Mouse colon sensory neurons detect extracellular acidosis via TRPV1

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Sugiura T, Bielefeldt K, Gebhart GF. Mouse colon sensory neurons detect extracellular acidosis via TRPV1. Am J Physiol Cell Physiol 292: C1768–C1774, 2007. First published January 24, 2007; doi:10.1152/ajpcell.00440.2006.—Extracellular acidification contributes to pain by activating or modulating nociceptor activity. To evaluate acidic signaling from the colon, we characterized acid-elicted currents in thoracolumbar (TL) and lumbosacral (LS) dorsal root ganglion (DRG) neurons identified by content of a fluorescent dye (DiI) previously injected into the colon wall. In 13% of unidentified LS DRG neurons (not labeled with DiI) and 69% of LS colon neurons labeled with DiI, protons activated a sustained current that was significantly and reversibly attenuated by the transient receptor potential vanilloid receptor 1 (TRPV1) antagonist capsazepine. In contrast, 63% of unidentified LS DRG neurons and 4% of LS colon neurons exhibited transient amiloride-sensitive acid-sensing ion channel (ASIC) currents. The peak current density of acid-elicited currents was significantly reduced in colon sensory neurons from TRPV1-null mice, supporting predominant expression of TRPV1 in LS colon sensory neurons, which was also confirmed immunohistochemically. Similar to LS colon DRG neurons, acid-elicited currents in TL colon DRG neurons were mediated predominantly by TRPV1. However, the pH producing half-activation of responses significantly differed between TL and LS colon DRG neurons. The properties of acid-elicited currents in colon DRG neurons suggest differential contributions of ASICs and TRPV1 to colon sensation and likely nociception.

Visceral pain; dorsal root ganglion neurons; acid-sensing ion channel; capsaicin receptor; acid-evoked currents; transient receptor potential vanilloid receptor 1

Protons are potent algogenes that produce significant pain in humans (15, 18, 35) and contribute to symptoms in pathological conditions such as ischemia or inflammation (2, 24). Within the last decade, several acid-sensitive ion channels have been identified and cloned. Some of these channels are primarily expressed in sensory neurons, suggesting a role in chemosensation. A drop in pH can directly gate acid-sensitive channels of degenerin (DEG) family acid-sensing ion channels (ASICs) (36) and transient receptor potential vanilloid receptor 1 (TRPV1) (8, 32). In addition, protons modulate the activity of background K+ (16) and ATP-gated channels (13, 20). Because chest pain can be an important warning of ischemic heart disease, acid-sensitive currents have attracted attention in cardiac sensory neurons as mediators of cardiac pain (4). In support of this, the fraction of retrogradely labeled cardiac sensory neurons responding to protons has been found to be greater compared with unlabeled dorsal root ganglion (DRG) neurons (3), suggesting that pH sensors in visceral sensory neurons may contribute to or modulate chemosensory properties of visceral sensory neurons that are likely relevant to visceral pain mechanisms. Our previous work in the rat stomach (31) and mouse colon (30) is consistent with this suggestion.

For example, >80% of mouse colon sensory neurons reportedly express immunoreactivity for TRPV1 (27), and we have provided electrophysiological evidence that mouse colon sensory neurons are activated by pH, heat, and capsaicin (30). Based on these findings and those of others (13, 14, 31), we hypothesized that visceral sensory neurons have unique chemosensory properties. The aim of the present study was to characterize the acid-evoked currents in DRG neurons that innervate the descending colon in the mouse. The colon is innervated by axons contained in the pelvic and lumbar splanchnic nerves; their cell bodies are located in thoracolumbar (TL) and lumbosacral (LS) DRGs, respectively. Because electrophysiological and mechanosensory properties as well as the receptive fields ofafferent fibers innervating the colon differ between these two pathways (7, 17), we examined differences in acid-sensitive currents in TL and LS DRG neurons innervating the mouse colon.

MATERIALS AND METHODS

Male CB57BL/6 mice (20–30 g, Harlan, Indianapolis, IN) and TRPV1-null (TRPV1+/−) mice (20–30 g, The Jackson Laboratory, Bar Harbor, ME) were used for all experiments. All experimental procedures were approved by the Institutional Animal Care and Use Committee of The University of Iowa.

