Enhanced excitability of guinea pig inferior mesenteric ganglion neurons during and following recovery from chemical colitis

David R. Linden
Department of Physiology and Biomedical Engineering and Enteric NeuroScience Program, Mayo Clinic College of Medicine, Rochester, Minnesota

Submitted 30 May 2012; accepted in final form 2 September 2012

Enhanced excitability of guinea pig inferior mesenteric ganglion neurons during and following recovery from chemical colitis. Am J Physiol Gastrointest Liver Physiol 303: G1067–G1075, 2012. First published September 6, 2012; doi:10.1152/ajpgi.00226.2012.—Postganglionic sympathetic neurons in the prevertebral ganglia (PVG) provide ongoing inhibitory tone to the gastrointestinal tract and receive innervation from mechanosensory intestinofugal afferent neurons primarily located in the colon and rectum. This study tests the hypothesis that colitis alters the excitability of PVG neurons. Intracellular recording techniques were used to evaluate changes in the electrical properties of inferior mesenteric ganglion (IMG) neurons in the trinitrobenzene sulfonic acid (TNBS) and acetic acid models of guinea pig colitis. Visceromotor IMG neurons were hyperexcitable 12 and 24 h, but not 6 h, post-TNBS during “acute” inflammation. Hyperexcitability persisted at 6 days post-TNBS during “chronic” inflammation, as well as at 56 days post-TNBS when colitis had resolved. In contrast, there was only a modest decrease in the current required to elicit an action potential at 24 h after acetic acid administration. Vasomotor neurons from inflamed preparations exhibited normal excitability. The excitatory effects of XE-991, a blocker of the channel that contributes to the A-type potassium current, and heteropodatoxin-2, a blocker of the channel that contributes to the A-type potassium current, were unchanged in TNBS-inflamed preparations, suggesting that these currents did not contribute to hyperexcitability. Riluzole, an inhibitor of persistent sodium currents, caused tonic visceromotor neurons to accommodate to sustained current pulses, regardless of the inflammatory state of the preparation, and restored a normal rheobase in neurons from TNBS-inflamed preparations but did not alter the rheobase of control preparations, suggesting that enhanced activity of voltage-gated sodium channels may contribute to colitis-induced hyperexcitability. Collectively, these data indicate that enhanced sympathetic drive as a result of hyperexcitable visceromotor neurons may contribute to small bowel dysfunction during colitis.

INFLAMMATION OF THE GASTROINTESTINAL tract is associated with numerous changes in the neuromuscular apparatus. Within the region of inflammation, there is generally smooth muscle hyperplasia with reduced contractility (11, 20, 43, 45, 47), enhanced excitability of intrinsic primary afferent neurons (32, 33, 46), and neuronal cell loss (12, 31). In addition to neuromuscular plasticity within the region of inflammation, there are often changes in neuromuscular function outside this area. These include reduced small bowel motility or intestinal secretory dysfunction during localized colitis in humans (2, 9, 35, 37, 48, 58) and in experimental models (3, 4, 10, 23, 24, 44). Systemic inflammatory cytokines or other endocrine signals may directly stimulate the upper bowel (4), but it is equally likely that there is a neural mechanism for altered upper gut dysfunction. One potential neural mechanism that could contribute to changes in gastrointestinal function is the enhanced excitability of extrinsic primary afferent neurons, the cell bodies of which reside in dorsal root ganglia (8, 42). While the direct effect of enhanced excitability in this population of neurons could be enhanced nociception (7), dorsal root ganglion neurons also initiate axonal, spinal, and supraspinal reflexes (18, 21, 29), which could contribute to bowel dysfunction beyond the inflamed region. Another population of neurons, the postganglionic sympathetic neurons located within the prevertebral ganglia (PVG), could also contribute to distant changes in bowel function during localized colitis.

