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An Intrinsic Neural Pathway for Long Intestino-Intestinal Inhibitory Reflexes

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We studied the mechanisms of initiation and pathways for the propagation of intestino-intestinal inhibitory reflexes induced by close intraarterial injections of neostigmine in conscious dogs. Two or three T-shaped catheters were surgically implanted in the intestinal branches of the superior mesenteric artery to inject pharmacologic agents locally in 10–15-cm-long segments. Migrating myoelectric complexes were recorded by a set of 10 electrodes and strain-gauge transducers. Close intraarterial injection of neostigmine initiated strong contractions of long duration in the perfused segment that terminated phase III activity in progress 90–150 cm distal or proximal to the cannulated sites and stopped its further migration. Atropine or 4-diphenylmethoxy-N-methylpiperidine methiodide injected just before neostigmine administration through the same catheter blocked both the local contractile effects and the reflex inhibition of phase III activity. Pirenzepine or hexamethonium injected in a similar manner did not affect the local response to neostigmine but blocked the reflex inhibition of phase III activity. A transection and reanastomosis in the mid-small intestine blocked the reflex inhibition by close intraarterial injection of neostigmine beyond the transection site. Pirenzepine, atropine, or hexamethonium injected through a middle catheter also blocked the reflex inhibition of phase III activity beyond the site perfused with these cholinergic antagonists. Close intraarterial administration of 4-diphenylmethoxy-N-methylpiperidine methiodide at a middle site had no effect on reflex inhibition. We concluded that strong spasmodic contractions in the small intestine initiate an intestino-intestinal inhibitory reflex in both directions. This reflex is mediated through an intrinsic neural pathway involving nicotinic and M_1 muscarinic receptors.

Two types of reflexes have been identified in the gastrointestinal tract, extrinsic and intrinsic. The extrinsic reflexes are those that involve a neural pathway extrinsic to the gut wall. These reflexes have further been subdivided into long extrinsic reflexes and short extrinsic reflexes (1). The long extrinsic reflexes are those that involve the spinal cord or the higher centers, and the short extrinsic reflexes are those that involve only the prevertebral ganglia. The intrinsic reflexes are those that involve only the nerves in the enteric plexuses of the gut. These reflexes have also been called myenteric reflexes (2,3). The intrinsic reflexes described thus far are effective only over a short distance (<10 cm) on each side of the stimulus.

Most previous studies on intrinsic intestino-intestinal reflexes were done in in vitro preparations, on isolated intestinal segments, or in anesthetized animals (2–9). These studies focused largely on reflexes over short distances in the gut because of the nature of the experimental model. The most common stimuli used in these studies were stroking of mucosa, mucosal contact of a chemical, stretching of a flap made out of intestinal wall, and distention of the lumen by a balloon. Some of the limitations of the above experimental approaches are as follows: (a) Some motor patterns, such as migrating motor complexes are not present in anesthetized animals, or in muscle strips. The effects of intestino-intestinal reflexes on these patterns of motor activity cannot,

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Abbreviations used in this paper: 4-DAMP, 4-diphenylmethoxy-N-methylpiperidine methiodide; MMC, migrating myoelectric complex.

therefore, be studied in these preparations. (b) The anesthetic agents may modulate nerve activity and function. These anesthetic agents may, therefore, alter or mask some of the reflex pathways. (c) Distention of the intestinal wall by a balloon or stroking the mucosa with a sharp object may not represent a physiologic stimulus in the intestine. During normal function, the intestinal wall contracts rather than distends because the contents are fluid. Normal filling of the intestine during digestion is not equivalent to distention by a balloon. Distention may occur, however, proximal to a site of organic or functional obstruction. In this case the distention or dilation may be the effect of a stimulus rather than a stimulus itself.

The objectives of our study were (a) to study the intestino-intestinal reflexes over long distances in conscious dogs with particular reference to their effects on migrating myoelectric complexes (MMCs); (b) to delineate the neural pathway for these reflexes, i.e., intrinsic or extrinsic to the intestinal wall; and (c) to study the role of ganglia cells and cholinergic receptors in the small intestine during the initiation and propagation of these reflexes. The reflexes were initiated by close intraarterial injections of neostigmine by the technique described previously by Sarna et al. (10). An abstract of this work was published previously (11).

Materials and Methods

Experiments were done on 7 healthy conscious dogs of either sex, each weighing from 35 to 40 kg. The dogs were divided into two groups. In the first group of 4 dogs, two intestinal branches of the superior mesenteric artery, one 40 cm distal to the ligament of Treitz and one 80 cm proximal to the ileocecal junction, were identified and isolated from their connective tissue for a length of 3–4 cm. A T-shaped silastic catheter (0.8 mm ID and 1.7 mm OD) was inserted in each of the arteries as shown in Figure 1*A*. The length of the intestine perfused by each of the cannulated arteries was 10–15 cm as determined by blanching due to the injection of a saline bolus. The catheters were tunneled subcutaneously and exteriorized in the subscapular region. The exteriorized catheters were protected by a jacket, and kept patent by daily injections of heparinized saline (1000 U/ml).

At the same time, a set of eight bipolar electrodes and two electrode-strain gauge pairs were implanted on the small intestine as illustrated in Figure 1*A*. An electrode-strain gauge pair consists of an electrode and a strain-gauge transducer mounted on the same silastic base (12). The pair records myoelectric and contractile activities from nearly the same site.

