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Ion channels, ion channel receptors, and visceral hypersensitivity in irritable bowel syndrome

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Abstract

Ion channels are expressed throughout the gastrointestinal system and regulate nearly every aspect of digestion, including fluid secretion and absorption, motility, and visceral sensitivity. It is therefore not surprising that in the setting of functional bowel disorders, such as irritable bowel syndrome (IBS), ion channels are often altered in terms of expression level and function and are a target of pharmacological intervention. This is particularly true of their role in driving abdominal pain through visceral hypersensitivity (VH), which is the main reason IBS patients seek medical care. In the study by Scanzi et al., in the current issue of this journal, they provide evidence that the T-type voltage-gated calcium channel (Ca_V) $Ca_V3.2$ is upregulated in human IBS patients, and is necessary for the induction of an IBS-like disease state in mice. In this mini-review, we will discuss the contribution of specific ion channels to VH in IBS, both in human patients and rodent models. We will also discuss how $Ca_V3.2$ may play a role as an integrator of multiple environmental stimuli contributing towards VH.

Abbreviated abstract

Ion channels are expressed throughout the gastrointestinal system and regulate nearly every aspect of digestion, including fluid secretion and absorption, motility, and visceral sensitivity. In this mini-review, we will discuss the contribution of specific ion channels and ion channel receptors to visceral hypersensitivity in irritable bowel syndrome, both in human patients and rodent models.

Keywords

Ion channels; Irritable bowel syndrome; microbiome; serotonin; TRP; visceral hypersensitivity

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that is generally characterized by chronic or recurrent abdominal pain or discomfort and altered bowel habits. The newly released Rome IV diagnostic criteria for screening functional gastrointestinal disorders has increased the stringency for diagnosing patients with IBS. Previously, patients needed to report abdominal pain or discomfort at least 2–3 times per month that was improved after defecation. The new requirements state that abdominal pain,

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and not discomfort, must occur at least weekly and be associated with changes in stool consistency and frequency (1). Visceral hypersensitivity (VH), which is defined as altered sensation of normal physiological stimuli (allodynia) and enhanced perception of noxious stimulus to the abdominal region (hyperalgesia), is thought to be the primary mediator of the pain experienced by IBS patients (2). This increased sensitivity has not been successfully correlated with changes in motor activity. Rather, it likely has a multifactorial etiology involving the sensitization of peripheral and central nociceptive pathways via inflammatory- and stress-mediated factors (2).

Ion channels are expressed throughout the gut and their cell specificity and location largely dictate their role and how their dysfunction contributes to the symptomology of functional bowel disease. Aspects involved in digestion, including fluid secretion and absorption, and motility, are driven by expression of ion channels in epithelial and smooth muscle cells, respectively. Sensory signals, including pain, are dependent on the activities of various ion channels expressed by extrinsic sensory neurons (3). Indeed, an entire catalog of ion channel receptors has been interrogated and shown to be involved in some aspect of the disease process of IBS. By far, the most attention has been paid to the role that ion channels play in altered pain signaling. Human biopsies have revealed altered expression of serotonin (5-hydrodytryptomine; 5-HT) receptors (4), transient receptor potential (TRP) channels (5), protease-activated receptors (PAR) (6), and assorted other nociception-related receptors in affected tissue from IBS patients. Accordingly, animal models of IBS have also demonstrated the necessity of these channels in mediating increased visceral sensitivity (7). In this mini-review, we will discuss what is known regarding the dysfunction of the main ion channels implicated in driving VH associated with IBS, both in human patients and relevant animal models. We will also discuss how T-type calcium channels, specifically $Ca_v3.2$, may play a role as an integrator of multiple environmental stimuli contributing towards VH.

