Properties of synaptic inputs from myenteric neurons innervating submucosal S neurons in guinea pig ileum

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Moore, B. A., and S. Vanner. Properties of synaptic inputs from myenteric neurons innervating submucosal S neurons in guinea pig ileum. Am. J. Physiol. Gastrointest. Liver Physiol. 278: G273–G280, 2000.—This study examined synaptic inputs from myenteric neurons innervating submucosal neurons. Intracellular recordings were obtained from submucosal S neurons in guinea pig ileal preparations in vitro, and synaptic inputs were recorded in response to electrical stimulation of exposed myenteric plexus. Most S neurons received synaptic inputs (>80% fast [f] excitatory postsynaptic potentials [EPSPs], ~30% slow [s] EPSPs) from the myenteric plexus. Synaptic potentials were recorded significant distances aboral (EPSPs, 25 mm; sEPSPs, 10 mm) but not oral to the stimulating site. When preparations were studied in a double-chamber bath that chemically isolated the stimulating “myenteric chamber” from the recording side “submucosal chamber,” all fEPSPs were blocked by hexamethonium in the submucosal chamber, but not by a combination of nicotinic, purinergic, and 5-hydroxytryptamine-3 receptor antagonists in the myenteric chamber. In 15% of cells, a stimulus train elicited prolonged bursts of fEPSPs (>30 s duration) that were blocked by hexamethonium. These findings suggest that most submucosal S neurons receive synaptic inputs from predominantly anally projecting myenteric neurons. These inputs are poised to coordinate intestinal motility and secretion.

intracellular recording; myenteric plexus; submucosal plexus; projections; communication

Since Bayliss and Starling (1) originally proposed that important intrinsic neural reflexes exist within the intestine, detailed descriptions of specific pathways have emerged. Most of this work has focused on the myenteric plexus, where interneurons form long polyneuronal pathways that coordinate ascending and descending motor reflexes throughout the intestine (28, 29). Detailed studies of the individual neurons forming these ascending and descending circuits have been described (10, 26, 30). Submucosal enteric reflexes have also been identified (4, 36), demonstrating that afferent and efferent elements confined to the mucosa and submucosa can control mucosal secretion and blood flow. These studies have significantly advanced our understanding of neural reflexes within the myenteric plexus controlling motility and within the submucosal plexus regulating secretion and blood flow, but there is considerably less information on how myenteric and submucosal reflexes may be coordinated.

Several lines of evidence suggest that important connections may exist between the myenteric and submucosal plexus. Anatomical connections were described as early as 1922 (18), when it was observed that myenteric neurons received synaptic “arborizations” from axons that originated from fiber tracts projecting from the submucosal plexus. Immunohistochemical analyses combined with lesioning studies identified several classes of neurons within the myenteric plexus that send out varicose processes that terminate within the submucosal plexus (5–7, 10, 11, 31). Indirect evidence that these neurons make synaptic contacts with submucosal neurons was obtained in electrophysiological studies in which it was shown that the numbers of cells receiving excitatory synaptic inputs in the submucosal plexus were decreased when axons from myenteric neurons had been selectively ablated (3). Several in vivo studies further strengthen the concept that important connections exist between the myenteric and submucosal plexus. Spontaneous jejunal motility was shown to be accompanied by fluctuations in transmural potential difference, suggesting that there is coordination of motility and secretion within the intestine (13, 27). In addition, secretory responses evoked by cholera toxin in the intestinal lumen (24) appear to be mediated by neural pathways that involve the myenteric plexus (16). Together, these in vitro and in vivo studies demonstrate that important connections exist between the myenteric and submucosal plexus, but there is little known about the cellular properties that underlie these connections.

Our recent studies (22, 36) as well as others (15) have demonstrated that neural reflexes exist within the submucosal plexus but that these circuits are confined to relatively short distances (a few millimeters) within the intestine (22). The objective of the current study was to address the possibility that these pathways may be coordinated by longer reflexes mediated through the myenteric plexus. Intracellular recordings were obtained from submucosal neurons in vitro in preparations containing both submucosal and myenteric plexuses, and synaptic inputs obtained in response to electrical stimulation of myenteric ganglia were examined. This enabled the direct study of the types of synaptic inputs received from the myentericplexus, the

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METHODS AND MATERIALS

Guinea pigs (140–225 g) of either sex were obtained from Charles River Laboratories (Quebec). Experiments were performed according to the guidelines of the Canadian Council of Animal Care. Animals were rendered unconscious by isoflurane inhalation and immediately killed by cervical transsection. The abdomen was opened, and segments of ileum were excised ~10 cm proximal to the ileocecal junction.