The recordings were begun 10 days after surgery. The dogs were fasted for 14–16 h before each experiment. The recordings were made on a 12-channel Grass recorder (model 7, Grass Instrument Co., Quincy, Mass.) with lower and upper cutoff frequencies set at 0.04 and 15 Hz for

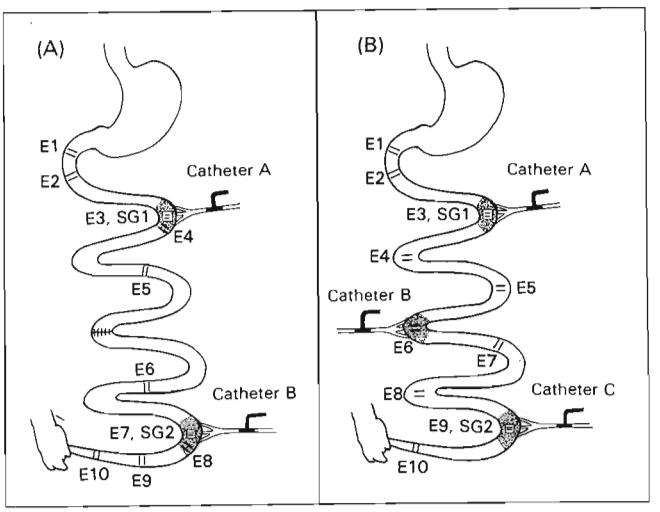

Figure 1. Diagram illustrating the arrangement of close intraarterial catheters, electrodes and electrode-strain gauge pairs, and site of transection and reanastomosis for the two groups of dogs. The distances between recording devices are indicated on the subsequent figures.

electrical recordings and direct current and 15 Hz for strain-gauge recordings, respectively. The signals were also recorded simultaneously on two 8-channel Hewlett-Packard tape recorders (Hewlett-Packard Co., Palo Alto, Calif.) for later electronic filtering to separate electrical response activity from electrical control activity and to condense the tracings in time as described previously by Sarna et al. (13). At least one complete MMC cycle was recorded at the most proximal electrode site in the duodenum at the beginning of each experiment. Neostigmine methylsulfate (25–50 μg; Elkins–Sinn Inc., Cherry Hill, N.J.) was injected during the next cycle at the proximal or the distal cannulated site when the phase III activity in progress was 60–150 cm distal or proximal to the perfused segment.

Three dogs were then reoperated and the small intestine was transected and reanastomosed between electrodes E5 and E6 (Figure 1*A*). The dogs were allowed to recover for 10 days and the experiments with close intraarterial injections of neostigmine were repeated. In the second group of 3 dogs, a set of three close intraarterial catheters was implanted, two as described above and one at a middle site as shown in Figure 1*B*.

The roles of cholinergic receptors in the initiation and propagation of intestino-intestinal reflexes were studied by close intraarterial injections of the muscarinic antagonist atropine sulfate (Elkins–Sinn), the nicotinic antagonist hexamethonium chloride (ICN Pharmaceuticals, Cleveland, Ohio), the M_1 muscarinic receptor blocker pirenzepine dihydrochloride (courtesy of Drs. A. Giachetti, R. Hammer, and A. Donetti of the Institute De Angelli, Milan, Italy) (14–16), and the M_2 muscarinic receptor blocker 4-diphenylmethoxy-*N*-methylpiperidine methiodide (4-DAMP, courtesy of Dr. R. B. Barlow, University of Bristol Medical School, Bristol, U.K.). The antagonists were injected 2–5 min before the administration of neostigmine. All local intraarterial injections were given

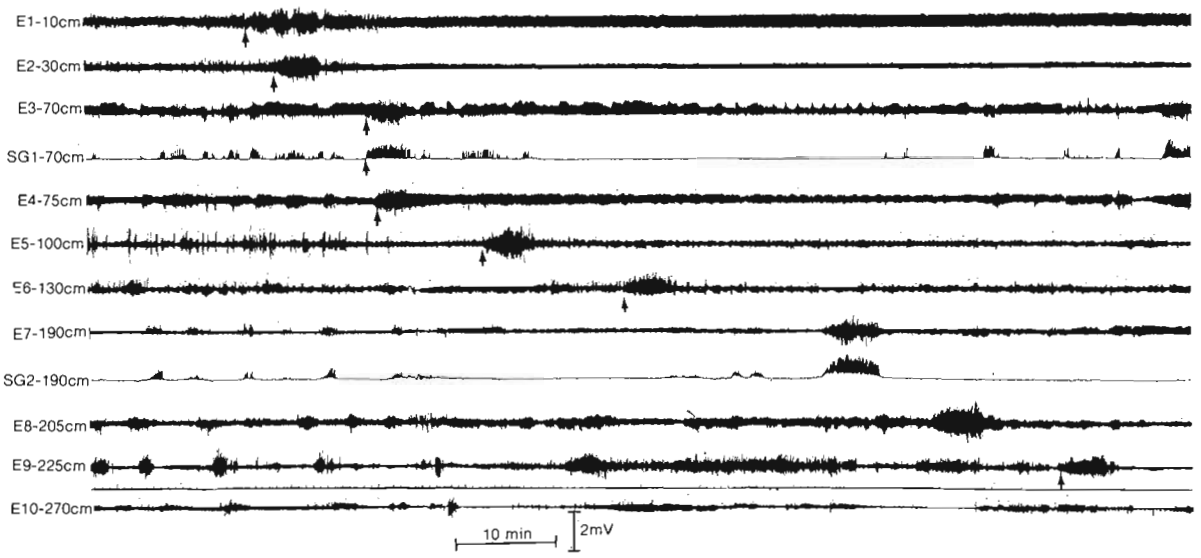

Figure 2. The normal migration of phase III activity over the study segment. *Arrows* indicate the onset of phase III activity at the corresponding recording device.

in a volume of 3 ml followed by a 3-ml saline flush. Each pharmacologic agent was administered at least three times in each dog.

Results

Initiation of Intestino-Intestinal Inhibitory Reflex by Close Intraarterial Injections of Neostigmine

The close intraarterial injection of neostigmine (25–50 μg) at either the proximal or the distal site initiated an intestino-intestinal reflex that inhibited the phase III activity in progress at the time of injection and blocked its further migration. The phase III activity was 60–150 cm proximal or distal to the site of close intraarterial injection when neostigmine was administered. Figure 2 shows the normal migration of phase III activity over the study segment in one experiment. During the next MMC cycle in this experiment 50 μg of neostigmine was injected at the site of electrode-strain gauge pair E7 and SG2. The phase III activity at this time was at the site of electrode E5, 90 cm proximal to injection site (Figure 3). The close intraarterial injection of neostigmine inhibited phase III activity in progress and its further migration stopped. In all cases, the inhibition took place within 45 s of neostigmine injection and flush.