Serotonin

Serotonin is the most important neurotransmitter and paracrine signaling molecule in the brain-gut axis, and is considered to be a contributing factor in IBS pathophysiology (3). Approximately 90–95% of the human body's 5-HT is produced and stored in enterochromaffin (EC) cells of the intestinal mucosa and 80% of the total body 5-HT is located in the GI tract, where it regulates secretion, motility, and sensation. 5-HT receptor subtypes 5-$HT_1$5-$HT_2$5-$HT_3$5-HT_4, and 5-HT_7 are expressed in the intestine (8) and altered 5-HT metabolism has been proposed as a potential cause of VH (2). Changes in 5-HT release by EC cells appear to be related to IBS subtype, with diarrhea-predominant (IBS-D) patients displaying an increase in 5-HT release and constipation-predominant (IBS-C) patients showing a decrease in 5-HT release (9). Decreased mucosal expression of the serotonin transporter (SERT) has been reported in IBS-D biopsies, which may explain the increase in extracellular 5-HT (9, 10). Another study of IBS-D patients reported an elevated expression of the 5-HT_3 receptor due to a non-coding polymorphism in the HTR3E subunit that altered mRNA binding to microRNA-510, both presumably located in EC cells of the gut epithelium (4).

Selective serotonin-reuptake inhibitors (SSRIs) are obvious potential treatment options due to the central role that 5-HT plays in the brain-gut axis. As such, paroxetine, fluoxetine, and citalopram (SSRIs) have all shown promising symptom relief for IBS patients (11–13). However, the most effective drugs for treating VH in IBS patients have targeted the 5-HT_3 receptor, the sole ion channel receptor among the 5-HT receptor subtypes, and 5-HT_4 receptors, either through inhibition or activation, respectively (14). Alosetron, a 5-HT_3 receptor antagonist, significantly improved GI symptoms for IBS patients with VH. Patients experienced higher volume thresholds and reduced colonic compliance (15). In a more recent study, alosetron also reduced emotional motor system activity that subsequently modified gut sensitivity (16). Another 5-HT_3 receptor antagonist, ondansetron, diminished abdominal pain and evacuation of IBS patients compared to placebo (17).

Rodent models of IBS have also demonstrated evidence of serotonin-induced pathology with improvements in VH following pharmacological intervention. In a study by Hicks et al. (18), approximately half of the lumbar splanchnic nerves innervating the rat distal colon were responsive to 5-HT and 30% responded to a specific 5-HT_3 receptor agonist. Sensitivity to colorectal distension was increased, as was colonic 5-HT and 5-HT_3 receptor expression in the distal colon, of adult rats that were subjected to early life stress through maternal separation (19). Intrathecal administration of 5-HT_3 receptor antagonist reversed VH in both an acute stress-induced model of VH (20) and a model of VH following noxious somatic stimulation (21), both in rats.

TRP channels

Several members of the TRP channel family, so named for the transient depolarization called “transient receptor potential” generated by the influx of positively charged ions into the cell when these channels are activated, have been investigated in IBS, including TRPV1, TRPV4, and TRPA1. TRPV1 plays a significant role in colorectal mechanosensation and inflammation-induced pain (22), making it a compelling target for pharmacological intervention for IBS. Biopsy studies have reported larger quantities of TRPV1-positive nerve fibers in colon samples taken from IBS and inflammatory bowel disease patients with VH than healthy controls (5). Increased activation or expression of TRPV1 is influenced by inflammatory mediators, such as histamine (23) and nerve growth factor (NGF) release (24). Mucosal biopsies from IBS patients showed a significant increase in NGF expression and supernatants obtained from these mucosal biopsies induced a greater amount of neuritogenesis when applied to cultured primary enteric neurons from control rats (25). Increased expression of glial cell-derived neurotrophic factor (GDNF) and neurotrophic tyrosine kinase receptors have also been observed in IBS biopsies (5). NGF can increase the expression of TRPV1, as well as promote the insertion of TRPV1 into the plasma membrane of peripheral nerve endings (24). One likely source of increased NGF, as well as histamine and tryptase, is from mast cells, which are innate immune cells that are increased in number and/or activation state in biopsies from IBS patients (26). Treatment with mast cell stabilizers or Ebastine, a histamine receptor H1 (HRH1) antagonist, has been shown to improve VH and associated IBS symptoms (23, 27).