PVG neurons provide sympathetic input to the gastrointestinal tract, pancreas, spleen, liver, and urogenital organs. In the gastrointestinal tract, PVG neurons control secretory, absorptive, vascular, and motor functions. Vasomotor, sometimes called vasoconstrictor, neurons in the PVG innervate and regulate the vasculature in the wall of the gastrointestinal tract and are similar in many respects to postganglionic sympathetic neurons in paravertebral sympathetic ganglia by serving as relays for preganglionic spinal input. Conversely, visceromotor neurons in the PVG regulate secretion, absorption, and motility of the gastrointestinal tract and integrate relatively weak, convergent synaptic input from peripheral and central preganglionic nerves.

Recently, Dong et al. (16) demonstrated that trinitrobenzene sulfonic acid (TNBS)-induced localized inflammation of the guinea pig ileum causes hyperexcitability of visceromotor neurons within the celiac ganglion. They suggested that visceromotor neurons might be differentially affected, because these neurons receive intestinofugal input from myenteric neurons within the inflamed region. Density of intestinofugal afferent neurons is greater in the colon than in the ileum, and these neurons innervate visceromotor neurons throughout the PVG (38, 39). This anatomic arrangement suggests that the colonofugal neurons inform the upper gut regarding the state of the distal bowel. The aim of this study was to test the hypothesis that colonic inflammation alters the excitability of inferior mesenteric ganglion (IMG) neurons. Two models of guinea pig experimental chemical colitis, intracolonic TNBS (a hapten) and intracolonic acetic acid, were used. Enhanced excitability was observed in visceromotor neurons of the IMG, so pharmacological approaches were used to determine potential mechanisms contributing to the excitability.

MATERIALS AND METHODS

Inflammatory models. All methods were approved by the Mayo Clinic Animal Use and Care Committee and are consistent with the
guidelines set forth by the National Institutes of Health, the US Department of Agriculture, and the Association for Assessment and Accreditation of Laboratory Animal Care. Two models of guinea pig colitis were used. The first model was induced by a single administration of 0.3 ml of TNBS (27 mg/ml) in 30% ethanol via enema 7 cm proximal to the anus. After the enema, animals were returned to a controlled environment for 6 h, 12 h, 24 h, 6 days, or 56 days. At the predetermined time, animals were euthanized by CO2 inhalation. Inflammatory damage was assessed as previously described (31), with the minor difference that tissue thickness was assessed in the typically less edematous region just proximal to the segment used in electrophysiological recordings (see below) and ulcers were visualized through the serosa as darkened circumferentially oriented lines, rather than through an opening in the lumen to observe the mucosa. These modifications were necessitated by the requirement to keep the damaged segment of colon intact for the electrophysiology preparation (see below). Control animals remained naive to treatment until euthanasia. The second model of colitis was induced by a single administration of acetic acid (4% vol/vol in water) via enema 7 cm proximal to the anus. Animals were returned to a controlled environment for 24 h and then euthanized by CO2 inhalation.

**Tissue preparation and electrophysiology.** After euthanasia, a segment of the distal colon, 4 cm proximal of the pelvic brim to the pelvic brim, along with the colonic mesenteric artery, abdominal aorta, and iliac artery, was removed and placed in ice-cold Krebs solution (in mM: 120 NaCl, 5.9 KCl, 2.5 CaCl2, 1.2 MgCl2, 15.5 NaHCO3, 1.2 NaH2PO4, and 11.4 glucose, aerated with 97% O2-3% CO2) for further dissection. For visualization of the IMG, the inferior mesenteric artery was cut at the aorta, and the aorta and vena cava were removed. The intermesenteric nerve was sectioned inferior to the superior mesenteric ganglion. The hypogastric nerves were sectioned superior to the pelvic ganglia. The preparation was transferred to a two-chamber recording dish, the colon on one side and the IMG on the other, with each chamber continuously perfused with 37°C aerated Krebs solution. Colonic nerves and the inferior mesenteric artery were draped over the barrier between the two chambers and kept moist with a small piece of absorbent paper. The anterior and posterior lobes of the IMG were visualized at ×30 magnification with a Wild dissecting microscope, and individual neurons were randomly impaled with glass microelectrodes filled to the shoulder with 1% (wt/vol) Neurobiotin (Vector Laboratories, Burlingame, CA) in 1 M KCl or with 3.0 M KCl; electrode resistance was 50–150 MΩ.