The local effect of neostigmine injection was to initiate a series of contractions of long duration followed by inhibition of motor activity. The long-duration contractions lasted for 10.2 ± 3.5 min (n = 15). The mean (±SE) duration of individual long-duration contractions was 54 ± 30 s (n = 61). In contrast, the mean duration of normal phasic contractions during phase III activity was 3.6 ± 0.4 s (n = 60). Similar results were obtained when neostigmine was injected at the proximal catheter site and phase III activity was distal to it. The period of the next normal MMC following interruption by neostigmine, 111 ± 37 min, was not significantly different from the control MMC period, 97 ± 43 min ($p > 0.05$). In about 10% of the experiments, the next phase III started at or distal to the site of neostigmine injection.

Effect of Transection and Reanastomosis on Long Intrinsic Intestino-Intestinal Reflexes

The MMC cycled independently in the proximal and the distal segments after transection and reanastomosis as reported previously by Sarna et al. (17). Neostigmine was injected at the proximal or the distal catheter site when phase III was migrating in the distal or the proximal segment, respectively. Transection and reanastomosis blocked the reflex inhibition of phase III activity beyond the transection site as shown in Figures 4 and 5. In Figure 4 neostigmine was administered at the distal site when phase III activity was at electrode E4 in the proximal segment, and in Figure 5 neostigmine was administered at the proximal catheter site when phase III activity was at electrode E6 in the distal segment.

Role of Cholinergic Receptors in the Initiation of Intestino-Intestinal Reflexes

Atropine (50 μg) or 4-DAMP (50–100 μg) injected close intraarterially 2–5 min before neostig-

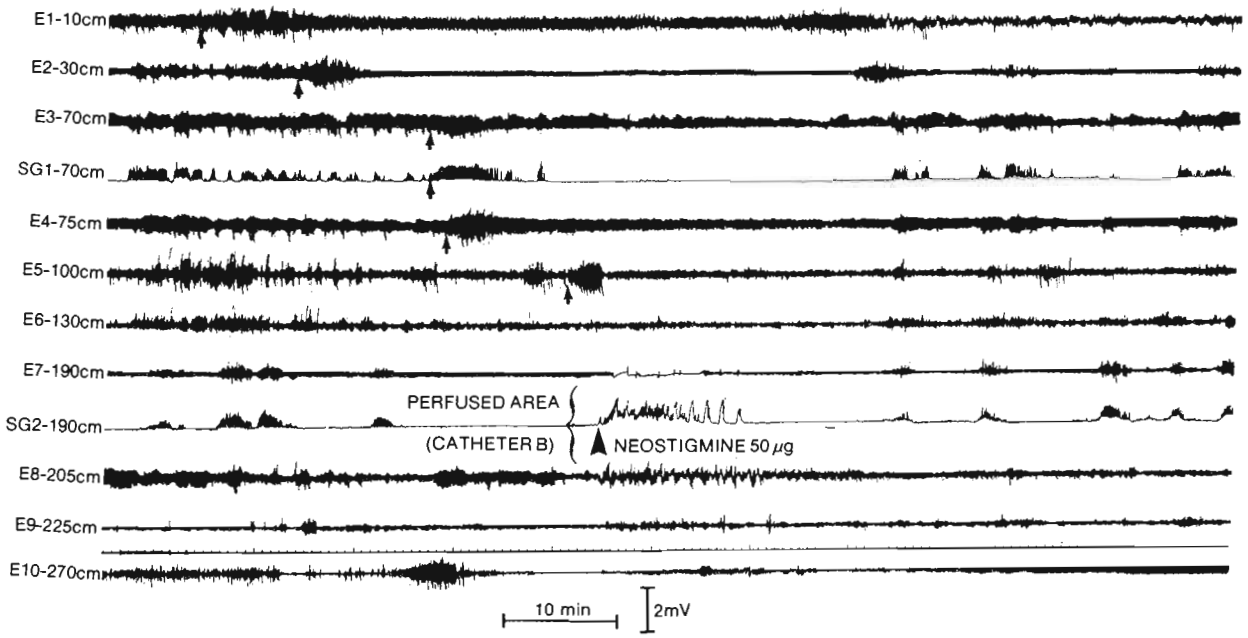

Figure 3. A close intraarterial injection of 50 μg of neostigmine was given at the distal catheter site when phase III activity was 90 cm proximal to it. The reflex initiated by strong local contractions inhibited phase III activity and stopped its further migration.

mine administration through the same catheter blocked both the local effects of neostigmine in the perfused segment and the reflex inhibition of phase III activity at the remote proximal or distal sites as shown in Figure 6 for 4-DAMP.

Pirenzepine, 60–100 μg, injected through either catheter 2–5 min before the administration of neostigmine blocked the reflex inhibition of phase III activity at the remote sites, but it did not block the local effects of neostigmine as shown in Figure 7. Pirenzepine injection itself induced local contractions, but these did not initiate the reflex to inhibit phase III activity (Figure 7).

Close intraarterial administration of hexamethonium, 5 min before neostigmine injection, had no significant effect on the local contractile response to neostigmine, but it blocked the reflex inhibition of phase III activity at the remote sites (Figure 8). Close