Dissection of conventional submucosal in vitro preparations (14) was modified to expose the submucosal plexus on one half and the myenteric plexus on the other. Briefly, segments of intestine were opened along the mesenteric border and pinned out flat with the mucosa facing upwards. The mucosa was stripped off one half to expose the submucosal plexus, and the mucosa, submucosa, and circular muscle were stripped off the other half to expose the myenteric plexus. The orientation of the preparation was marked by cutting a small slit in the aboral end. Preparations (~0.75 cm in width and 1.5–3.0 cm in length) were pinned out in small organ baths. The bath was continuously superfused at 35–36°C with oxygenated Krebs buffer containing (in mM) 126 NaCl, 2.5 NaH2PO4, 1.2 MgCl2, 2.5 CaCl2, 5 KCl, 25 NaHCO3, and 11 glucose. Nifedipine (1 µM) and atropine (1 µM) were added to inhibit muscle movement. All other drugs were added to the superfusate as required. In some studies, a double-chamber bath was employed as previously described (35). A small Plexiglas divider was placed over the tissue at the junction of the exposed submucosa and myenteric plexus, and silicone gel was placed between the divider and tissue to ensure that the ‘‘seal’’ between the chambers was checked after each experiment by determining whether there was leakage of trypan blue dye between the chambers.

Synaptic inputs to submucosal neurons were evoked by electrical stimulation of the submucosal and myenteric plexuses and recorded using conventional intracellular recording techniques. Stable impalements were obtained using glass microelectrodes filled with 2 M KCl with tip resistances of 70–120 MΩ. Changes in membrane potential were recorded with an Axoclamp 2A amplifier and displayed on a Gould TA240 chart recorder or digitized at 5–10 kHz using a Digidata 1200A acquisitions board and Axoscope software (Axon Instruments). S neurons were identified by recording synaptic inputs received in response to electrical stimulation of submucosal ganglia (14, 23) using a bipolar tungsten electrode placed one or two interconnecting ganglionic nodes from the recording site. Synaptic inputs originating from the myenteric plexus were activated using two types of stimulating electrodes. A focal stimulus was evoked using tungsten wire placed inside small glass focal stimulating electrodes (20–40-µm tip diameter) (see Fig. 1). A more global stimulus was evoked using a bipolar tungsten electrode modified to stimulate several myenteric ganglia simultaneously. These electrodes were fashioned from insulated tungsten wire (75-µm diameter) by bending a ~3 mm distal portion parallel with the preparation and removing the insulation from this segment (see Fig. 5).

Materials. TTX, hexamethionium, nifedipine, and atropine were supplied by Sigma. Suramin and tropisetron were from FBA (Germany) and Sandoz Pharma (Switzerland), respectively. All other materials were reagent grade.

RESULTS

Identification of submucosal S neurons. Submucosal neurons (n = 180) were classified as S-type neurons based on the types of synaptic inputs (14, 23) received following electrical stimulation of submucosal ganglia positioned one or two interconnecting ganglionic nodes from the intracellular recording site. All neurons were S-type neurons (resting membrane potentials ~49 to ~63 mV); 180 received both fast and slow excitatory postsynaptic potentials (EPSPs) of at least 5 mV in amplitude and 130 also received inhibitory postsynaptic potentials (IPSPs). There is some selection bias in these recordings, because impalements are most easily obtained from the center of ganglia where vasoactive intestinal polypeptide (VIP) immunoreactive neurons are predominantly found (2,9). Compared with conventional in vitro myenteric preparations in which the circular muscle is removed (23), muscle movement was a greater factor in the preparations used in this study because the circular muscle was still attached. In preliminary studies, stable impalements could not be maintained during electrical stimulation with only nifedipine added to the superfusate to inhibit muscle movement. Both nifedipine and atropine were required to suppress muscle movement adequately and were added to the superfusate in all subsequent studies.