Colon sensory neuron labeling. Mice (18 C57BL/6 and 3 TRPV1+/−) were anesthetized with a mixture of ketamine (17.5 mg/ml) and xylazine (2.5 mg/ml) (5 ml/g ip), and the descending colon was exposed through an incision in the peritoneal cavity. A Hamilton microsyringe with a 30-gauge needle was inserted into the wall of the descending colon using a Hamilton microsyringe with a 30-gauge needle. Thirty seconds after the injection, the needle was carefully removed, avoiding leakage of dye into the peritoneal cavity. The abdomen was then closed, and mice were allowed to recover for 14–21 days, by which time DiI had been retrogradely transported to cell bodies in T11-L1 and L6-S2 DRGs.

Cell preparation. Fourteen to twenty-one days after the Dil injection into the colon wall, mice were anesthetized with ketamine-xylazine (as above) and killed by cervical dislocation. L6-S2 and T11-L1 DRGs were quickly removed bilaterally under a dissection microscope, transferred into ice-cold culture media, and minced with a surgical blade. A total of 118 DRGs from 18 C57BL/6 mice and 18 DRGs from 3 TRPV1−/− mice were used in these experiments. The tissue was incubated in Gibco-BRL Neurobasal-A media (Invitrogen, Carlsbad, CA) containing collagenase (type 1A, 2 mg/ml), trypsin (type III, 1 mg/ml), and 3 mM CaCl2 at 37°C for 50 min. Tissue fragments were then gently triturated with a sterile Pasteur pipette coated with silicon and centrifuged. DRG neurons were resuspended in Neurobasal-A media supplemented with 5% B27 supplement, 0.25% l-glutamine (200 mM), and 1% penicillin-streptomycin.

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tomycin (all from Invitrogen), plated on poly-D-lysine-coated glass cover slips, and incubated at 37°C in a 95% air-5% CO2 atmosphere saturated with water vapor. Experiments were carried out 2–10 h after cell isolation.

**Electrophysiology.** Patch pipettes were prepared using borosilicate glass (PG52151-4, World Precision Instruments, Sarasota, FL) with a tip resistance of 2–5 MΩ after being fire polished. They were filled with an internal solution containing (in mmol/l) 120 KCl, 1.8 CaCl2, 5 MgCl2, 5.55 glucose, and 20 HEPES. For solutions below pH 4.5, HEPES was exchanged with 20 mmol/l MES and pH was adjusted with NaOH or HCl. Solutions were applied through a three-barreled glass tubing manifold (inner diameter: 700 μm) located ~150 μm from the cell. Rapid solution exchange was achieved within 20 ms by movement of the manifold (SF-77B, Warner Instruments, Hamden, CT). To avoid desensitization, we allowed 1 min between solution exchanges. Colon sensory neurons were identified by their red-orange color under Hoffman Contrast Optics (×400) in fluores-

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**Fig. 1.** Dil-labeled colon sensory neurons. A: Dil-labeled neurons (arrows) in L6 dorsal root ganglions (DRGs) (fixed tissue). Note the punctuate Dil staining throughout the cytoplasm except for the nucleus. B and C: bright-field (B) and fluorescence (C) images of Dil-labeled, dissociated DRGs (arrows) and unlabeled (UL) neurons (arrowhead). Scale bars = 30 μm. D: cell size distribution of dissociated lumbosacral (LS) DRG neurons labeled with Dil (colon, n = 21) and UL neurons (n = 39).

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**Fig. 2.** Acid-elicited currents in UL and Dil-labeled colon sensory neurons. A: representative responses of UL LS DRG neurons to pH 4.5 showing typical fast transient, fast transient + sustained, slow, and sustained currents (left to right). B: mean peak current density (Ipeak; normalized to cell capacitance) evoked by pH 4.5 (5 s) in 39 UL LS DRG neurons. Numbers of neurons tested for each type of current are given within or above each bar. C: representative responses of DiI-labeled colon neurons to low pH (pH 4.5). D: distribution of types of acid-evoked currents responding to low pH (pH 4.5) in UL DRG neurons (n = 39) and Dil-labeled LS (n = 26) and thoracolumbar (TL; n = 14) colon sensory neurons. Vertical scales were as follows (from left to right): 2 nA in A; 250 pA, 250 pA, and 2 nA in B; and 3.5 nA, 250 pA, and 2.25 nA in C.