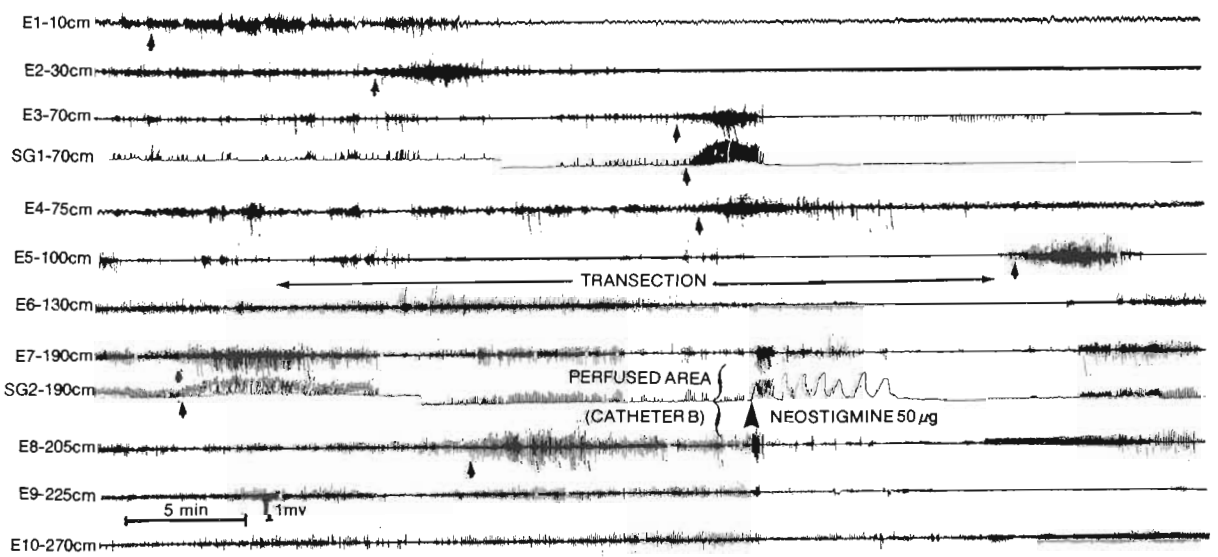

Figure 4. A transection and reanastomosis was made between electrodes E5 and E6. A close intraarterial injection of neostigmine at the distal catheter site did not inhibit phase III activity proximal to the transection site.

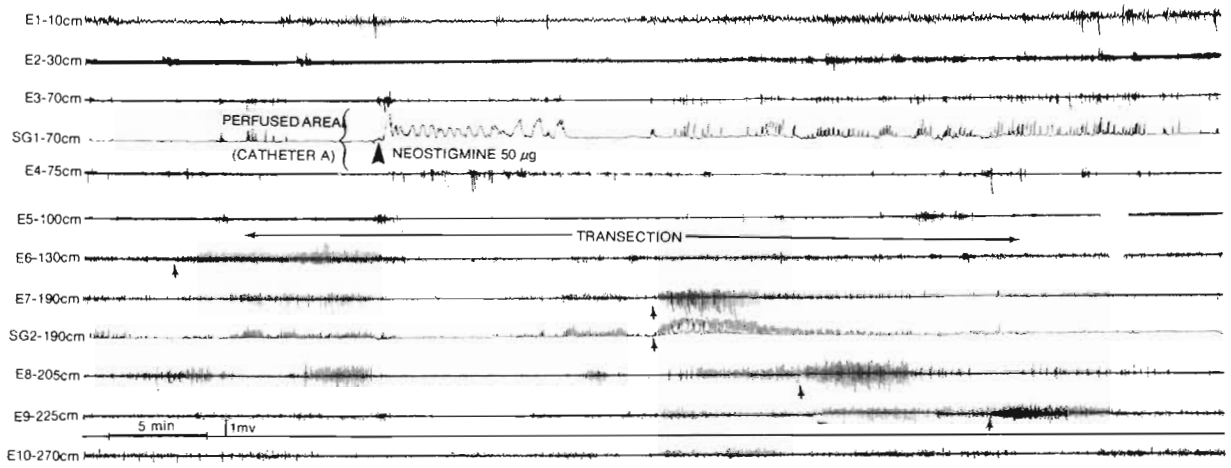

Figure 5. A transection and reanastomosis was made between electrodes E5 and E6. A close intraarterial injection of neostigmine at the proximal catheter site did not inhibit phase III activity distal to the transection site.

intraarterial administration of heparinized saline in the same manner as above had no effect on the local or the reflex actions of neostigmine.

Role of Cholinergic Receptors in the Transmission of Neural Signals for Intestino-Intestinal Reflexes

Atropine (50 μg), pirenzepine (60 μg), or hexamethonium (15 mg) injected through the middle catheter in the second group of dogs, 2–5 min before neostigmine administration at the proximal or the distal catheter site, blocked the intestino-intestinal inhibitory reflex beyond the site of middle catheter as shown in Figures 9–11. The necessary condition for this action was that the phase III activity must be on the opposite side of the middle catheter site at the time of neostigmine injection. If phase III activity was on the same side of the middle catheter as the segment infused with neostigmine, it was interrupted as described earlier. In contrast, 4-DAMP injected through the middle catheter did not block the intestino-intestinal inhibitory reflex initiated by close intraarterial administration of neostigmine at the proximal or the distal catheter site (Figure 12).

Discussion

Our findings suggest that intestino-intestinal inhibitory reflexes may be initated in the conscious state by close intraarterial injection of neostigmine. We called this response an intestino-intestinal inhib-

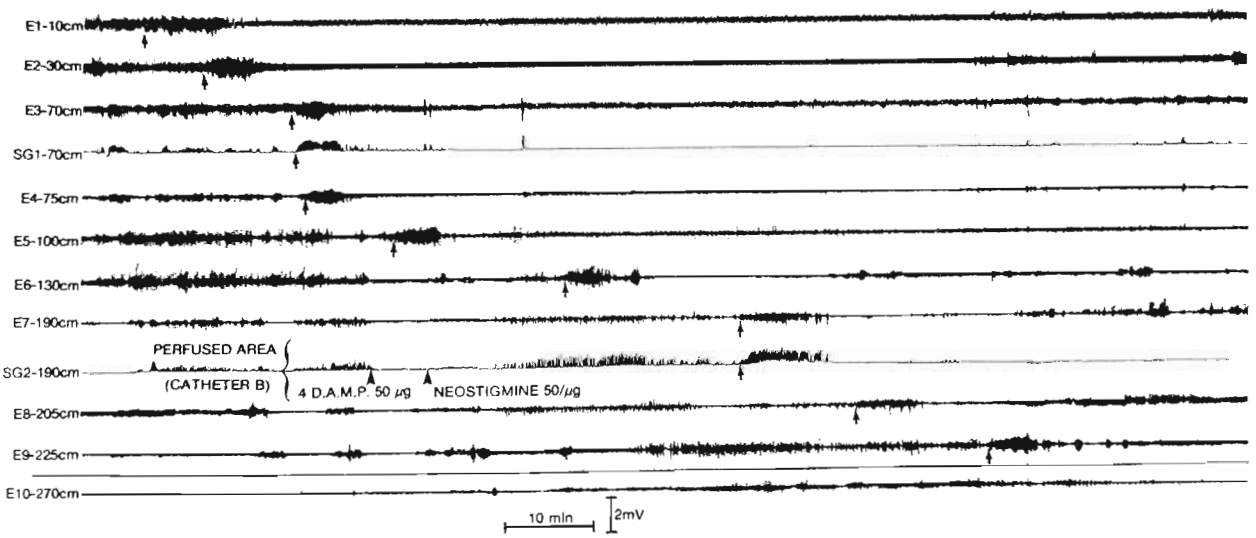

Figure 6. 4-Diphenylmethoxy-*N*-methylpiperidine methiodide injected before neostigmine administration at the distal catheter site blocked the local response and the intestino-intestinal inhibitory reflexes normally initiated by neostigmine.