Increased frequency of synaptic input in response to distension of the colonic segment was used to identify visceromotor neurons. The colon was distended by 1.5 ml of air via a catheterized syringe from the anal end. Resting membrane potential was measured as the difference between the potential before impalement and the stable potential reached following impalement (usually within the first 3 min of recording). With use of Ohm’s law, membrane resistance was calculated from the average ratio of the electrotonic potential difference and the injected current for three current pulses of 0.5 to 100 pA. The threshold current or rheobase was measured as the current required to elicit a single action potential at the onset of a 0.5-s square-wave current pulse after the current was increased from zero, decreased to failure, and increased again. Stimuli were delivered at a frequency of 0.2 Hz. Immediately after determination of the threshold current, the current was increased to 2.5 times the threshold current, and the maximum number of action potentials elicited by a single 0.5-s square-wave current pulse was recorded.

The effect of drug treatments, which were delivered by the perfusion setup, on the excitability of neurons was determined by three measurements. 1) The effect of the drug on the resting membrane potential (depolarization) was measured as the potential difference between the mean potential just before drug application and the peak potential reached after drug application. For XE-991 and heteropodatoxin-2, this occurred within 2 min. For riluzole, maximum depolarization was reached after 5 min. 2) The number of action potentials elicited by a 5-s square-wave pulse of depolarizing current at 2.5 times the threshold current was measured before (basal) and ±8 min after drug application. 3) A reassessment was performed of the threshold current, which was determined as described above. All recordings lasted ≥8 min in the presence of drug. Only rarely did impalements last for washout of the drug, and they did not reverse the effects during the recording. In cells recorded in the same preparations subsequent to drug application, values for resting membrane potential, threshold current, and number of action potentials were not outside the range of values for their group after ~45 min of drug washout. Cells recorded within 45 min of drug washout were not included in any analysis.

**Chemicals.** All chemicals were purchased from Sigma Aldrich (St. Louis, MO). XE-991 and riluzole were dissolved in DMSO and diluted to the working concentrations in Krebs solution. Vehicle (0.01% DMSO) had no effect on passive or active properties of the impaled neurons (data not shown). Heteropodatoxin-2 was dissolved in water and diluted to the working concentration in Krebs solution. Drugs were delivered to the chamber of the recording dish that contained the IMG by switching the reservoir from which the superfusion pump drew.

**Statistical analyses.** All statistical analyses were completed using GraphPad Prism software. For all tests, P < 0.05 was considered significant.

**RESULTS**

Intracellular recordings were obtained from 220 neurons in 66 preparations. Neurons were classified as visceromotor (tonic) or vasomotor (phasic) on the basis of responses to depolarizing current delivered through the recording electrode and the response or lack of response to colonic distension, respectively, similar to previous descriptions (13, 27). In all, 202 visceromotor neurons (92%) and 18 vasomotor neurons (8%) were randomly impaled from the anterior or posterior lobes of the guinea pig IMG.

*Hapten-induced colitis causes hyperexcitability of visceromotor neurons.* A single enema of TNBS caused robust, reproducible damage to a discrete region of the distal colon. Gross damage scores revealed a significant increase in inflammatory damage as early as 6 h post-TNBS that resolved by 56 days: 0.74 ± 0.02 (n = 23) in control and 7.6 ± 0.6 (n = 3) at 6 h, 7.7 ± 0.6 (n = 2) at 12 h, 8.3 ± 0.3 (n = 16) at 24 h, 5.2 ± 0.3 (n = 14) at 6 days, and 0.83 ± 0.07 (n = 5) at 56 days post-TNBS (P < 0.001 by ANOVA with Newman-Keuls multiple comparison test). These data are quite similar to a previous study using the same model and time course (31). Acetic acid treatment also caused robust damage to a discrete region of the distal colon that was reflected in a significant increase in the gross damage score (8.6 ± 0.4, n = 3) compared with control animals (0.74 ± 0.02, n = 23) but was not different from the TNBS model at the same time point (8.3 ± 0.3, n = 16, P > 0.05 by ANOVA with Newman-Keuls multiple comparison test). Not reflected in the score is the relative degree of hyperemia, which appeared to be greater in guinea pigs treated with acetic acid.

