TRP channels: new targets for visceral pain — **Source link** ↗

L A Blackshaw, Stuart M. Brierley, Patrick A. Hughes

Institutions: Royal Adelaide Hospital

Related papers:

- The ion channel TRPA1 is required for normal mechanosensation and is modulated by algesic stimuli.

- Selective Role for TRPV4 Ion Channels in Visceral Sensory Pathways

- 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

- Transient receptor potential vanilloid-4 has a major role in visceral hypersensitivity symptoms.

- Transient receptor potential vanilloid 4 mediates protease activated receptor 2-induced sensitization of colonic afferent nerves and visceral hyperalgesia

PUBLISHED VERSION

Blackshaw, Laurence Ashley; Brierley, Stuart Matthew; Hughes, Patrick Anthony
TRP channels: new targets for visceral pain, Gut, 2010; 59(1):126-135.

PERMISSIONS

http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse

Thus authors may use their own articles for the following non commercial purposes without asking our permission (and subject only to acknowledging first publication in the *BMJ* and giving a full reference or web link, as appropriate).

- Posting a pdf of their own article on their own personal or institutional website for which no charge for access is made.

10th January 2013

http://hdl.handle.net/2440/58410

TRP channels: new targets for visceral pain

L A Blackshaw,[1,2,3] S M Brierley,[1,2] P A Hughes[1,2]

[1] Nerve-Gut Research Laboratory, Department of Gastroenterology & Hepatology, Hanson Institute, Royal Adelaide Hospital, Adelaide, South Australia, Australia; [2] Discipline of Physiology, School of Molecular and Biomedical Sciences, The University of Adelaide, Adelaide, South Australia, Australia; [3] Discipline of Medicine, The University of Adelaide, Adelaide, South Australia, Australia

Correspondence to:
Professor L A Blackshaw, Nerve-Gut Research Laboratory, Department of Gastroenterology & Hepatology, Hanson Institute, Royal Adelaide Hospital, Adelaide, South Australia, Australia 5000; ashley.blackshaw@adelaide.edu.au

INTRODUCTION

How often do gastroenterologists advise patients to "avoid spicy food" without really knowing why? The answer may lie in the family of transient receptor potential (TRP) channels, which includes receptors for compounds found in common herbs and spices. This aim of this review is not really to answer this question, but it will shed light on why spices may cause symptoms. Instead, its aim is to explore the TRP family for potential targets that may in fact reduce gut symptoms. Chronic pain and discomfort of unknown origin in functional gastrointestinal disorders represent a large unmet need for treatment and consequent economic impact. There are also features of other gut disease which generate symptoms with obscure origins. In order to understand how symptoms are generated in the gut and transmitted to the central nervous system, we need to know at least three principles of extrinsic sensory nerve function—first, what types are there and what do they signal?; secondly, what is the molecular basis of sensory transduction?; and thirdly, how does all of this change in disease? These questions are a key focus of this article, with a particular emphasis on the role of TRP channels in each case. Although there are no drugs yet available for clinical use that target TRP channels, some of the early pointers are identified that hold promise for their use in pharmacotherapy of gastrointestinal sensory dysfunction.

DETECTION AND SIGNALLING OF GUT SYMPTOMS
Subtypes of sensory fibres

Peripheral endings of sensory afferent fibres can be classified into five subtypes in the mouse gastrointestinal tract according to the location of their mechanoreceptive fields.[1 2] These are: mucosal, muscular (or tension receptor), muscular–mucosal (or tension–mucosal), serosal and mesenteric afferents (fig 1).[1–4] Mucosal afferents respond exclusively to fine tactile stimulation of the luminal surface. Anatomically, they appear as bare endings in the lamina propria of villi.[5] Muscular afferents (or tension receptors) respond to distension at physiological levels (<20 mm Hg), and have specialised terminals that surround myenteric ganglia.[6–8] Serosal and mesenteric afferents respond at noxious levels of distension (>40 mm Hg),[1 4 9 10] and correspond to varicose branching axons close to blood vessels.[11] Muscular–mucosal afferents respond to both tactile and distension stimuli, but their anatomy has not been confirmed. These five classifications were made based primarily on functional observations, and we are still in the process of matching structure with function. This has probably led to the overlap in terminology between tension-sensitive afferents in the upper gastrointestinal tract (whose adequate stimulus defines their nomenclature), and afferents sensitive to distortion of muscle layers (defined according to location of receptive field). Other classifications have arisen in this and other species, but the consensus appears to be that there are fibres with low and high thresholds to distension, fibres that are distension insensitive (probably mucosal afferents) and a separate class of genuine mechanically insensitive fibres that respond only to chemical stimuli.[12 13] To name fibres based on the layer of the gut wall from which responses are most readily evoked is probably misplaced until the structural identity is confirmed anatomically. Thus, high threshold afferents are not exclusively in the serosa and mesentery, and may also be located in the submucosa.[11]