Rodent models of IBS have expanded on the human observations of TRPV1, as well as extended them to TRPV4 and TRPA1. Mice lacking TRPV1 showed a reduced response to colorectal distension, compared to wildtype mice (28). This is in contrast to the relatively normal somatosensory responses that TRPV1−/− mice have to cutaneous stimulation, illustrating a baseline difference in afferent types that innervate somatic versus visceral structures (7). Numerous murine models of IBS, including neonatal colon irritation, have shown an increase in TRPV1 expression (29) and/or TRPA1 function (30) in sensory ganglia or the colon, respectively. Importantly, histamine, serotonin, and tryptase can all directly or indirectly sensitize TRPV1 and TRPV4 expressed on sensory nerve endings (31, 32). Mice that received intracolonic administration of histamine or serotonin displayed VH during colorectal distension for up to 6 hours, which was blocked by an inter-vertebral injection of TRPV4 siRNA (31). Histamine and serotonin also increased the calcium response of dissociated, colon-specific dorsal root ganglion (DRG) neurons to a TRPV4 agonist, as well as increased the insertion of TRPV4 into the plasma membrane. Unlike the TRPV1−/− mice, the TRPV4−/− mice exhibited normal baseline responses to colorectal distension; however, intracolonic application of a PAR2 agonist did not increase VH in TRPV4−/− mice, unlike its actions in wildtype mice (32). Supernatants from IBS-D patient biopsies, but not from IBS-C patient biopsies, increased the excitability of mouse colon-specific DRG neurons (33). The increase in excitability was not observed in DRG neurons cultured from PAR2−/− mice or following the application of a cysteine protease inhibitor, highlighting the importance of PAR2 in the pathogenesis of VH. Together these observations illustrate the interconnected actions of the immune and nervous systems in the development and maintenance of VH in the setting of IBS and other functional bowel disorders.

Voltage-gated ion channels

Voltage-gated ion channels are activated by tissue-damaging stimuli, which cause a change in nociceptive signaling and increase peripheral neuron excitability (34). Voltage-gated sodium channels (Na_V) are comprised of α subunits that form a transmembrane pore and at least one accessory β subunit. The β subunits regulate channel gating, expression level, and interaction with cell adhesion molecules with the extracellular matrix and cytoskeleton. The nine known types of Na_V channels, $Na_V1.1$ through $Na_V1.9$, are named for the types of α subunits of the pore-forming region. The channels $Na_V1.1$, $Na_V1.3$, and $Na_V1.6$ through $Na_V1.9$ are involved in the function of nociceptors under normal and pathological conditions (34). These channels are responsible for the initiation and propagation of the action potential facilitated by enhancing Na^+ permeability of neuronal cell membranes. Na_V channels can regulate excitability of sensory neurons by reducing the activation threshold and increasing current density (34). In a double-blind crossover study of IBS patients, intra-rectal administration of lidocaine, a Na_V channel blocker, reduced abdominal pain and rectal hypersensitivity (35). Another study observed $Na_V1.7$ immunoreactive nerve fibers were increased in biopsy samples taken from patients suffering from idiopathic rectal hypersensitivity compared to healthy controls (36). In an *in vivo* rat study, blockade of $Na_V1.8$ with A-803476 attenuated mechanical allodynia and thermal hyperalgesia in visceral tissues of neuropathic and inflammatory pain models (37).

Non-neuronal Na_v channels have also been implicated in IBS and other functional GI disorders. The $Na_v1.5$ channel is important for proper functioning of intestinal smooth muscle cells and interstitial cells of Cajal (38). Mutations in *SCN5A*, which encodes the pore-forming α-subunit of $Na_v1.5$, have been found in IBS and functional dyspepsia patients (39). An estimated 2% of IBS patients carry mutations in SCN5a, the majority of which are loss-of-function mutations and are mostly associated with constipation, as opposed to diarrhea-predominant subtypes (40).