Fifty-eight visceromotor neurons and 5 vasomotor neurons were recorded from 17 preparations from control animals. The electrophysiological properties of these neurons were similar to previous reports (13, 27, 40). There were time-dependent changes in the excitability of visceromotor neurons following induction of colitis with TNBS (Fig. 1). The current required to elicit an action potential (rheobase) was significantly lower in neurons recorded from animals at 12 h, 24 h, 6 days, and 56 days after TNBS administration. There was no difference in
rheobase between neurons recorded from guinea pigs at 6 h after TNBS and neurons from control preparations. The reduced rheobase in visceromotor neurons was likely not due to changes in resting membrane potential or membrane resistance, as these measurements were not different between groups (Table 1). The number of action potentials elicited in visceromotor neurons in response to a 0.5-s depolarizing current pulse set at 2.5 times the threshold current was also increased at 12 h, 24 h, 6 days, and 56 days, but not 6 h, after TNBS administration (Fig. 1). The decreased rheobase and increased number of action potentials indicated a state of hyperexcitability in visceromotor neurons that began as early as 12 h after the inflammatory insult and lasted for as long as 8 wk, when inflammatory damage in the colon was no longer grossly evident.

In contrast to the TNBS model of colitis, the excitability of visceromotor neurons was relatively unchanged 24 h following acetic acid administration (Fig. 1). Recordings of 13 visceromotor neurons from guinea pigs at 24 h after acetic acid administration were compared with recordings of 21 neurons from 6 preparations from control guinea pigs. There was no difference in the rheobase between these two groups of neurons. There was a significant increase in the mean number of action potentials recorded in response to a 0.5-s depolarizing current pulse set at 2.5 times the threshold current. This increase in action potentials, however, was relatively low compared with the increase caused by TNBS.

While recordings from vasomotor neurons were rare compared with recordings from visceromotor neurons, five cells were recorded from control preparations, six cells were recorded from preparations at 24 h after TNBS administration, four cells were recorded from preparations at 6 days after TNBS administration, and two cells were recorded from preparations at 56 days after TNBS administration. There was no difference in the rheobase or the number of action potentials elicited by 2.5 times the threshold current (Fig. 2). There were also no differences in the resting membrane potential or the membrane resistance between these groups (Table 2). There was a single recording of a vasomotor neuron from a preparation obtained from a guinea pig at 24 h after administration of acetic acid. The resting membrane potential (~52 mV), membrane resistance (61 MΩ), rheobase (537 pA), and number of action potentials (1) were not

Table 1. Passive electrical properties of visceromotor inferior mesenteric ganglion neurons from control and inflamed preparations

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 58)</th>
<th>6 h (n = 6)</th>
<th>12 h (n = 6)</th>
<th>24 h (n = 50)</th>
<th>6 days (n = 40)</th>
<th>56 days (n = 8)</th>
<th>Control (n = 21)</th>
<th>24 h (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting membrane potential, mV</td>
<td>−57 ± 1</td>
<td>−60 ± 3</td>
<td>−55 ± 1</td>
<td>−57 ± 1</td>
<td>−56 ± 1</td>
<td>−52 ± 2</td>
<td>−57 ± 2</td>
<td>−56 ± 2</td>
</tr>
<tr>
<td>Membrane input resistance, MΩ</td>
<td>83 ± 6</td>
<td>111 ± 33</td>
<td>62 ± 3</td>
<td>81 ± 5</td>
<td>71 ± 6</td>
<td>78 ± 13</td>
<td>89 ± 10</td>
<td>89 ± 12</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of cells. There were no differences in passive electrical properties of visceromotor neurons between control and inflamed tissue. Neurons from trinitrobenzene sulfonic acid (TNBS)-treated preparations were compared with controls using ANOVA. Neurons from acetic acid (AA)-treated preparations were compared with controls using t-test (all P > 0.05).
outside the range of values obtained for the other 17 vaso-
motor neurons.