Mucosal afferents are abundant throughout the innervation of the gut, although scarce in the midcolon.[1] The role of mucosal receptors is unlikely to be in direct conscious perception of events in the gut, except in the anal and pharyngeal regions, where discrimination of solid, liquid and gas is required. It is likely that elsewhere they are important in refining the perception of other events such as distension and contraction, and/or in subliminal autonomic reflexes controlling gut function and behaviour. Stimulation of mucosal afferents in the stomach and small intestine is commonly associated with reduced food intake behaviour, nausea and vomiting, particularly after activation by enteroendocrine mediators.[14] Their functions in the lower bowel remain to be elucidated. Muscular–mucosal (or tension–mucosal) receptors exist in the oesophagus and distal colon/rectum which detect both tactile and distending stimuli, combining the functions of muscular and mucosal afferents in the same fibre. Their functional role is undetermined, but it is possible they may play a specialised role in detecting bolus or stool passage. The roles of other populations of sensory fibres are perhaps easier to envisage, with muscular (or tension) receptors providing input into perception of distension or contraction, and serosal mesenteric afferents detecting overdistension, high amplitude contraction, and distortion of blood vessels[15 16] Although the structure and localisation of afferent endings are very important in determining their physiological and pathophysiological roles, the range of ion channels, receptors and enzymes they express may be equally important.
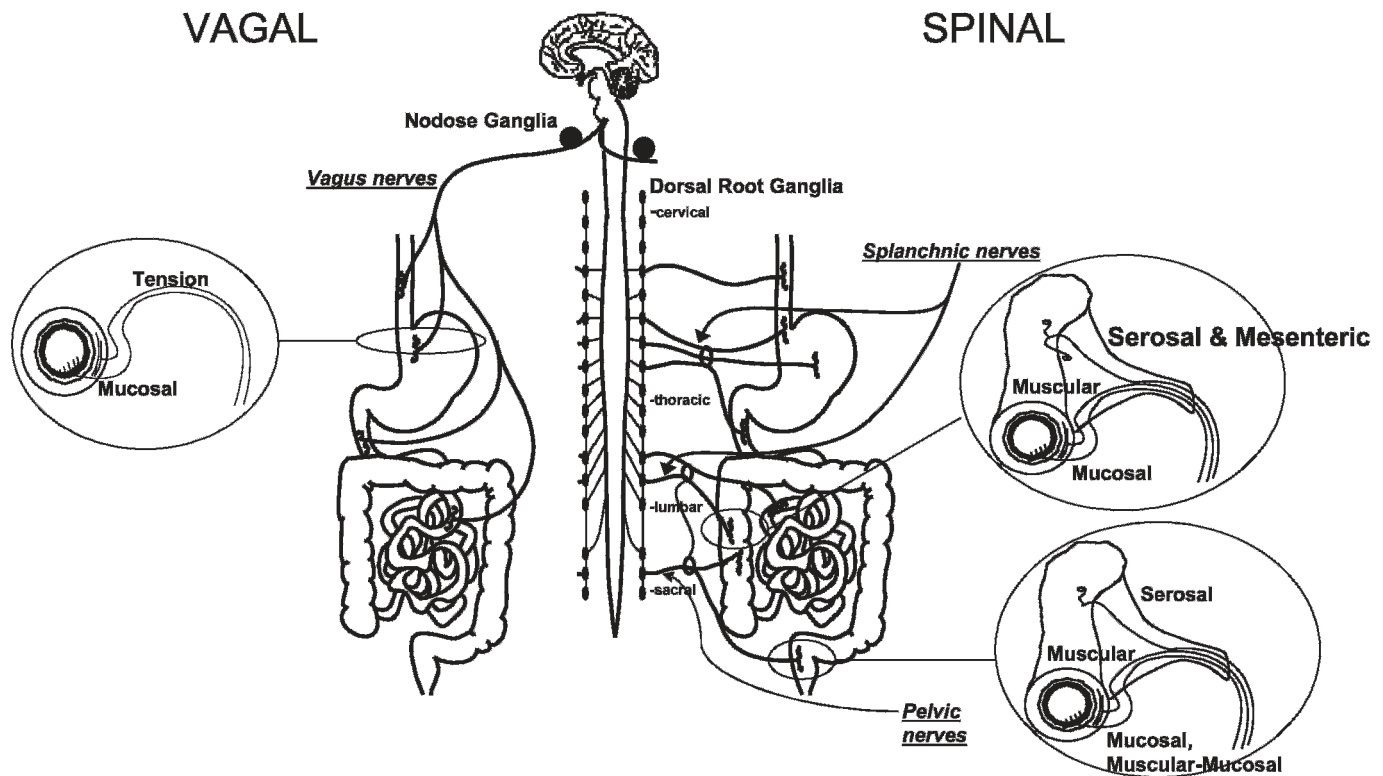
Figure 1 Schematic diagram showing the pathways and subtypes of gastrointestinal afferents, based mainly on our evidence from mouse experiments for simplicity. The vagal and spinal pathways are shown on mirror images of the gut for clarity. The locations of endings are based on functional localisation of mechanoreceptive fields, which in some cases is confirmed by anatomical studies. The splanchnic and pelvic innervations of the colon overlap in the distal colon (not shown), otherwise they are distinct. Tension–mucosal and muscular–mucosal afferents are not shown, but have properties consistent with a location of endings in both layers of the gut.