Voltage-gated calcium channels (Ca_V) conduct extracellular Ca^{2+} to the cytosol of electrically excitable cells. These channels are formed by six subunits that come together to form a pore. The primary subunit is α1, but other smaller subunits include β, γ, α2, and δ (34). The α1 subunit is encoded by ten human genes and organized into three subfamilies: Ca_V1 (1.1-1.4) channels, Ca_V2 (2.1-2.3) channels, and Ca_V3 (3.1-3.3) channels. High-voltage-activated Ca_V1 channels conduct long lasting (L-type) currents. High-voltage-activated Ca_V2 channels conduct Purkinje/Q-type (P/Q-type) currents and neuronal/non-L (N-type) currents; intermediate-voltage-activated Ca_V2 channels conduct residual (R-type) currents. Lastly, low-voltage-activated Ca_V3 channels conduct transient (T-type) currents (34, 41).

Studies have recognized L-type Ca_V channels to play a role in abdominal pain. α1c subunits compose L-type Ca_V channels and their expression can be either positively or negatively modulated depending on the pathogenic stimuli and type of muscle cells. Studies have shown large quantities of α1c in post-infectious IBS rat circular smooth muscle cells of the colon (42). Knock out mice lacking the α1c subunit displayed reduced amplitude, but not frequency, of spontaneous colonic contraction (43). Neonatal maternal separation has been shown to induce colonic motility dysfunction in rats, concordant with an up regulation of α1c expression and increased influx of Ca^{2+} in colon smooth muscle cells (44).

The role of T-type calcium channels in VH has not been well established; however, as evidenced by the paper published by Scanzi et al. (45), $Ca_V3.2$ may be a potentially powerful target for pharmacological intervention in the treatment of functional bowel disease. The T-type calcium channels regulate neuronal excitability in both the central and peripheral nervous systems and are linked to several pathophysiological disorders of the nervous system, including epilepsy, cardiovascular disease, and pain. Low threshold activation of $Ca_V3.2$ channels in the periphery regulates neuronal excitability, particularly in nociceptors, and even very small changes in membrane potential can elicit action potential firing. Presynaptic expression of $Ca_V3.2$ on central terminals of primary sensory neurons is capable of regulating spontaneous excitatory synaptic neurotransmission in the dorsal horn (46). At supraspinal levels, $Ca_V3.2$ contributes to thalamic processing of nociceptive signals (47). Recent rat studies have shown that increased $Ca_V3.2$ channel density in DRG neurons innervating the colon exacerbates VH and that antagonizing these channels prevented the development of VH (48). Scanzi *et al.* reported $Ca_V3.2$ to be overexpressed in the colonic mucosa of IBS patients compared to healthy controls. The group also found $Ca_V3.2$ knock-out mice were resistant to Dextran Sodium Sulfate (DSS) induced colonic hypersensitivity, and wild type mice treated with DSS compared to untreated had significantly increased $Ca_V3.2$ mRNA (45).

Impact of $Ca_v3.2$ on visceral hypersensitivity

Interestingly, $Ca_V3.2$ may act as an integrator of a variety of noxious inputs. It is activated by hydrogen sulfide (H_2S), which is produced endogenously in the intestinal lumen by sulfate-reducing bacteria, and has been shown to produce VH in otherwise healthy animals (49). A current topic of great interest in the field of IBS research is the role of intestinal flora on the gut-brain axis and its contribution towards functional bowel disease, as well as many other common maladies (50). While the true impact of the microbiome on the sensitivity of the gut is being actively pursued, it is widely accepted that the intestinal flora of IBS patients differs depending on symptomology-type and generally contains a larger population of sulfate-reducing bacteria (51) and rodent models of IBS are being adapted to incorporate alterations in the microbiome (52). It is important to note that expression of $Ca_V3.2$ is normally not observed in TRPV1-positive DRG neurons; however, it is upregulated in this population following systemic inflammation (53). Therefore, it is possible that novel $Ca_V3.2$ expression by TRPV1-positive afferent endings may contribute to increased neuronal excitability by integrating multiple environmental stimuli, including inflammatory and bacterial products, into the signaling properties of these important nociceptive endings.

