscular transmission.

In the bipolar recordings used in these studies, small hyperpolarizations or spikeless depolarization could not be recorded. However, frequencies of 1 and 2 Hz showed slow fluctuations in base line without any spike bursts. These changes may represent hyperpolarizing responses described by Diamant (17).

We did not examine for the presence or absence of

central sequencing in the vagus during swallowing. Although such a sequencing may be present, it does not appear to be essential, as simultaneous activation of all vagal efferents can cause peristaltic responses resembling swallow-induced peristalsis. It should be pointed out, however, that central sequencing could only act to slow the speed of peristalsis. The only way central influences can increase the speed of peristalsis and make responses nonperistaltic is by altering the stimulus intensity and frequency of vagal fibers. These observations may be of importance in elucidating the pathophysiology of diffuse esophageal spasm and related esophageal motor disorders.

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REFERENCES

1. Roman, C. 1966. Contrôle nerveux du péristaltisme oesophagien. *J. Physiol. (Paris)*. **58**: 79–108.
2. Diamant, N. E., and T. Y. El-Sharkawy. 1977. Neural control of esophageal peristalsis. A conceptual analysis. *Gastroenterology*. **72**: 546–556.
3. Weisbrodt, N. W. 1976. Neuromuscular organization of esophageal and pharyngeal motility. *Arch. Intern. Med.* **136**: 524–531.
4. Roman, C., and L. Tieffenbach. 1972. Enregistrement de l'activité unitaire des fibres motrices vagues destinées à l'oesophage du Babouin. *J. Physiol. (Paris)*. **64**: 479–506.
5. Christensen, J. 1970. Patterns and origin of some esophageal responses to stretch and electrical stimulation. *Gastroenterology*. **59**: 909–916.
6. Christensen, J., and G. F. Lund. 1969. Esophageal responses to distension and electrical stimulation. *J. Clin. Invest.* **48**: 408–418.
7. Weisbrodt, N. W., and J. Christensen. 1972. Gradients of contractions in the opossum esophagus. *Gastroenterology*. **62**: 1159–1166.
8. Sarna, S. K., E. E. Daniel, and W. E. Waterfall. 1977. Myogenic and neural control systems for esophageal motility. *Gastroenterology*. **73**: 1345–1352.
9. Mukhopadhyay, A. K., and N. W. Weisbrodt. 1975. Neural organization of esophageal peristalsis: role of vagus nerve. *Gastroenterology*. **68**: 444–447.
10. Christensen, J., C. Arthur, and J. L. Conklin. 1979. Some determinants of latency of off-response to electrical field stimulation in circular layer of smooth muscle of opossum esophagus. *Gastroenterology*. **77**: 677–681.
11. Dodds, W. J., J. Christensen, J. Dent, J. D. Wood, and A. C. Arndorfer. 1978. Esophageal contractions induced by vagal stimulation in the opossum. *Am. J. Physiol.* **235**(4): E392–E401.
12. Goyal, R. K., and J. S. Gidda. 1981. Relation between electrical and mechanical activity in esophageal smooth muscle. *Am. J. Physiol.* **240**: G305–G311.
13. Goyal, R. K., and S. Rattan. 1976. Genesis of basal sphincter pressure: effect of tetrodotoxin on lower esophageal sphincter pressure in opossum *in vivo*. *Gastroenterology*. **71**: 62–67.
14. Rattan, S., and R. K. Goyal. 1974. Neural control of the lower esophageal sphincter. Influence of the vagus nerves. *J. Clin. Invest.* **54**: 899–906.
15. Snedecor, G. W., and W. G. Cochran. 1976. Statistical methods. Iowa State University Press, Ames, Iowa. 258–275.
16. Tieffenbach, L., and C. Roman. 1972. Rôle de l'innervation extrinsèque vagale dans la motricité de l'oesophage à musculature lisse: Étude électromyographique chez le Chat et le Babouin. *J. Physiol. (Paris)*. **64**: 193–226.
17. Diamant, N. E. 1973. Electrical activity of the cat smooth muscle esophagus: a study of hyperpolarizing responses. Proceeding of the IV International Symposium on Gastrointestinal Motility, Alberta, Canada. Mitchell Press, Ltd., Vancouver, Canada. 593–605.