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Colon sensory neurons (and its absence in TRPV1 at room temperature. Whole cell voltage-clamp recordings were performed with an Axopatch 200B amplifier (Axon Instruments, Foster City, CA). Re-measurement (H11002 10 h in culture), cells were round and had no 400-fold magnification as previously described (31). At the time of was obtained, cell diameter was measured using a calibrated grid at 580 nm; Fig. 1, cent light with a rhodamine filter (excitation wavelength of 546 nm and barrier filter at 580 nm; Fig. 1, B and C). Before whole cell access was obtained, cell diameter was measured using a calibrated grid at 400-fold magnification as previously described (31). At the time of measurement (<10 h in culture), cells were round and had no processes. Whole cell voltage-clamp recordings were performed with an Axopatch 200B amplifier (Axon Instruments, Foster City, CA). Recordings were filtered at 5 kHz and digitized at 1 kHz using a Digidata 1320A interface (Axon Instruments). All experiments were performed at room temperature.

Immunohistochemistry. To establish the presence of TRPV1 in colon sensory neurons (and its absence in TRPV1−/− mice), whole DRGs (L6, S1) and acutely dissociated DRG cells (see Cell prepa ration) were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer for 1 h and 10 min, respectively. Whole DRGs were cryoprotected in 20% sucrose in 0.01 M PBS overnight, embedded and frozen on Tissue-Tek OCT compound (Sakura Finetek, Torrance, CA), and cut into 10-μm sections. After being washed with 0.01 M PBS, specimens (sliced DRGs and cultured DRG neurons) were incubated in 3% normal goat serum (NGS; Sigma Chemical, St. Louis, MO) for 30 min at room temperature to reduce nonspecific binding and then with rabbit anti-capsaicin receptor antibody (1:200, Alexa Fluoro 488, Molecular Probes, Eugene, OR) and coverslipped. Control experiments were performed by preincubating antibody with the unconjugated capsaicin receptor control peptide (4 h, 4°C) or by incubating without primary antibody. Slides were examined under a fluorescence microscope (Nikon, Tokyo, Japan) equipped with separate filters. Images were captured with a model 2.3.1 SPOT digital camera (Diagnostic Instruments, Sterling Heights, MI).

Chemicals. N-[2-(4-chlorophenyl)ethyl]-1,3,4,5-tetrahydro-7,8-dihydroxy-2H-2-benzazepine-2-carbothioamide (capsazepine), 8-methyl-N-vanillyl-trans-6-nonenamide (capsaicin), and N-amidino-3,5-dia-mino-6-chloropyrazinecarboxamide hydrochloride (amiloride) were purchased from Sigma. All chemicals were dissolved in distilled water or DMSO and applied in a final concentration of <0.1% DMSO.

Data analysis. The software package pCLAMP9.0 (Axon Instruments) and SigmaPlot 8.02 and SigmaStat 2.03 (SPSS, Chicago, IL) were used for data acquisition and analysis. Concentration-response curves were fitted by the following Hill equation: \( I = (I_{\text{max}}) \times [\text{H}]^{(H)} \times (\text{EC}_{50} + [\text{H}]^{(H)}, \text{EC}_{50} = \text{concentration, } I \text{ is the current density at different } [\text{H}], I_{\text{max}} \text{ is the maximum response of the cell, } n_{\text{H}} \text{ is the Hill slope, and } \text{EC}_{50} \text{ is the concentration eliciting a half-maximal response.}

Data were compared using the \( \chi^2 \)-test, Student’s two-tailed unpaired \( t \)-tests, or one-way ANOVA as appropriate. Statistical significance was determined at \( P < 0.05. \)

RESULTS

Size of colon sensory neurons. Colon sensory neurons could be easily identified based on their fluorescence in fixed tissue (Fig. 1A) or after acute dissociation (Fig. 1, B and C). Gastrointestinal tract and bladder sensory neurons, virtually all of which are associated with unmyelinated or very thinly myelinated axons, have been reported to be larger in size than nonvisceral sensory neurons associated with unmyelinated or thinly myelinated axons within the same ganglia (e.g., Refs. 13, 17, 25, and 31). We measured the cell sizes of dissociated neurons studied electrically.
physiologically and found that 95% of 21 labeled LS colon sensory neurons were medium to large in size (>25 μm), whereas 34% of 39 unlabeled LS sensory neurons were small in size (<25 μm; χ² = 17.5, P < 0.01; Fig. 1D).