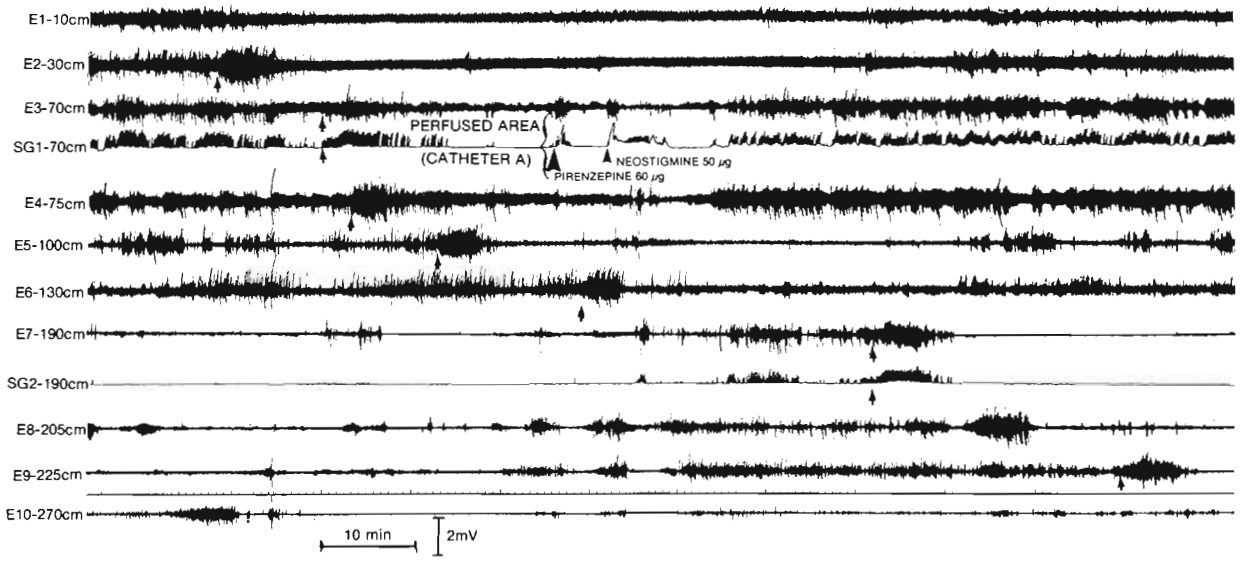

Figure 7. Pirenzepine injected before neostigmine administration at the proximal catheter site blocked the intestino-intestinal inhibitory reflex normally initiated by neostigmine.

itory reflex because the stimulation and response sites were both in the small intestine and the response was inhibitory and mediated via a neural pathway. This intestino-intestinal inhibitory reflex terminated phase III activity in progress at distal sites and stopped its caudad migration. Locally, neostigmine induced strong contractions of long duration, indicating spasm of the perfused segment. The mean duration of these contractions was several times longer than that of phasic contractions controlled by electrical control activity. Lower doses of neostigmine that did not induce long-duration contractions did not initiate the inhibitory reflex.

Other investigators reported earlier that distention of the gut wall by a balloon also inhibits contractile activity at remote sites (18,22). As both contractions and distention initiate the inhibitory reflex, it is likely that the tension receptors in the intestinal wall are in series with the smooth muscle. This hypothesis is supported by the observations of Iggo (23), who

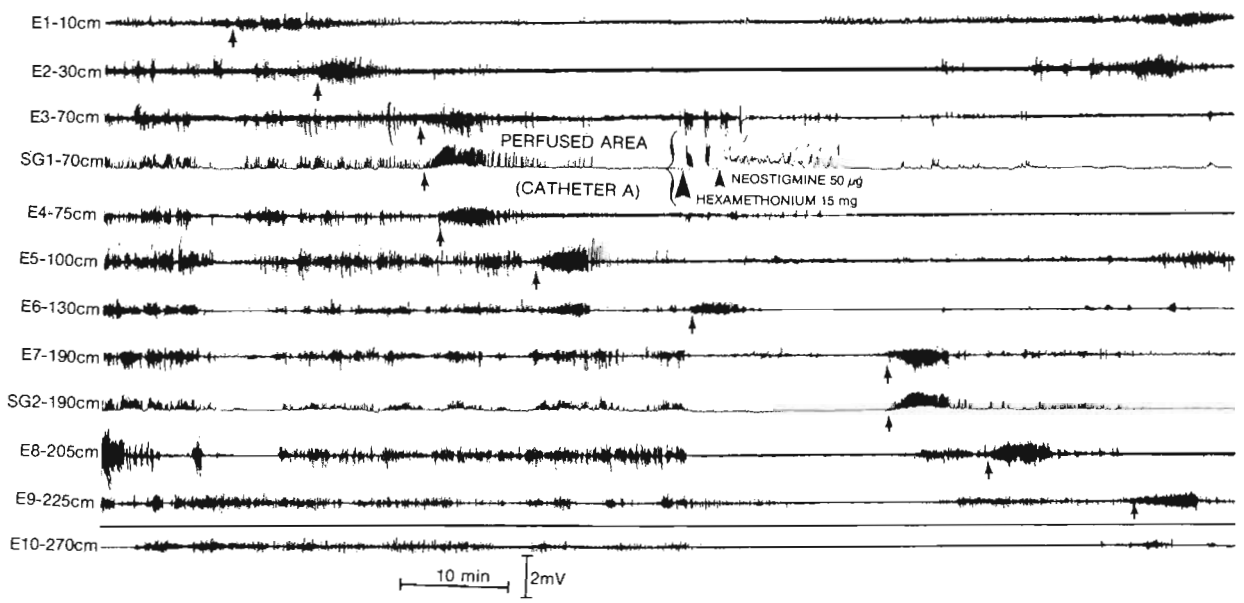

Figure 8. Hexamethonium injected before neostigmine administration at the proximal catheter site blocked the intestino-intestinal inhibitory reflex normally initiated by neostigmine. Hexamethonium had no effect on local response to neostigmine. Phase III activity migrated as usual but phase II activity was inhibited at the distal recording sites.