Properties of synaptic inputs from anally projecting myenteric neurons. Initial studies examined synaptic inputs from myenteric neurons projecting short distances (~2 mm). The focal glass stimulating electrode was placed on a single myenteric ganglion in preparations in single-chamber baths and positioned ~0.5 mm oral from the cut edge of the submucosa. The intracellular electrode was positioned 0.5–1.5 mm aboral from the edge (Fig. 1). Intracellular recordings were obtained from 37 submucosal S neurons. Sixty-two percent (23/37) received synaptic inputs in response to stimulation of the myenteric ganglia. A single pulse (0.7-ms duration) elicited fast EPSPs in 41% (15/37; Fig. 2). In two cells, a single pulse failed to elicit a fast EPSP, but several fast EPSPs were consistently evoked during the pulse train (20 Hz, 400 ms). In those cells in which fast EPSPs were not recorded, cells were hyperpolarized to ~90 mV to ensure that small-amplitude fast EPSPs had not been overlooked. Pulse trains of electrical stimulation (20 Hz, 400 ms) elicited slow EPSPs (6.9 ± 0.8 mV, range 4–10 mV) in 34% (12/35) of cells. Slow EPSPs were recorded in 35% (6/17) of cells that also received fast EPSPs and in 33% (6/18) of cells that did not receive fast EPSPs. IPSPs were not elicited by stimulation of myenteric ganglia (20–30 Hz, 400 ms to 3-s duration).

Several steps were taken to confirm that the synaptic potentials originated from myenteric neurons. To ensure that synaptic responses were the result of action potential conduction in neurons, the effects of the sodium-channel blocker TTX were studied. Fast and...
slow EPSPs were abolished by TTX (1 µM; n = 4; Fig. 2). Fast EPSPs were also abolished by hexamethonium (200–500 µM; n = 4), but slow EPSPs were unaffected (Fig. 2B). The amplitude of the slow EPSP was reduced as the cell was current-clamped at membrane potentials closer to the potassium equilibrium potential and was increased when the cell was current-clamped at membrane potentials more positive than the resting potential (n = 3). These findings are consistent with previous findings characterizing slow EPSPs in the enteric nervous system (17). The possibility that current spread from the myenteric stimulating electrode might have activated submucosal neurons directly in the adjacent submucosa was also excluded in two separate experiments. In one series, the effects of moving the stimulating electrode were carefully studied by using a calibrated micromanipulator to record distances (Fig. 3). Synaptic potentials were abolished by raising the stimulating electrode a short distance (40–50 µm) off the myenteric ganglion (n = 4). Responses were restored when the electrode was lowered back onto the ganglion. When the electrode was moved laterally off the ganglion (50–100 µm) to a position closer to the submucosa (200–250 µm from the edge), synaptic potentials were also abolished (n = 4). Doubling the stimulus intensity failed to elicit a response. Our previous studies (22) and others (3, 9, 14, 33) have shown that most submucosal neurons receive IPSPs following submucosal fiber-tract stimulation. In the current study, none of the submucosal neurons received IPSPs following stimulation of the myenteric plexus, but the majority (130/180) received IPSPs when submucosal ganglia were activated. Previous studies (22) also showed that most submucosal neurons synapsing onto other submucosal neurons projected over very short distances (i.e., 1–2 mm). In the second series of experiments, the preparation was cut between the exposed submucosal and myenteric halves and the tissue pinned together. Myenteric stimulation failed to elicit synaptic potentials in these preparations (n = 3).

Distance and orientation of myenteric projections. The focal glass stimulating electrode was positioned oral to the submucosal intracellular recording electrode at increasing distances from the 2-mm site employed in the initial studies described above (Fig. 1). It was centered at ~4 and 6 mm from the recording electrode. The number of cells receiving synaptic inputs decreased significantly at increasing distances (Fig. 4). When the distance separating the stimulating and intracellular electrodes was ~4 mm, 28% (8/29) of S cells received fast EPSPs. At 6 mm of separation, 16% (5/31) received fast EPSPs. Only 5% (3/60) of S cells received slow EPSPs at these distances. When the...
The degree of current spread was assessed by positioning the tip of the stimulating electrode at three different distances from the edge of the submucosal plexus. When stimulating electrode was positioned 2 mm orally (see above). None of the neurons received slow EPSPs when the stimulating electrode was positioned aborally (Fig. 4).