Acid-evoked currents in unlabeled neurons. Rapid application of low-pH solution (pH 4.5) triggered inward currents in 30 of 39 unlabeled LS DRG neurons (77%). Most cells showed a transient current response that could be distinguished based on kinetics. At a pH of 4.5, the fast transient component peaked at 258 ± 23 ms (n = 14) compared with 1,527 ± 153 ms for the slow transient component (n = 11; Fig. 2A). A small number (n = 5, 13%) of LS DRG neurons exhibited only a sustained acid-elicited current (Fig. 2A, right). Mixed currents with transient and sustained components were seen in six neurons (15%; Fig. 2A). The distribution of these kinetically distinct acid-evoked currents is shown in Fig. 2D. The slow transient and sustained acid-evoked currents predominated in small cells (22.3 ± 1.1 μm, n = 10, and 25.1 ± 1.6 μm, n = 5, respectively), whereas fast transient currents were observed in medium to large DRG neurons (32.3 ± 1.1 μm, n = 13). To take into account the differences in cell size, we converted data to current density and compared peak values for the distinct acid-evoked currents. As shown in Fig. 2B, the peak current density of the sustained-type acid-evoked current (154.6 ± 61.8 pA/pF) was significantly greater compared with transient currents (F = 10.93, P < 0.001).

Acid-evoked currents in visceral DRG neurons. Of the 26 LS DRG neurons labeled from the colon, 21 neurons (81%) responded to rapid proton application (pH 4.5). As described for unlabeled neurons, the currents could be distinguished as transient and sustained, with the former having fast or slow activation kinetics. In contrast to unlabeled DRG neurons, most (86%) of the 21 responsive colon sensory neurons expressed only sustained currents with 1 and 2 colon sensory neurons, respectively, showing fast and slow transient acid-sensitive currents (Fig. 2, C and D).

Similar to the results obtained from LS colon DRG neurons, application of acid triggered inward currents in 12 of 14 (86%) TL DRG neurons labeled from the colon, with 11 of the 12 responsive TL colon neurons studied (92%) exhibiting sustained currents; only 1 TL colon sensory neuron responded with a transient current (Fig. 2D).

To characterize the properties of the predominant, sustained acid-elicited current in colon sensory neurons, we examined the pH dependence of the current using solutions with pH between 7.0 and 3.5. As shown in Fig. 3, the sustained acid-elicited current in LS colon sensory neurons was activated at a significantly lower pH (half-activation at pH 4.8 ± 0.1, n = 18) than in TL colon sensory neurons [half-activation at pH 5.5 ± 0.1, n = 10, time (t) = −4.31, P < 0.001].

**Pharmacological properties of acid-evoked currents.** To examine the contribution of ASICs to the acid-elicited currents,
we applied amiloride, a known blocker of the DEG/epithelial Na\(^+\) channel family. At a concentration of 200 \(\mu\)M, amiloride blocked transient but not sustained acid-evoked currents in unlabeled DRG neurons (Fig. 4A). Similarly, amiloride failed to block sustained acid-elicited currents in LS colon DRG neurons (89 ± 3\% of control, \(n = 9, P = 0.2\); Fig. 4B). We also examined the relative contribution of the capsaicin receptor (TRPV1), another channel gated by protons, to acid-elicited currents using the channel blocker capsazepine. In contrast to the effects of amiloride, capsazepine (10 \(\mu\)M) significantly and reversibly attenuated the sustained current in colon sensory neurons (35 ± 8\% of control, \(n = 9, t = 5.52, P < 0.001\) vs. vehicle; Fig. 4C).

**TRPV1 immunoreactivity in visceral sensory neurons.** DRG neurons were retrogradely labeled from the colon with DiI and immunostained for TRPV1. Immunofluorescence confirmed the expression of TRPV1 on the cell bodies of DiI-positive LS colon DRG neurons (Fig. 5, A–C). Using the same protocol, we also demonstrated the expression of TRPV1 in acutely dissociated LS colon DRG neurons (Fig. 5, D–F), upon which we previously performed patch-clamp recordings for acid-evoked currents. No specific staining was observed in the absence of primary antibody or in the presence of blocking peptide (Fig. 5, G and H). We did not attempt to quantify the percentage of colon sensory neurons expressing TRPV1. Previous electrophysiological (30) and immunohistochemical (10, 27) studies have suggested that most colon sensory neurons in the mouse express TRPV1.