Potential avenues for future research

It is clear that ion channels and ion channel receptors are an integral part of proper functioning of the gastrointestinal system. More importantly, the cross-talk and integration between different receptor types has highlighted the need to consider the system as a whole, rather than to dissect the role of individual channels and receptors. It will be imperative to keep in mind the complex relationship between ion channels and receptors expressed on the same cells, as well as signals from adjacent cells, when deciphering potential mechanisms that contribute to VH in IBS, as well as in other functional pain disorders.

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References

1. Palsson OS, Whitehead WE, van Tilburg MA, Chang L, Chey W, Crowell MD, Keefer L, Lembo AJ, et al. Rome IV Diagnostic Questionnaires and Tables for Investigators and Clinicians. Gastroenterology. 2016
2. Azpiroz F, Bouin M, Camilleri M, Mayer EA, Poitras P, Serra J, Spiller RC. Mechanisms of hypersensitivity in IBS and functional disorders. Neurogastroenterol Motil. 2007; 19:62–88. [PubMed: 17280586]
3. Camilleri M. Physiological underpinnings of irritable bowel syndrome: neurohormonal mechanisms. The Journal of physiology. 2014; 592:2967–2980. [PubMed: 24665101]
4. Kapeller J, Houghton LA, Monnikes H, Walstab J, Moller D, Bonisch H, Burwinkel B, Autschbach F, et al. First evidence for an association of a functional variant in the microRNA-510 target site of the serotonin receptor-type 3E gene with diarrhea predominant irritable bowel syndrome. Human molecular genetics. 2008; 17:2967–2977. [PubMed: 18614545]