Pathways to the central nervous system

Sensory nerves follow three main pathways from the gastrointestinal tract to the central nervous system—the vagal, splanchnic and pelvic nerves. Vagal afferent fibres have neuronal cell bodies in the nodose and jugular ganglia, whilst the splanchnic and pelvic innervations have cell bodies in spinal thoracolumbar and lumbosacral dorsal root ganglia (DRGs), respectively. Gastrointestinal afferents in the vagal pathway (tension and mucosal) are typically associated with sensations such as satiety and nausea, although a subpopulation of oesophageal vagal afferents responds at high thresholds, implicating them in pain.[17] Spinal pathways innervate all viscera and are associated with sensations of pain, discomfort, bloating and urgency to void.[15] Correspondingly, the majority of vagal afferents innervating smooth muscle respond over a restricted range of distension pressures, whereas spinal afferents respond over a wide dynamic range.[4 18 19] There are differences within the spinal innervation, such that the pelvic pathway contains both non-nociceptive and nociceptive afferents, whilst splanchnic afferents have generally higher mechanical thresholds, with few mucosal and muscular afferents, constituting primarily a nociceptive pathway.[1] Understanding the specialised roles of TRP channels in visceral pain will depend on determining which of the afferent subtypes and pathways express particular channels, and the consequence of blocking their function in each subtype.

ROLES OF TRP CHANNELS IN SENSORY SIGNALLING
### The range available, and their localisation

The TRP family comprises five subfamilies (TRPA, TRPC, TRPM, TRPP and TRPV) in mammals, which share several key properties: they are non-selective cation channels and most have six transmembrane domains (fig 2). As their name suggests, they were first identified as channels mediating brief excitatory events in non-mammalian sensory systems, although their roles have outgrown this original label as evident from the discussion below. They are grouped according to their structural similarities, and are discussed below in order of the interest that has been expressed in them in visceral sensory pathways. For a more complete review of their functions in various physiological systems, see reviews by Clapham,[20] Dhaka et al[21] and Christensen and Corey.[22] TRP channels have received fame and/or notoriety in a number of fields, including pain,[23] respiratory and cardiac function,[24 25] ion metabolism and absorption.[26]

TRPV

The TRPV, or vanilloid family, is probably the best known subfamily of TRP channels, notably TRPV1