Inhibition of KCNQ2/3 does not contribute to visceromotor hyperexcitability. A common mechanism of increasing the excitability of postganglionic sympathetic neurons is inhibition of potassium (KCNQ) channels that contribute to the M-type current (19, 26, 54, 55). If KCNQ channel activity in visceromotor neurons is constitutively downregulated following TNBS-induced colitis, it is reasonable to hypothesize that an inhibitor of the M-type current would be less effective in altering the excitability of these neurons. The KCNQ2/3 channel blocker XE-991 (55, 57) was used to block the M-type current. Six neurons recorded from control preparations were compared with a group containing four neurons recorded from preparations at 24 h after TNBS administration and two neurons recorded from preparations at 6 days after TNBS administration compared with controls: $P > 0.05$ (by ANOVA).

Inhibition of Kv4 does not contribute to visceromotor hyperexcitability. Another mechanism of increasing the excitability of postganglionic sympathetic neurons is receptor-mediated blockade of the A-type potassium current ($I_A$) (13, 26, 54). The Kv4 channel contributes to $I_A$ in sympathetic neurons (15, 36). Similar to testing the contribution of KCNQ2/3 channels to the depolarization of neurons during slow synaptic transmission, 20 μM XE-991 depolarized visceromotor neurons by $-6 \text{ mV}$. This level of depolarization was the same in neurons from control and inflamed preparations. XE-991 (20 μM) significantly reduced the rheobase of neurons from control and inflamed preparations by 33% and 47%, respectively. These data suggest that KCNQ2/3 channel activities contribute to the resting membrane potential of visceromotor neurons and also support the concept that KCNQ2/3 channel activity is similar in the control and inflamed preparations.

Table 2. Passive electrical properties of vasomotor inferior mesenteric ganglion neurons from control and inflamed preparations

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 5)</th>
<th>24 h (n = 6)</th>
<th>6 days (n = 4)</th>
<th>56 days (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting membrane potential, mV</td>
<td>$-61 \pm 2$</td>
<td>$-66 \pm 3$</td>
<td>$-63 \pm 2$</td>
<td>$-61 \pm 1$</td>
</tr>
<tr>
<td>Membrane input resistance, MΩ</td>
<td>$85 \pm 6$</td>
<td>$86 \pm 6$</td>
<td>$71 \pm 6$</td>
<td>$78 \pm 13$</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of cells. There were no differences in passive electrical properties of vasomotor neurons between control and inflamed tissue ($P > 0.05$ by ANOVA).
one neuron recorded from a preparation at 6 days after TNBS (Fig. 4). In both groups of neurons, heteropodatoxin-2 (50 nM) caused an increase in the number of action potentials elicited by 5-s depolarizing current pulses set at 2.5 times threshold current. While there were more action potentials in the neurons from inflamed preparations, consistent with hyperexcitability in these cells, the proportional increase in the number of action potentials was similar between the inflamed (135% of baseline) and control (136% of baseline) preparations. Heteropodatoxin-2 (50 nM) depolarized visceromotor neurons by 3–4 mV. This level of depolarization was not different between neurons from control and inflamed preparations, which also supports the concept that KV4 channel activity is similar in the control and inflamed preparations. Heteropodatoxin-2 (50 nM) did not alter the rheobase of neurons from control or inflamed preparations.

**Effect of the persistent sodium channel blocker riluzole.** Riluzole (5, 41) has been demonstrated to reduce persistent sodium channel currents with greater potency than its reduction of transient peak currents in nonadapting postganglionic sympathetic neurons of the rat and mouse superior cervical ganglion (30). Riluzole was used to test the hypotheses that 1) it affects tonic firing of visceromotor neurons in the guinea pig IMG and 2) its effects are greater in neurons from inflamed guinea pigs. Four neurons from control preparations and four neurons from preparations at 24 h after TNBS were recorded in these experiments. Riluzole (10 μM) inhibited tonic firing of visceromotor neurons from control and inflamed preparations (Fig. 5). As observed in the previous experiments, there were more action potentials in response to a 5-s depolarizing current pulse set at 2.5 times the threshold current in the neurons from inflamed preparations, consistent with hyperexcitability in these cells. After riluzole application, the mean number of action potentials elicited in both groups was the same. Riluzole depolarized the neurons by ~2 mV, which was not different between neurons from control and inflamed preparations. The lowest current required to elicit an action potential in visceromotor neurons from inflamed preparations was increased following the application of riluzole, yet riluzole did not change the rheobase of neurons from control preparations.
DISCUSSION WITH CONCLUSIONS