5. Cenac N, Bautzova T, Le Faouder P, Veldhuis NA, Poole DP, Rolland C, Bertrand J, Liedtke W, et al. Quantification and Potential Functions of Endogenous Agonists of Transient Receptor Potential Channels in Patients With Irritable Bowel Syndrome. Gastroenterology. 2015; 149:433–444. e437. [PubMed: 25911511]
6. Zhao JH, Dong L, Shi HT, Wang ZY, Shi HY, Ding H. The expression of protease-activated receptor 2 and 4 in the colon of irritable bowel syndrome patients. Digestive diseases and sciences. 2012; 57:58–64. [PubMed: 21800160]
7. Christianson, JA.; Davis, BM. The Role of Visceral Afferents in Disease. In: Kruger, L.; Light, AR., editors. Translational Pain Research: From Mouse to Man. Boca Raton, FL: 2010.
8. Greenwood-van Meerveld B. Importance of 5-hydroxytryptamine receptors on intestinal afferents in the regulation of visceral sensitivity. Neurogastroenterol Motil. 2007; 19(Suppl 2):13–18. [PubMed: 17620083]
9. Spiller R. Serotonin and GI clinical disorders. Neuropharmacology. 2008; 55:1072–1080. [PubMed: 18687345]
10. Coates MD, Mahoney CR, Linden DR, Sampson JE, Chen J, Blaszyk H, Crowell MD, Sharkey KA, et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. Gastroenterology. 2004; 126:1657–1664. [PubMed: 15188158]
11. Tabas G, Beaves M, Wang J, Friday P, Mardini H, Arnold G. Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial. The American journal of gastroenterology. 2004; 99:914–920. [PubMed: 15128360]
12. Tack J, Broekaert D, Fischler B, Van Oudenhove L, Gevers AM, Janssens J. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. Gut. 2006; 55:1095–1103. [PubMed: 16401691]
13. Vahedi H, Merat S, Rashidioon A, Ghoddoosi A, Malekzadeh R. The effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study. Alimentary pharmacology & therapeutics. 2005; 22:381–385. [PubMed: 16128675]
14. Holzer P. Gastrointestinal afferents as targets of novel drugs for the treatment of functional bowel disorders and visceral pain. European journal of pharmacology. 2001; 429:177–193. [PubMed: 11698040]
15. Delvaux M, Louvel D, Mamet JP, Campos-Oriola R, Frexinos J. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. Alimentary pharmacology & therapeutics. 1998; 12:849–855. [PubMed: 9768527]
16. Mayer EA, Berman S, Derbyshire SW, Suyenobu B, Chang L, Fitzgerald L, Mandelkern M, Hamm L, et al. The effect of the 5-HT3 receptor antagonist, alosetron, on brain responses to visceral stimulation in irritable bowel syndrome patients. Alimentary pharmacology & therapeutics. 2002; 16:1357–1366. [PubMed: 12144587]
17. Steadman CJ, Talley NJ, Phillips SF, Zinsmeister AR. Selective 5-hydroxytryptamine type 3 receptor antagonism with ondansetron as treatment for diarrhea-predominant irritable bowel syndrome: a pilot study. Mayo Clinic proceedings. 1992; 67:732–738. [PubMed: 1434911]
18. Hicks GA, Coldwell JR, Schindler M, Ward PA, Jenkins D, Lynn PA, Humphrey PP, Blackshaw LA. Excitation of rat colonic afferent fibres by 5-HT(3) receptors. The Journal of physiology. 2002; 544:861–869. [PubMed: 12411529]
19. Ren TH, Wu J, Yew D, Ziea E, Lao L, Leung WK, Berman B, Hu PJ, et al. Effects of neonatal maternal separation on neurochemical and sensory response to colonic distension in a rat model of irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2007; 292:G849–G856. [PubMed: 17110521]
20. Bradesi S, Lao L, McLean PG, Winchester WJ, Lee K, Hicks GA, Mayer EA. Dual role of 5-HT3 receptors in a rat model of delayed stress-induced visceral hyperalgesia. Pain. 2007; 130:56–65. [PubMed: 17161536]
21. Miranda A, Peles S, McLean PG, Sengupta JN. Effects of the 5-HT3 receptor antagonist, alosetron, in a rat model of somatic and visceral hyperalgesia. Pain. 2006; 126:54–63. [PubMed: 16844296]