The possibility that myenteric neurons projected over greater distances was examined using the modified bipolar stimulating electrode (see METHODS AND MATERIALS, Fig. 5). The degree of current spread was assessed by positioning the tip of the stimulating electrode 300–500 µm from the edge of the submucosal preparation. The preparation was cut at the junction of the exposed submucosal and myenteric halves, and tissue was repinned. Single pulses and trains of stimuli failed to elicit synaptic potentials in these preparations (n = 4), even with stimulus strengths two to five times those used in these experiments. Synaptic inputs were examined in response to myenteric stimulation with the tip of the stimulating electrode at three different distances orad to the intracellular electrode (ranges 3–6, 7–10, and 11–25 mm). Bipolar electrical stimulation elicited fast EPSPs in 67% (12/18) of S neurons at the 3- to 6-mm range, 73% (8/11) in the 7- to 10-mm range, and 82% (14/17) in the 11- to 25-mm range. The mean latencies from a single stimulus pulse to onset of fast EPSPs increased with distance between the stimulating and recording sites from 22 ± 1 ms at 3–6 mm to 67 ± 5 ms at 21–25 mm. These studies demonstrated that fast EPSPs could be elicited at the maximum distances studied (25 mm; Fig. 5). Slow EPSPs, however, were not observed beyond 10 mm. When the stimulating electrode was positioned aborally to the recording electrode at a maximum distance of ~15 mm, only 15% (3/20) of neurons received fast EPSPs and none received slow EPSPs (Fig. 5).

The effect of hexamethonium, tropisetron, and suramin on synaptic potentials. A double-chamber bath was used to chemically isolate these regions. Preparations and recording devices were as described in Fig. 1. Straight line with arrows designates direction and distance of stimulating electrode relative to position of intracellular electrode (position designated by thicker short line intersecting arrowed line). When stimulating electrode was positioned orad to recording electrode (orad to recording site), percentage of neurons receiving fast and slow EPSPs declined significantly by 6 mm. n = 14 or more neurons at each distance. * and ** compare proportion of neurons receiving fast and slow EPSPs with corresponding responses observed at 2 mm orad to recording site (P = 0.03 and 0.003, respectively). When stimulating electrode was positioned 2 mm aborally to recording electrode (aboral to recording site), only a small percentage of neurons received fast EPSPs. No slow EPSPs were recorded. † and ‡ compare proportion of neurons receiving fast and slow EPSPs with corresponding responses observed at 2 mm position orad to recording site (P = 0.04 and 0.009, respectively).
MYENTERIC SYNAPTIC INPUTS TO SUBMUCOSAL NEURONS

The mean amplitude of three or more fast EPSPs was calculated for seven neurons in the presence and absence of hexamethonium. In each case, there was no decrease in the mean amplitude of the fast EPSP when hexamethonium was added to the bath. Previous studies have shown that a subpopulation of myenteric neurons evoke noncholinergic fast EPSPs mediated by 5-hydroxytryptamine (HT) or ATP (8, 19). The effects of hexamethonium in combination with the 5-HT3 antagonist tropisetron and the purinergic (P2)-receptor antagonist suramin were studied in three cells, and these also had no effect on the fast EPSPs. The second pattern was observed in the remaining 48% (11/23) of neurons at the more distant ranges (Fig. 6B). In this pattern, fast EPSPs could not be elicited by a single stimulus pulse but were recorded in response to a pulse train. Once again, hexamethonium applied in the myenteric chamber failed to have a detectable effect on the number or amplitude of fast EPSPs (n = 9). Similarly, the combination of hexamethonium, tropisetron and suramin also had no effect (n = 2). The third pattern was associated with either of the first two and was characterized by a burst of fast EPSPs that persisted for up to 3 min after cessation of a pulse train (Fig. 6C, n = 6). These “run-on” fast EPSPs were almost completely blocked by the combination of hexamethonium, tropisetron, and suramin in three of four cells tested. In two of these cells in which hexamethonium alone could be tested, hexamethonium had the same effect.