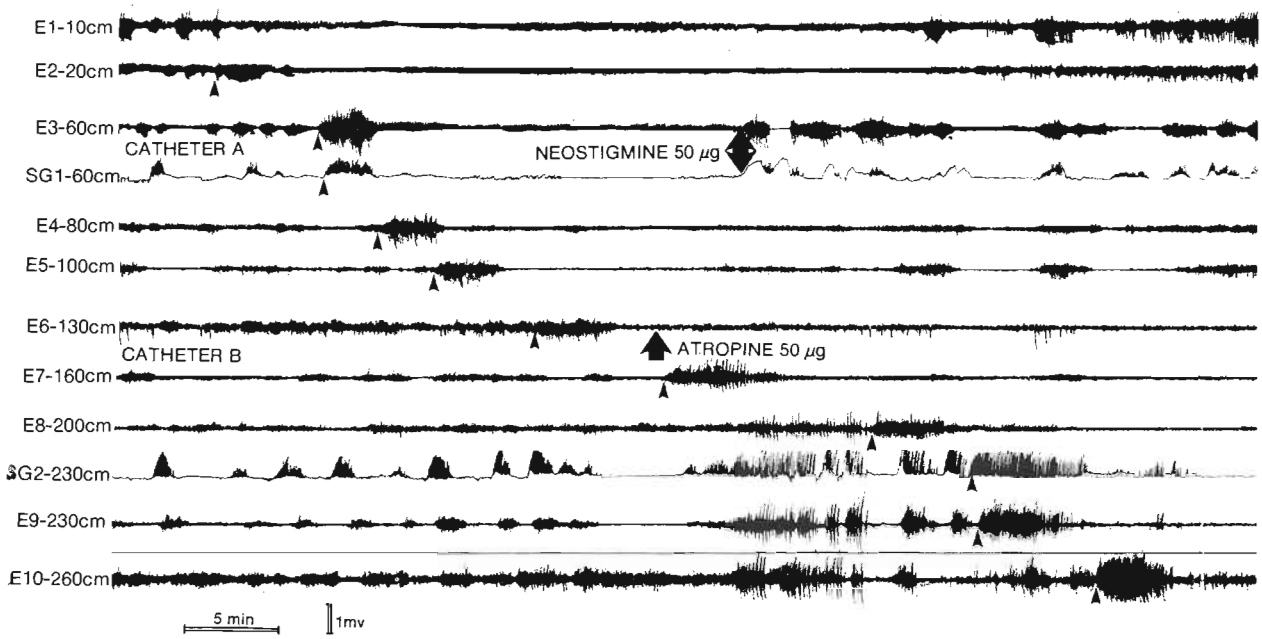

Figure 9. Atropine was injected at the middle catheter site 5 min before neostigmine injection at the proximal catheter site. Atropine blocked the intestino-intestinal inhibitory reflex normally initiated by neostigmine.

reported that contractions of isolated jejunal segments initiated discharges of impulses in afferent fibers. Iggo recorded these impulse discharges from the vagus nerve, but our findings suggest that these tension receptors may also initate impulse discharges for reflex action in the enteric neurons.

There may be different thresholds for initiating different types of reflexes by contractile activity. We

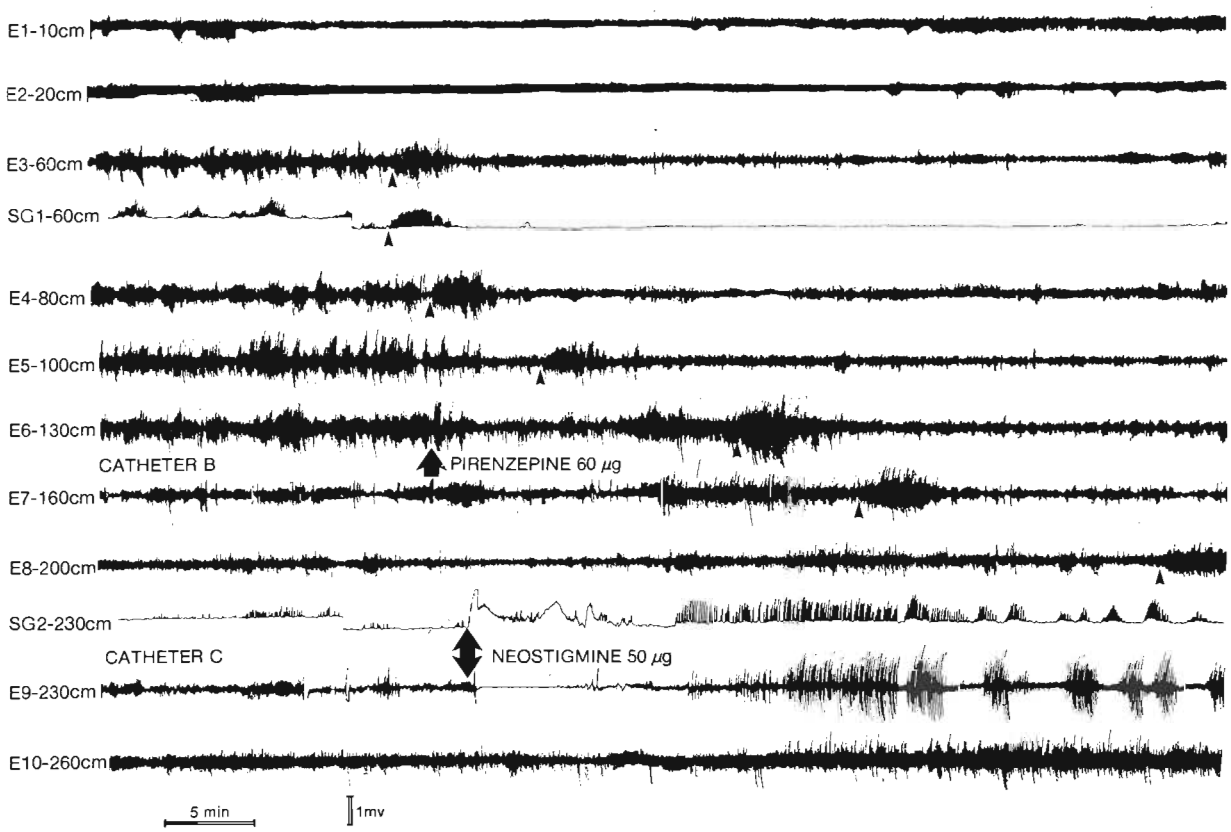

Figure 10. Pirenzepine was injected at the middle catheter site 2 min before neostigmine injection at the distal catheter site. Pirenzepine blocked the intestino-intestinal inhibitory reflex normally initiated by neostigmine.