Figure 2 Schematic structure of transient receptor potential (TRP) channels discussed in this review. Extracellular is shown uppermost. Note the ankyrin repeats in putative mechanosensitive channels, and several of them have interaction sites where effector function can be modulated. Modified from Dhaka et al.[21] PIP2, phosphatidylinositol bisphosphate.
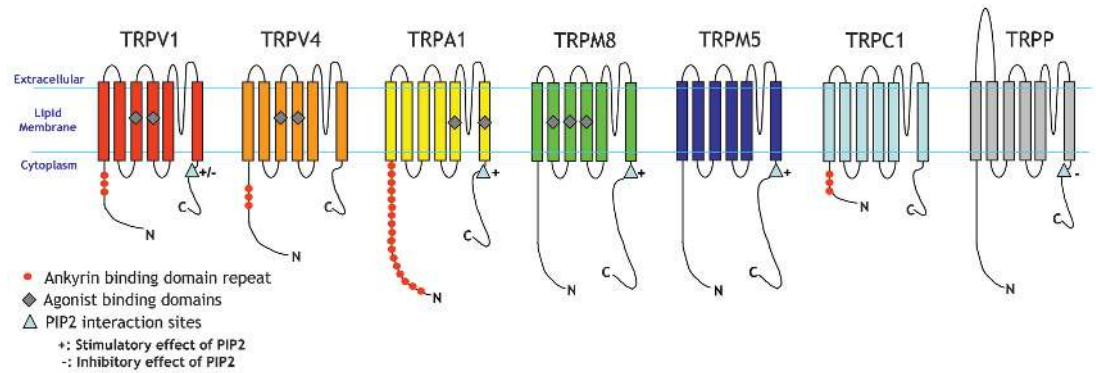
which is activated by the vanilloid chilli extract capsaicin. TRPV1 expression is greater in gut-innervating neurons that in those innervating the skin,[27] with 50–60% of lumbosacral and 82% of thoracolumbar colonic DRG neurons displaying TRPV1 immunoreactivity,[13 27 28] similar to the proportion of thoracic gastric DRG neurons.[29] TRPV1 is also found in peripheral terminals throughout the gut,[30] and in 40–80% of nodose ganglion neurons innervating the stomach.[29 31] TRPV4 is the mammalian homologue of the *Caenorhabditis elegans* osmosensory gene Osm-9[32]; it responds to extracts of the herb *Andrographis paniculata*.[33] TRPV4 is located at sites of mechanical stimulus detection including inner-ear hair cells, sensory neurons and somatic mechanosensory structures.[32] TRPV4 appears to be enriched within certain populations of sensory neurons in the DRGs. There is greater TRPV4 mRNA expression in colonic sensory neurons than in whole DRGs. Within the thoracolumbar (splanchnic) DRGs, TRPV4 mRNA in identified colonic neurons is 20 times that in whole DRGs. Differences between pathways are also evident, with colonic sensory neurons expressing 3–8 times the levels of TRPV4 in identified gastric vagal sensory neurons. TRPV4 is found in 38% of gastro-oesophageal vagal neurons, 65–76% of splanchnic colonic DRG neurons and 58% of pelvic colonic DRG neurons.[3] In the periphery, TRPV4 protein co-localises with calcitonin gene-related peptide (CGRP) in colonic nerve fibres in the outermost (serosal and mesenteric) layers but is scarce in intramuscular or mucosal endings. This pattern of localisation is apparent in both mouse and human tissue,[3] and correlates well with the functional role of TRPV4 (see below). Other members of the vanilloid family include TRPV2, 3, 5 and 6, whose function in the gut has not yet been investigated. TRPV2 is expressed in gastric vagal afferents, but not TRPV3.[34]

TRPA

The ankyrin, or TRPA family has only one member—TRPA1—which is the mammalian orthologue of the *Drosophila* gene painless, where it is expressed in polymodal nociceptor endings and contributes to the detection of intense mechanical stimuli. It has a characteristic large number of ankyrin protein repeats, thought to act as a spring and intracellular anchor, which may contribute to mechanosensory transduction[35] (fig 2). It responds to a range of environmental irritants[36–38] and extracts of mustard, cinnamon, garlic and oregano[39–42] (table 1). TRPA1 is localised in 55% of gastro-oesophageal vagal afferents, 54% of splanchnic colonic afferents and 58% of pelvic colonic afferents.[43]