All fast synaptic inputs were abolished when hexamethonium was added to the submucosal chamber (n = 11; Fig. 6A). The P2-receptor antagonist suramin (100 µM) plus tropisetron (1 µM) alone had no effect on synaptic inputs (n = 4). Slow EPSPs were recorded in 9% (4/43) of neurons and were only elicited by a pulse train. Fast EPSPs were also recorded in all cases except one in which only a slow EPSP was elicited. Hexamethonium, suramin, and tropisetron applied to either chamber (myenteric, n = 3; submucosal, n = 2) had no effect on the slow EPSPs.

TTX (1 µm) superfused into the myenteric chamber blocked all synaptic responses elicited by myenteric stimulation (n = 3).

DISCUSSION

Neural projections from the myenteric plexus that innervate submucosal neurons have been demonstrated in a number of previous studies, but the nature and extent of this connection have been unclear. These pathways were implicated in studies in vivo (13, 27) in which coordination of motility and secretory activity was mediated by enteric reflexes. Anatomical studies identified a number of projections from the myenteric plexus to the submucosal plexus that could fulfill such a role (7, 10, 11, 31), and electrophysiological studies in vitro provided indirect evidence for synaptic connections (5). In the latter study, the proportion of synaptic connections in the submucosal plexus decreased following selective ablation of axons from the myenteric plexus, but the organization and extent of these connections could not be determined. The present study provides direct evidence of fast and slow EPSPs from myenteric neurons innervating submucosal neurons and suggests that most submucosal neurons receive inputs from the myenteric plexus. Given this high degree of coupling between the myenteric and submucosal plexuses, it appears that myenteric neurons are poised to play a major role in modulating the function of the submucosal plexus.
The interpretation of the results of this study was influenced by several considerations. Firstly, due to the close association between the myenteric and submucosal plexus, it was not possible to stimulate myenteric neurons directly above the site where the intracellular impalement was made. Similarly, the partition for the double-chamber bath (Fig. 5) could not be positioned directly above the site of impalement. Therefore, projections from myenteric neurons, whose cell bodies were located directly on top of the recording site in the submucosal plexus, could not be directly evaluated. The second issue was the use of the muscarinic antagonist atropine to inhibit muscle movement. Previous studies in the myenteric plexus have shown that the early phase of the slow EPSPs evoked by repetitive stimuli can be inhibited by muscarinic antagonists (25), suggesting that a component of the slow EPSP is cholinergic, acting at muscarinic receptors. In functional studies, however, muscarinic antagonists appear to have little impact on the activation of interneuronal pathways (34).

Fast EPSPs were elicited from myenteric neurons located up to 25 mm oral from the recording site, the maximum distance that could be examined in our study. Previous studies in the myenteric plexus have described chains of interneurons that form long polysynaptic pathways (20, 26). Moreover, single interneurons have been found that project for long distances, as much as 100 mm (30). In the present study, none of the fast EPSPs elicited by single stimuli in the myenteric plexus was blocked by the combination of nicotinic, purinergic, and 5-HT_3-receptor antagonists when applied in the myenteric chamber (see Fig. 5), suggesting that these potentials originated from myenteric neurons with long projections that did not synapse with other myenteric neurons in this chamber. Vagal fibers travelling through the myenteric to the submucosal plexus cannot be implicated, because previous anatomical (12) and electrophysiological studies (14) suggest that vagal fibers do not project to the submucosal plexus in the ileum (32). Most of the fast EPSPs, particularly those that originated from neurons within 6 mm, could be elicited by a single stimulus pulse and had very reproducible latencies during stimulus trains. This finding is consistent with a model in which individual myenteric neurons project directly from the myenteric plexus to the submucosal neuron from which the synaptic potential was recorded. It cannot be ruled out, however, that these neurons synapse with other myenteric neurons in the submucosal chamber that, in turn, descend directly to the submucosal plexus (see above). Alternatively, the myenteric neuron synapses...
with a submucosal neuron that, in turn, projects to the submucosal neuron from which the intracellular recording was obtained. In a smaller percentage of cells, clearer evidence for polysynaptic pathways emerged. In ~50% of cells positioned >6 mm away from the stimulating electrode, a single stimulus failed to elicit a fast EPSP, but fast EPSPs were evident during a train of stimuli. The number and distribution of the fast EPSPs elicited during repeated pulse train were variable (Fig. 6B), suggesting that multiple pathways were being differentially activated. These fast EPSPs were also unaffected by antagonists in the myenteric chamber and thus must presumably result from activation of myenteric neurons that, in turn, activated either myenteric neurons in the submucosal chamber and/or submucosal neurons projecting to other submucosal neurons. Further evidence for polysynaptic pathways was observed in a smaller subset of neurons that displayed a prolonged discharge of fast EPSPs following a stimulus train (see Fig. 6C). These were inhibited by hexamethonium in the myenteric chamber, suggesting that they originated from prolonged excitability in cholinergic polysynaptic pathways within the myenteric plexus. Previous studies of neural reflexes mediated solely by submucosal neurons suggest that projections between submucosal neurons are largely confined to distances of a few millimeters (22, 36). The pathways described in this study demonstrate that much longer neural reflexes coordinating the activity of submucosal neurons exist and that they are mediated through the myenteric plexus.