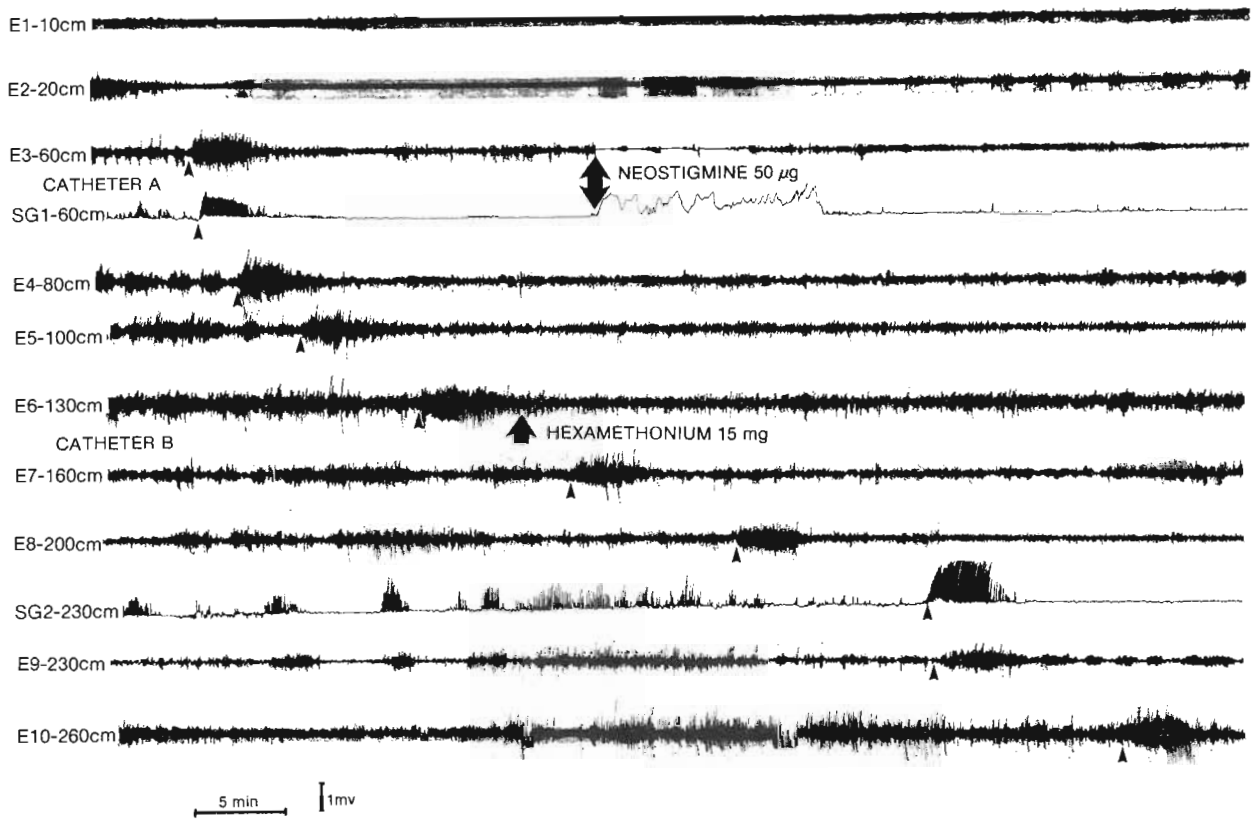

Figure 11. Hexamethonium was injected at the middle catheter site 4 min before neostigmine injection at the proximal catheter site. Hexamethonium blocked the intestino-intestinal inhibitory reflex normally initiated by neostigmine.

reported earlier that regular large-amplitude contractions during phase III activity that persist for several minutes may inhibit motor activity at proximal sites to produce phase I activity (24). This type of reflex inhibition is effective only in the orad direction because phase II activity is present distal to phase III activity. Our present findings show that long-duration spasmodic contractions of the intestinal wall may inhibit contractile activity in both the orad and aborad directions. In contrast, regular low-amplitude and intermittent contractions during phase II activity in the fasted state, and similar contractions during the fed state, may not initiate a reflex because the tension receptors are not stretched to or above the threshold level.

Pirenzepine and 4-DAMP are preferentially selective antagonists of muscarinic M_1 and M_2 receptors (14–16,25,26). The M_1 muscarinic receptors reside on the ganglia, whereas M_2 muscarinic receptors are located on the smooth muscle (27,28). The doses of these two antagonists used in our study seemed to act selectively because 4-DAMP administered at the middle site did not block the intestino-intestinal inhibitory reflex, but pirenzepine did. Likewise, 4-DAMP blocked the local contractile response to neostigmine, whereas pirenzepine enhanced it. Using these muscarinic antagonists as well as atropine and hexamethonium, we found that both long-duration contractions and intact synaptic transmission may be necessary for the initiation of an intestino-intestinal inhibitory reflex. The reflex was blocked when contractions were inhibited by 4-DAMP but presumably the ganglia were functioning. The intestino-intestinal inhibitory reflex was also not initiated when the muscarinic M_1 or nicotine receptors on the ganglia were blocked in the perfused segment by pirenzepine or hexamethonium, respectively.