**Acid-evoked currents in TRPV1 \(^{-/-}\) mice.** Next, to confirm whether the sustained type of acid-elicited current is mediated by TRPV1, we examined acid-elicited currents in colon sensory neurons from TRPV1 \(^{-/-}\) mice (Fig. 6A). All acid-evoked currents in LS colon sensory neurons from TRPV1 \(^{-/-}\) mice were transient, with no cells showing sustained responses to application of an acidic solution. Acidic solution (pH 4.5) triggered transient inward currents in only 5 of 16 (31\%) LS colon DRG neurons from TRPV1 \(^{-/-}\) mice, with the remaining 11 (69\%) cells not responding to low pH (\(\chi^2 = 8.3, P < 0.01\) compared with colon neurons from wild-type mice; Fig. 6B). The peak density of current evoked by pH 4.5 solution was significantly less in TRPV1 \(^{-/-}\) mice (2.9 ± 1.3 pA/pF, \(n = 16, t = 4.42, P < 0.001\)) compared with peak current density in cells from wild-type mice (49.2 ± 8.4 pA/pF, \(n = 24\); Fig. 6C). TRPV1 staining was not detected in DRGs from TRPV1 \(^{-/-}\) mice (Fig. 5I).

**DISCUSSION**

We (30) have recently reported that the majority of mouse LS colon sensory neurons respond to heat, protons, and capsaicin, consistent with the expression of TRPV1 channels. In the present report, we examined, in greater detail, the acid-sensitive currents in this population of colon sensory neurons as well as in a second TL sensory pathway innervating the distal colon. We found that visceral sensory neurons labeled from the colon are functionally distinct from unlabeled neurons, which likely project to nonvisceral targets, such as the skin or muscle. Whereas most unlabeled DRG neurons generated transient amiloride-sensitive currents in response to acid, most LS and TL colon sensory neurons responded with slowly activating, sustained currents that were reversibly inhibited by the TRPV1 blocker capsazepine. Consistent with the role of TRPV1 as the principal mediator of acid-sensitive currents in colon sensory neurons, the peak current and fraction of neurons responding to acid were significantly lower in TRPV1 \(^{-/-}\) mice compared with wild-type controls. Finally, the proton sensitivity of acid-evoked currents differed between colon TL and LS neurons, with TL neurons exhibiting significantly greater sensitivity to protons.

Consistent with prior investigations, protons activated an inward current in the majority of DRG neurons studied (e.g., Ref. 1). In most unlabeled neurons, kinetic and pharmacological properties of acid-evoked currents have suggested activation of members of the ASIC family of ion channels (e.g., Ref. 3, 31, 35). In contrast, the acid-sensitive current in colon sensory neurons is primarily carried by the TRPV1 channel, as supported by physiological properties, inhibition by capsazepine, and experiments in TRPV1 \(^{-/-}\) mice. A similarly high percentage of capsaicin-responsive neurons has been reported for DRG neurons innervating other viscera, such as the urinary tract.\(^{29,30}\)

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**Fig. 6.** Acid-evoked currents in colon sensory neurons from TRPV1 \(^{-/-}\) mice. A: representative responses of DiI-labeled LS cDRG neurons from TRPV1 \(^{-/-}\) mice to pH 4.5. **B:** distribution of kinetic subtypes of acid-evoked currents in LS cDRG neurons from TRPV1 \(^{-/-}\) mice (\(n = 16\)). C: peak current density of acid-evoked currents in DiI-labeled LS colon neurons from TRPV1 \(^{-/-}\) knockout (KO) mice (\(n = 16\)) was significantly less (2.9 ± 1.3 pA/pF) than in DiI-labeled colon neurons from wild-type mice (\(n = 24, 49.2 ± 8.4\) pA/pF). Current was normalized to cell capacitance. \(*P < 0.001.\)
bladder (13) and stomach (11, 14, 31). These physiological data are consistent with complementary studies (10, 27, 30) reporting TRPV1 immunoreactivity in 70–80% of colon sensory neurons in the mouse. TRPV1 is preferentially found in small-diameter DRG neurons, which typically have unmyelinated axons (as is also true for most visceral sensory neurons) (5, 8). While DRG neuron size generally correlates with physiological properties and presumed function, cell size appears to be a poor predictor of functional properties of visceral sensory neurons; more than half of colon sensory neurons were large in diameter compared with only 10% of unlabeled neurons. Thus, present and previous (13, 17, 25, 30, 31) findings have documented that gastrointestinal tract and bladder sensory neurons, virtually all of which are associated with unmyelinated or thinly myelinated axons, differ significantly from nonvisceral sensory neurons associated with unmyelinated or thinly myelinated axons.