Noncholinergic slow EPSPs observed in this study were elicited only by stimulation at relatively close distances to the submucosal recording site, suggesting that these neurons projected shorter distances compared with those eliciting fast EPSPs. Although it is possible that polysynaptic pathways were activated in the myenteric plexus, particularly as these synaptic potentials were only elicited with a pulse train, this seems less likely given that hexamethonium had no effect on these potentials when placed in either the myenteric or submucosal chamber (see Fig. 2). Several substances present in enteric neurons can mimic these potential changes when applied exogenously, including substance P, 5-HT, and VIP (21, 33), and immunohistochemical studies suggest these putative neurotransmitters are contained in several classes of myenteric neurons that project to the submucosal plexus (5, 6, 10). Slow EPSPs play an important role in controlling cellular excitability (23, 37), and, given the large numbers of submucosal neurons receiving slow EPSPs from the myenteric plexus, these projections should have a major impact on modulating the motor functions of the submucosal plexus.

There were significantly fewer synaptic potentials elicited by stimulation of myenteric ganglia located aboral to the recording site compared with those positioned orad (see Figs. 4 and 5), suggesting a predominant orad-to-aboral polarity to the myenteric projections. With the selection bias inherent to intracellular recording techniques in the submucosal plexus, it remains to be determined whether this observation extends to all subclasses of submucosal neurons or is confined to the population examined in this study. This population is likely comprised predominantly of VIP-immunoreactive secretomotor neurons given the properties of these cells. Firstly, previous studies (2, 9) suggest that IPSPs are largely confined to these neurons, and the majority of submucosal neurons in this study exhibited IPSPs when the submucosal plexus was stimulated. In addition, intracellular recording has an inherent bias toward these neurons because they are preferentially located in the center of the ganglia (2) where intracellular impalements tend to be made. Interestingly, a similar orad-to-aboral orientation has been described for synaptic connections to these neurons from other cholinergic submucosal neurons (22). This orad-to-aboral organization of inputs from the myenteric to submucosal plexus may be important for coordinating digestion within the intestine. For example, activation of distal submucosal secretomotor neurons could result in “priming” of luminal secretions downstream of a bolus as it is propelled distally within the intestine.

Previous studies have described slow IPSPs in the submucosa that are thought to originate from axonal projections from myenteric neurons (2). The neurotransmitters that mediate these responses are unknown, but potential candidates include somatostatin and/or enkephalin. In the current study, IPSPs were not recorded following myenteric stimulation. It is possible that the myenteric neurons that elicit these slow IPSPs have very short projections from cell bodies located in myenteric ganglia directly above the submucosal ganglia to which they project. Both somatostatin and enkephalin-immunoreactive myenteric neurons with short projections to the submucosal plexus have been reported (7, 11). Taken together, it seems unlikely that there are inhibitory neural pathways projecting for significant distances within the myenteric plexus before descending to the submucosal plexus, but it remains possible that a population of inhibitory neurons exist with very short projections to the submucosal ganglia.

In summary, this study suggests that most submucosal S neurons receive fast and/or slow EPSPs from myenteric neurons and that these neurons project for significant distances aborally within the myenteric plexus. The majority of these S-type submucosal are motoneurons that activate secretion within the mucosa (4, 9). The current findings suggest that reflexes mediated through the myenteric plexus could have a profound influence on the regulation of these functions and are poised to coordinate the regulation of motility and secretion.
REFERENCES