Most intestino-intestinal inhibitory reflexes affecting remote sites have previously been reported to have an extrinsic neural pathway (19,21,29). For example, balloon distention in a Thiry–Vella loop inhibited motor activity in another Thiry–Vella loop or in the remainder of the small intestine (21,29). This inhibition was not affected by vagotomy but was blocked by splanchnicectomy. Our results show that intestino-intestinal inhibitory reflexes that affect remote sites may also have an intrinsic neural pathway. Transection and reanastomosis blocked these reflexes beyond the site of neural interruption. The intrinsic pathway seems to be synaptic because blocking of the nicotinic receptors on ganglia by hexamethonium at an intermediate site blocked the transmission of the reflexes beyond that site. The

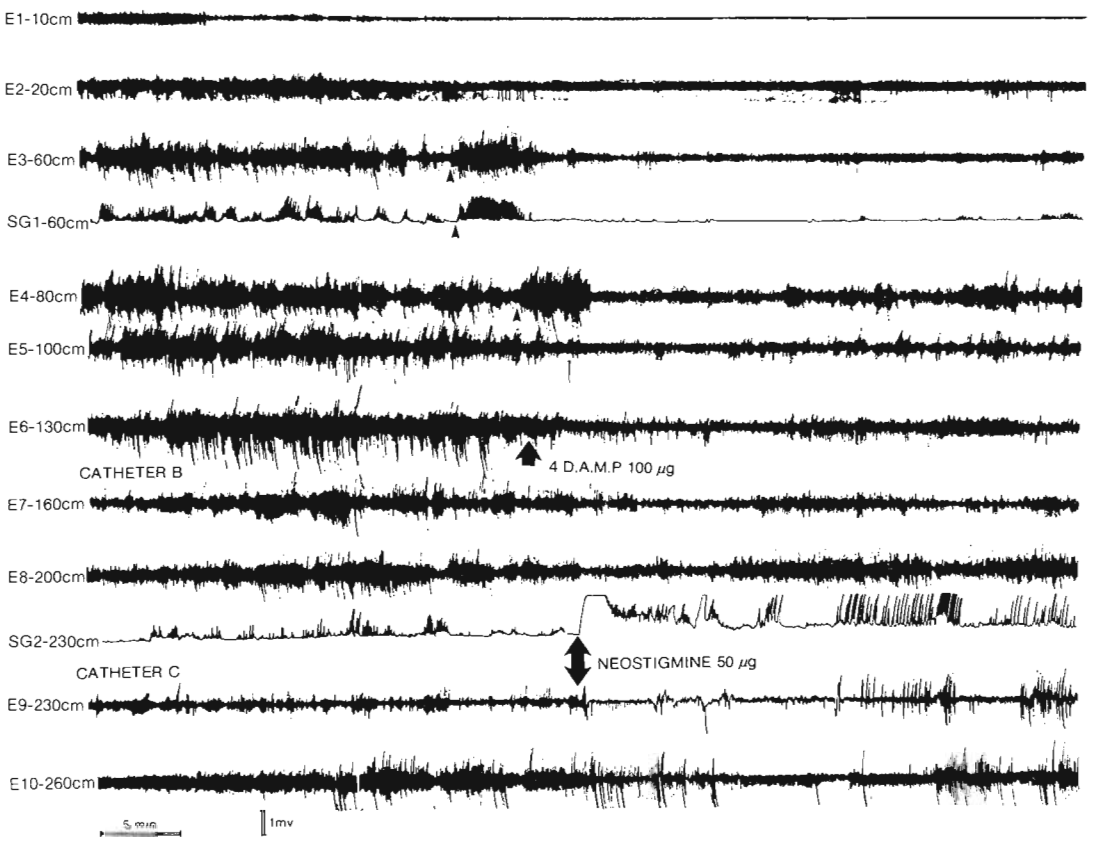

Figure 12. 4-Diphenylmethoxy-*N*-methylpiperidine methiodide was injected at the middle catheter site 3 min before neostigmine injection at the distal catheter site. 4-Diphenylmethoxy-*N*-methylpiperidine methiodide had no effect on the intestino-intestinal inhibitory reflex initiated by neostigmine. Phase III activity at electrode E4 was inhibited and its further migration stopped.

mechanism of blockade of reflexes by pirenzepine is not clear because M_1 receptors are thought to excite intrinsic inhibitory neurons (25–28). It seems that pirenzepine may have a more generalized effect on the ganglia. 4-Diphenylmethoxy-*N*-methylpiperidine methiodide, which acts preferentially at the M_2 muscarinic receptor on the smooth muscle, did not block the transmission of the intestino-intestinal inhibitory reflex, but atropine did. Presumably, atropine also affected synaptic transmission.

The orad and caudad transmission of the intestino-intestinal inhibitory reflex involves cholinergic pathways, but we do not know what is the lateral inhibitory neural pathway between the enteric plexuses and the smooth muscle. Postsynaptic cholinergic nerves are excitatory and adrenergic nerves do not have cell bodies in the intestinal wall. Therefore, a nonadrenergic, noncholinergic postsynaptic inhibitory nerve is likely to be involved in the lateral pathway for this inhibition. The inhibitory action of nonadrenergic noncholinergic nerves is well-established in other parts of the gastrointestinal tract, particularly the esophagus and the lower esophageal sphincter (26,30–32).

The myenteric plexuses constitute a highly organized network of different types of neurons (33–37). Using silver stain, Christensen et al. (38) reported that the myenteric plexuses in the small intestine consist of a network of interacting nerve bundles with ganglia at the intersections. Costa and Furness (39) reported that, based on their immunohistochemical studies, in the guinea pig small intestine, cell bodies that have vasoactive intestinal polypeptide, somatostatin, or serotoninlike immunoreactivity project their neuronal processes only in the caudad direction. Cell bodies that have substance P-like immunoreactivity project neuronal processes in both the orad and the aborad direction in the guinea pig and human small intestine. Cell bodies that have enkephalinlike immunoreactivity project their neuronal processes in the orad direction in the guinea pig small intestine. The organization and branching patterns of cholinergic neurons has not yet been reported using immunohistochemical techniques, but our results provide physiologic evidence that these neurons may project in both orad and aborad directions.

In conclusion, long intrinsic intestino-intestinal

inhibitory reflexes may be initiated by strong spasmodic contractions in the conscious dog. These reflexes utilize synaptic pathways with muscarinic M_1 and nicotine receptors in the enteric plexuses for the transmission of neural signals.

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