The results of this study support the concept that intestinal inflammation causes enhanced excitability of postganglionic sympathetic neurons in the PVG. Hapten-induced colitis caused hyperexcitability of visceromotor neurons in the guinea pig IMG. These results are consistent with a previous finding that hapten-induced ileitis causes hyperexcitability of visceromotor, but not vasomotor, neurons in the guinea pig celiac ganglion (16). In addition to this finding, four novel observations are made in the present study. The first observation was a time-dependent relationship of the increased excitability. Visceromotor neurons were not hyperexcitable at 6 h after TNBS administration but were hyperexcitable after 12 h. Hyperexcitability of visceromotor neurons in the guinea pig IMG occurred along the same time course of myenteric neuronal loss in the TNBS-inflamed colon (31). In addition, hyperexcitability persisted in these neurons at 56 days after TNBS administration, after inflammation of the colon had resolved. The persistent hyperexcitability of visceromotor neurons in the IMG following recovery of inflammation after colonic administration of TNBS in the present study is similar to the persistent hyperexcitability in submucosal and myenteric neurons within the region of TNBS colitis (28, 34) and the prolonged excitability of spinal afferent neurons that innervate the colon following resolution of TNBS-induced colitis (22) or dextran sodium sulfate-induced colitis (1). The possibility that such long-lasting changes in neuronal activity following resolution of inflammation could contribute to functional disorders of the bowel remains a viable explanation for a subset of human functional bowel disorders (6, 51).

A second novel observation of the present study is that mucosal damage and colonic inflammation were not sufficient to cause the hyperexcitability, because colonic administration of acetic acid caused significant inflammatory damage to the colon; yet changes in the excitability of visceromotor neurons were modest at best. A lack of excitability of IMG neurons in response to colonic acetic acid was observed previously using immunohistochemical detection of immediate-early genes (50).
Differences between the immune responses caused by TNBS and those caused by acetic acid may underlie the difference in visceromotor hyperexcitability (14, 25, 56). However, the activation of T lymphocytes, a known difference between these models, is likely not involved, because 12 h after TNBS is prior to engagement of an adaptive immune response (52, 56).

A third novel observation of the present study was the ability of potassium channel blockers to enhance the excitability of visceromotor neurons from control and inflamed preparations. This observation suggests that colitis-induced downregulation of neither the M-type (KM) current nor IA contributed to inflammation-induced hyperexcitability of visceromotor neurons (19, 26, 54, 55). KM is a K⁺ conductance, carried by KCNQ2/3 channels, that is inhibited during slow synaptic transmission to cause increased excitability of visceromotor neurons (19, 26, 54, 55). IA contributes to neuronal excitability by setting the interval between action potentials. Inhibition of this current causes increased excitability of IMG visceromotor neurons (13, 26, 54, 55). Consistent with previous findings, inhibition of KM with XE-991 and inhibition of IA with heteropodatoxin-2 increased action potential frequency in IMG visceromotor neurons. The excitability of the already hyperexcitable neurons from inflamed preparations was further enhanced by the inhibition of these currents, suggesting that these currents are not downregulated following the inflammatory insult. As expected, XE-991 depolarized visceromotor neurons. This is consistent with the concept that KM contributes to resting membrane potential. The change in resting membrane potential may contribute to the altered rheobase observed following XE-991 application in control and inflamed preparations. Consistent with our conclusion that KM is unchanged during inflammation, XE-991 caused the same level of depolarization and the same decrease in rheobase, regardless of inflammatory state. It was somewhat surprising that heteropodatoxin-2 depolarized visceromotor neurons, as IA is not expected to contribute to resting membrane potential. In neurons from control and inflamed preparations, the mean depolarization by heteropodatoxin-2 was less than that observed for XE-991, and these depolarizations were not different from each other. This suggests that, regardless of whether heteropodatoxin-2 acts at IA to depolarize the neurons, the target is unchanged by inflammation. Consistent with the concept that IA does not contribute to resting conductances, heteropodatoxin-2 did not alter rheobase in control or inflamed preparations.