TRPM

The melastatin, or TRPM family, was originally named for the antimelanoma properties of TRPM1. There are two members of interest: TRPM8 is now widely researched because it mediates the cooling and soothing sensation of menthol, icilin and eucalyptol.[21 44] Thus, TRPM8 may be critical in alleviating pain. TRPM8 is localised in DRG neurons that do not co-localise with the "algesic" TRP channels V1 and A1.[45] It would be most valuable to determine TRPM8 expression and function in specific subpopulations of visceral afferents, which, by analogy with skin, may have an antinociceptive function. TRPM5 is localised in taste buds, where it is part of the pathway leading to release of neurotransmitters involved in various taste modalities.[46 47] It is also found in the gut epithelium, where it may serve a similar function.[48 49]

TRPC

The canonical, or TRPC family has six members, most of which operate as classical calcium channel effectors, rather than sensors. Their sensory role in the gut is currently being investigated. TRPC1 was of interest, since it was shown to play a role in mechanosensation in recombinant systems.[50] However, this evidence has been refuted, and the role of TRPC1 in mechanosensation has been cast in doubt.[51]

TRPP

The polycystin, or TRPP family has four members, TRPP1, 2, 3 and 5. Their name is derived from an association between a TRPP mutation and polycystic kidney disease. They play roles in developmental guidance and ciliary function. TRPP1 (an 11-domain protein) and TRPP3 must couple

Table 1 A select list of transient receptor potential (TRP) channels, their natural ligands, physical stimuli and localisation, where known

Channel	Natural ligand	Physical stimuli	Direct endogenous stimuli	Indirect endogenous stimuli	Locations found
TRPV1	Capsaicin, acid	Thermal > 43°C	Acid, anandamide	Cannabinoids, bradykinin, serotonin, proteases	Sensory neurons, oesophageal stratum granulosum and muscularis mucosa
TRPV4	*Andrographis paniculata* (Chinese herbal medicine)	Mechanical, thermal > 25°C	Anandamide, arachidonic acids, epoxyeicosatrienoic acid metabolites	Proteases	Sensory neurons, inner ear, colonic brush-bordered epithelial cells
TRPA1	Mustard, oregano, cinnamon, garlic	Mechanical, thermal <17°C	4-Hydroxnonenal	Cannabinoids, bradykinin, prostaglandins, proteases	Sensory neurons, inner ear, enteroendocrine cells
TRPM8	Peppermint, eucalyptus	Thermal <28°C	Lysophospholipids		Sensory neurons, bladder, prostate
TRPM5			Phospholipase Cβ2	Sugars	Taste cells, enteroendocrine cells
TRPC1		Mild mechanical			Sensory neurons, brain
TRPP2 and 3	Acid	Mild mechanical			Central canal spinal cord

together as a heterodimer to act as a signalling complex (also known as PKD1L3 and PKD2L1), which is unlike other TRP channels where homo-tetramers are the normal configuration. They recently received interest in connection with a role in acid sensing,[52][53] although such a role in the gut remains to be tested.

TRPML

The mucolipin, or TRPML family has three members, one of which is associated with muco-lipidosis. They have an intracellular function putatively in vesicle formation[20] and will not be considered further here.

TRP channels as detectors

TRP channels are proposed to be primary transducers of thermal, mechanical and chemical stimuli. Thermal transduction is unlikely to be important in the gut and will not be discussed in detail. There are several mechanosensory and chemosensory properties (table 1 and outlined below) that make particular TRP channels important targets for investigation in gastrointestinal sensory pathways. In contrast to their established roles as chemosensors, conclusive evidence that TRP channels function as mechanosensors has been elusive as this requires mechanosensory function studies from isolated channels to intact sensory fibres to intact animals.

TRPV

TRPV1 is activated by capsaicin, noxious heat, low pH and a range of herb and spice extracts (table 1). We are all familiar with the burning sensation evoked by capsaicin applied to the mouth or mucous membranes, and when administered intra-colonically it causes pronounced pain.[54] However, capsaicin also activates non-nociceptive upper