Because the colon is innervated by splanchnic (TL) and pelvic (LS) nerve pathways, we examined the possible differences in colon DRG neuron responsiveness to protons. Previous studies of urinary bladder and colon sensory neurons have revealed that the functional properties of visceral sensory neurons differ between the two pathways of innervation (i.e., TL and LS neurons). TL neurons projecting to the rat colon have been reported to have higher thresholds for activation by current injection than LS colon sensory neurons, thus requiring a stronger stimulus to trigger action potentials (17). While it is certainly difficult to relate data obtained in isolated cells to properties of visceral afferent fibers (7), pelvic (LS) rather than splanchnic (TL) afferents are generally considered more important in controlling normal defecation and micturition as well as aversive responses to noxious distending stimuli (21, 34). Consistent with these results, detailed characterizations of mouse colonic afferents in vitro have demonstrated that the majority of splanchnic afferents require stronger mechanical stimuli compared with pelvic afferents (7). In the present study, we found that both TL and LS colon neurons exhibited predominantly sustained currents when exposed to protons. This differs from results obtained in rat bladder and gastric sensory neurons, which typically respond to acid with mixed currents comprised of transient and sustained components (13, 31). Additional experiments are required to determine whether differences between sensory neurons innervating the mouse colon and rat stomach or urinary bladder reflect distinct properties of visceral sensory neurons innervating different organs or reflect differences between species.

The high fraction of visceral sensory neurons responding to capsaicin or expressing TRPV1 immunoreactivity (10, 13, 22, 27–29, 31) raises questions about the physiological role of TRPV1 in visceral sensory neurons. The TRPV1 channel can be activated by heat, protons, and endogenous lipid mediators (8, 32). In mammals, core body temperature is stably regulated, thus arguing against heat as an important stimulus for TRPV1-positive colon sensory neurons. Similarly, the relatively low proton sensitivity of TRPV1 in colon sensory neurons (EC50 around pH 5) suggests that TRPV1 also does not normally play a significant role in mediating sensory input from the colon. However, the present experiments were carried out at room temperature, and it is likely that the pH sensitivity would be within the physiological range at body temperature (32). In addition, the TRPV1 channel is modulated by numerous endogenous mediators. For example, we (30) have recently shown that serotonin modulates TRPV1 function in colon sensory neurons, leading to channel activation and action potential firing around the normal core temperature and significantly shifting the pH of half-activation leftward. Similar sensitizing effects have been reported for purinergic agonists, prostaglandins, proteinase-activated receptors, bradykinin, and nerve growth factor, all of which play important roles in sensitizing neurons during inflammation (11, 12, 26, 33), which is commonly associated with reduced tissue pH. Thus, TRPV1 may integrate different signals and modulate the excitability of visceral sensory neurons. Consistent with such a role, TRPV1 knockout mice showed blunted responses to visceral distension, even though TRPV1 is not directly gated by mechanical stimuli (19, 28).

The present data add to a growing body of literature pointing at a significant role of TRPV1 in visceral sensation. The principal conscious sensations arising from the viscera are discomfort and pain, and stretch (tension) of hollow organ muscle is the most common stimulus leading to conscious sensations from the stomach, urinary bladder, and colon. We (19) have previously documented a role for TRPV1 in both colon mechanosensation and sensitization of mechanosensitive endings in mouse colon. Correspondingly, changes in TRPV1 expression have recently been demonstrated in many human disorders, including rectal urgency and pain, esophagitis, and cystitis (6, 9, 23). Considering the high proportion of visceral sensory neurons functionally expressing this channel, selective antagonists may be especially useful in the treatment of the common visceral disorders associated with pain and discomfort.

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GRANTS

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