22. Stucky CL, Dubin AE, Jeske NA, Malin SA, McKemy DD, Story GM. Roles of transient receptor potential channels in pain. Brain research reviews. 2009; 60:2–23. [PubMed: 19203589]
23. Wouters MM, Balemans D, Van Wanrooy S, Dooley J, Cibert-Goton V, Alpizar YA, Valdez-Morales EE, Nasser Y, et al. Histamine Receptor H1-Mediated Sensitization of TRPV1 Mediates Visceral Hypersensitivity and Symptoms in Patients With Irritable Bowel Syndrome. Gastroenterology. 2016; 150:875–887. e879. [PubMed: 26752109]
24. Jankowski, MP.; Koerber, HR. Neurotrophic Factors and Nociceptor Sensitization. In: Kruger, L.; Light, AR., editors. Translational Pain Research: From Mouse to Man. Boca Raton, FL: 2010.
25. Dothel G, Barbaro MR, Boudin H, Vasina V, Cremon C, Gargano L, Bellacosa L, De Giorgio R, et al. Nerve fiber outgrowth is increased in the intestinal mucosa of patients with irritable bowel syndrome. Gastroenterology. 2015; 148:1002–1011. e1004. [PubMed: 25655556]
26. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004; 126:693–702. [PubMed: 14988823]
27. Klooker TK, Braak B, Koopman KE, Welting O, Wouters MM, van der Heide S, Schemann M, Bischoff SC, et al. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. Gut. 2010; 59:1213–1221. [PubMed: 20650926]
28. Jones RC 3rd, Xu L, Gebhart GF. The mechanosensitivity of mouse colon afferent fibers and their sensitization by inflammatory mediators require transient receptor potential vanilloid 1 and acid-sensing ion channel 3. J Neurosci. 2005; 25:10981–10989. [PubMed: 16306411]
29. Winston J, Shenoy M, Medley D, Naniwadekar A, Pasricha PJ. The vanilloid receptor initiates and maintains colonic hypersensitivity induced by neonatal colon irritation in rats. Gastroenterology. 2007; 132:615–627. [PubMed: 17258716]
30. Christianson JA, Bielefeldt K, Malin SA, Davis BM. Neonatal colon insult alters growth factor expression and TRPA1 responses in adult mice. Pain. 2010; 151:540–549. [PubMed: 20850221]
31. Cenac N, Altier C, Motta JP, d'Aldebert E, Galeano S, Zamponi GW, Vergnolle N. Potentiation of TRPV4 signalling by histamine and serotonin: an important mechanism for visceral hypersensitivity. Gut. 2010; 59:481–488. [PubMed: 20332520]
32. Sipe WE, Brierley SM, Martin CM, Phillis BD, Cruz FB, Grady EF, Liedtke W, Cohen DM, et al. Transient receptor potential vanilloid 4 mediates protease activated receptor 2-induced sensitization of colonic afferent nerves and visceral hyperalgesia. Am J Physiol Gastrointest Liver Physiol. 2008; 294:G1288–G1298. [PubMed: 18325985]
33. Valdez-Morales EE, Overington J, Guerrero-Alba R, Ochoa-Cortes F, Ibeakanma CO, Spreadbury I, Bunnett NW, Beyak M, et al. Sensitization of peripheral sensory nerves by mediators from colonic biopsies of diarrhea-predominant irritable bowel syndrome patients: a role for PAR2. The American journal of gastroenterology. 2013; 108:1634–1643. [PubMed: 23958521]
34. de Carvalho Rocha HA, Dantas BP, Rolim TL, Costa BA, de Medeiros AC. Main ion channels and receptors associated with visceral hypersensitivity in irritable bowel syndrome. Ann Gastroenterol. 2014; 27:200–206. [PubMed: 24976114]
35. Verne GN, Sen A, Price DD. Intrarectal lidocaine is an effective treatment for abdominal pain associated with diarrhea-predominant irritable bowel syndrome. J Pain. 2005; 6:493–496. [PubMed: 16084463]
36. Yiangou Y, Facer P, Chessell IP, Bountra C, Chan C, Fertleman C, Smith V, Anand P. Voltage-gated ion channel Nav1.7 innervation in patients with idiopathic rectal hypersensitivity and paroxysmal extreme pain disorder (familial rectal pain). Neuroscience letters. 2007; 427:77–82. [PubMed: 17928139]
37. Jarvis MF, Honore P, Shieh CC, Chapman M, Joshi S, Zhang XF, Kort M, Carroll W, et al. A-803467, a potent and selective Nav1.8 sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104:8520–8525. [PubMed: 17483457]