The fourth novel observation is that application of the persistent sodium channel blocker riluzole to the IMG eliminated tonic firing of visceromotor neurons and increased the rheobase of neurons from inflamed, but not control, preparations.

Fig. 5. Riluzole increases accommodation in visceromotor neurons and restores normal rheobase in neurons from inflamed preparations. Top: representative traces of the inhibitory effect of riluzole (10 μM) on the number of action potentials elicited by depolarizing current pulses set at 2.5 times threshold current in visceromotor neurons from control and inflamed preparations. Bottom: number of action potentials at 2.5 times rheobase before (basal) and after riluzole (left), riluzole-induced depolarization (middle), and mean threshold current (right) for neurons recorded from control preparations (n = 4) and preparations from animals treated with TNBS at 24 h prior to recording (n = 4). Values are means ± SE. Riluzole caused a significant decrease in number of action potentials in control and inflamed preparations: *P < 0.05 (by 2-way repeated-measures ANOVA and Bonferroni’s post test). There was a significant increase in the number of action potentials in neurons from inflamed preparations compared with control preparations prior to riluzole: †P < 0.05 (by 2-way repeated-measures ANOVA and Bonferroni’s post test); no such difference was detected after riluzole. Depolarization caused by riluzole was not different between control and inflamed preparations: P > 0.05 (by t-test). Riluzole caused a significant increase in threshold current in inflamed preparations: *P < 0.05 (by 2-way repeated-measures ANOVA and Bonferroni’s post test); no such difference was detected in control preparations.
tions. In the present study riluzole was used at 10 μM, because this concentration does not activate two pore-domain potassium channels (17) and has minimal effects on the peak sodium current in sympathetic neurons but almost completely blocks the persistent current (30). Riluzole-mediated inhibition of persistent sodium currents and/or leftward shift in the steady-state inactivation of sodium currents could contribute to the effects observed and suggests that sodium channels contribute to the hyperexcitability of viscercmotor neurons during and following recovery from colitis.

In conclusion, the results of this study support the concept that hapten-induced colitis causes hyperexcitability of viscercmotor neurons in the guinea pig IMG. The onset of hyperexcitability occurred 12 h following administration of TNBS and persisted to 8 wk, the maximum time tested. Differences between the inflammatory responses to TNBS and acetic acid may explain why the former inflammogen causes marked hyperexcitability, while only modest changes in excitability were caused by the latter. Finally, persistent sodium currents may contribute to the underlying mechanism of colitis-induced hyperexcitability, while K_M and I_A likely do not. While the causal mechanisms of the observed changes were not studied directly, it is unlikely that axon projections of IMG neurons within the inflamed region of the colon can account for the changes, because many IMG neurons innervate unaffected regions in the more proximal colon (53). Rather, it seems more likely that circulating humoral mediators, or changes in the synaptic input to IMG neurons, whether intestinofugal, spinal afferent, or preganglionic spinal, are the precipitating signals. Because PVG neurons coordinate motor activity over relatively large distances of the gastrointestinal tract, hyperexcitability of viscercmotor neurons in the PVG may contribute to colitis-induced upper bowel motor dysfunction.

ACKNOWLEDGMENTS

The author gratefully acknowledges the secretarial support of Janice Applequist as well as valuable input from Drs. Lei Sha, Steven Miller, Arthur Beyder, and Joseph Szurszewski.

GRANTS

This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-76665.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

REFERENCES

Abstract

The mammalian sympathetic prevertebral ganglia: an overview of their physiological properties and potential therapeutic applications. 

The prevertebral sympathetic ganglia are a key component of the autonomic nervous system, playing a critical role in the regulation of various physiological functions. Despite their importance, little is known about the physiological properties of these ganglia. In this review, we provide an overview of the current understanding of these ganglia, including their anatomy, physiology, and potential therapeutic applications.

Keywords

Prevertebral sympathetic ganglia, physiological properties, therapeutic applications.