38. Verstraelen TE, Ter Bekke RM, Volders PG, Masclee AA, Kruimel JW. The role of the SCN5A-encoded channelopathy in irritable bowel syndrome and other gastrointestinal disorders. Neurogastroenterol Motil. 2015; 27:906–913. [PubMed: 25898860]
39. Beyder A, Farrugia G. Ion channelopathies in functional GI disorders. Am J Physiol Gastrointest Liver Physiol. 2016 ajpgi 00237 02016.
40. Beyder A, Mazzone A, Strege PR, Tester DJ, Saito YA, Bernard CE, Enders FT, Ek WE, et al. Loss-of-function of the voltage-gated sodium channel NaV1.5 (channelopathies) in patients with irritable bowel syndrome. Gastroenterology. 2014; 146:1659–1668. [PubMed: 24613995]
41. Cribbs LL. T-type Ca2+ channels in vascular smooth muscle: multiple functions. Cell Calcium. 2006; 40:221–230. [PubMed: 16797699]
42. Choudhury BK, Shi XZ, Sarna SK. Gene plasticity in colonic circular smooth muscle cells underlies motility dysfunction in a model of postinfective IBS. Am J Physiol Gastrointest Liver Physiol. 2009; 296:G632–G642. [PubMed: 19136376]
43. Wegener JW, Schulla V, Koller A, Klugbauer N, Feil R, Hofmann F. Control of intestinal motility by the Ca(v)1.2 L-type calcium channel in mice. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2006; 20:1260–1262. [PubMed: 16636102]
44. Zhang M, Leung FP, Huang Y, Bian ZX. Increased colonic motility in a rat model of irritable bowel syndrome is associated with up-regulation of L-type calcium channels in colonic smooth muscle cells. Neurogastroenterol Motil. 2010; 22:e162–e170. [PubMed: 20122129]
45. Scanzi J, Accarie A, Muller E, Pereira B, Aissouni Y, Goutte M, Joubert-Zakeyh J, Picard E, et al. Colonic overexpression of the T-type calcium channel Cav 3.2 in a mouse model of visceral hypersensitivity and in irritable bowel syndrome patients. Neurogastroenterol Motil. 2016
46. Sekiguchi F, Kawabata A. T-type calcium channels: functional regulation and implication in pain signaling. Journal of pharmacological sciences. 2013; 122:244–250. [PubMed: 23903007]
47. Liao YF, Tsai ML, Chen CC, Yen CT. Involvement of the Cav3.2 T-type calcium channel in thalamic neuron discharge patterns. Molecular pain. 2011; 7:43. [PubMed: 21639922]
48. Marger F, Gelot A, Alloui A, Matricon J, Ferrer JF, Barrere C, Pizzoccaro A, Muller E, et al. T-type calcium channels contribute to colonic hypersensitivity in a rat model of irritable bowel syndrome. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108:11268–11273. [PubMed: 21690417]
49. Kawabata A, Ishiki T, Nagasawa K, Yoshida S, Maeda Y, Takahashi T, Sekiguchi F, Wada T, et al. Hydrogen sulfide as a novel nociceptive messenger. Pain. 2007; 132:74–81. [PubMed: 17346888]
50. Moloney RD, Desbonnet L, Clarke G, Dinan TG, Cryan JF. The microbiome: stress, health and disease. Mamm Genome. 2014; 25:49–74. [PubMed: 24281320]
51. Chassard C, Dapoigny M, Scott KP, Crouzet L, Del'homme C, Marquet P, Martin JC, Pickering G, et al. Functional dysbiosis within the gut microbiota of patients with constipated-irritable bowel syndrome. Alimentary pharmacology & therapeutics. 2012; 35:828–838. [PubMed: 22315951]
52. O'Mahony SM, Felice VD, Nally K, Savignac HM, Claesson MJ, Scully P, Woznicki J, Hyland NP, et al. Disturbance of the gut microbiota in early-life selectively affects visceral pain in adulthood without impacting cognitive or anxiety-related behaviors in male rats. Neuroscience. 2014; 277:885–901. [PubMed: 25088912]
53. Watanabe M, Ueda T, Shibata Y, Kumamoto N, Shimada S, Ugawa S. Expression and Regulation of Cav3.2 T-Type Calcium Channels during Inflammatory Hyperalgesia in Mouse Dorsal Root Ganglion Neurons. PloS one. 2015; 10:e0127572. [PubMed: 25974104]

Key points

- Ion channels regulate every aspect of digestion: fluid secretion and absorption, motility, and visceral sensitivity.
- Visceral hypersensitivity (VH) in functional bowel disease, including irritable bowel syndrome, is largely driven by altered ion channel expression and function.
- T-type voltage-gated calcium channels (Ca_V) may provide a unique role as integrators of multiple environmental stimuli that drive VH.