gastrointestinal vagal afferents,[55] which may be relevant to symptoms generated in humans, discussed later. Genetic deletion of TRPV1 has no significant effect on mechanosensory function of somatic nociceptors,[56] but there are deficits in TRPV1$^{-/-}$ visceral mechanoreceptors (table 2). In the gastro-oesophageal region TRPV1 knockouts had reduced vagal afferent responses to distension.[57] TRPV1 knockouts also have significantly reduced responses of jejunal wide-dynamic range afferents to distension, but had normal function of low or high threshold afferents.[58] In the distal colon/rectum TRPV1 deletion significantly reduced the distension responses of pelvic muscular and muscular–mucosal afferents,[59] but not responses to mucosal stroking. Effects on serosal afferents were not reported. Therefore, TRPV1 deletion consistently reduces the mechanosensitivity of distension-sensitive gastro-oesophageal, jejunal and pelvic colonic afferents. Similar deficits were found in bladder afferents.[60] Capsaicin potently activates splanchnic and pelvic colonic serosal afferents, which is followed by pronounced mechanical desensitisation in splanchnic but not pelvic afferents.[13] This suggests that the coupling of TRPV1 differs between pathways. Whereas TRPV1$^{-/-}$ mice had normal somatic mechanical pain sensitivity,[56] their behavioural responses to colorectal distension were reduced.[59] Therefore, TRPV1 is important in the signalling of physiological mechanical stimuli from throughout the viscera.

Since TRPV1 normally responds to low pH,[61] this makes it a prime candidate for the sensing of refluxed acid in the oesophagus, and giving rise to the sensation of heartburn. Indeed it has been detected in fibres innervating the human oesophageal mucosa.[62][63] Mice lacking TRPV1 channels develop significantly less oesophagitis after acid exposure compared with wild-type mice,[64] suggesting a role beyond sensory function. In the guinea-pig, oesophageal tension-sensitive vagal afferents termed "nociceptive-like" are distinguishable from "non-nociceptive-like" afferents by their responsiveness to capsaicin.[17] These "nociceptive-like" tension receptors in the oesophagus are stimulated by acid.[65] In contrast, the responses of "non-nociceptive" tension receptors to acid are less well defined. Rong et al[58] showed that responses of jejunal afferents to acid were reduced up to 50% in TRPV1 knockouts, indicating a major, but not exclusive role for TRPV1 in detecting low pH.

TRPV4 is involved in the transduction of osmotic stimuli and is also implicated in mechanosensory function, since TRPV4$^{-/-}$ mice show reduced behavioural sensitivity to noxious somatic mechanical stimuli.[32][66] The role of TRPV4 in the viscera is more discrete (table 2): deletion of TRPV4 had no effect on vagal afferent function,[3] consistent with low TRPV4 expression in gastro-oesophageal vagal afferents. However, in colonic afferents, where TRPV4 is enriched, mechanosensory responses were dramatically reduced in TRPV4 knockouts, and mechanosensory thresholds were increased. This was the case for both

Table 2 A summary of the effects of selected transient receptor potential (TRP) channel deletion, utilising knockout mice, on intestinal afferent mechanosensory function and of TRP channel antagonists on mouse afferent function

Channel	Vagal gastro-oesophageal afferents		Vagal/spinal jejunal afferents			Splanchnic distal colon afferents		Pelvic colorectal afferents				Response to colorectal balloon distension
	Mucosal	Tension	Low threshold	Wide dynamic range	High threshold	Mesenteric	Serosal	Serosal	Mucosal	Muscular	Muscular–Mucosal	
TRPV1												
−/−		↓	↔	↓	↔			↔	↔	↔	↓↓	↓↓
Antagonist			↓	↓	↓			↔			↓↓	
TRPV4												
−/−	↔	↔				↓↓	↓↓	↓↓	↔	↔	↔	↓↓
Antagonist						↓↓	↓↓	↓↓				
TRPA1												
−/−	↓	↔				↓↓	↓↓	↓↓	↓	↔	↔	
Antagonist												

Arrows indicate the degree of change in mechanosensory function. Empty cells indicate not tested.

splanchnic and pelvic high threshold (serosal and mesenteric) afferents, which was consistent with TRPV4 expression in the periphery. These deficits were restricted to mechanosensory function, since afferent excitability, electrical thresholds and conduction velocities were identical in TRPV4$^{-/-}$ and TRPV4$^{+/+}$ mice. However, as was the case in the vagal pathway, pelvic mucosal and muscular afferents were normal. Thus, TRPV4 makes a specific and major contribution to colonic high threshold mechanosensory afferent function, and as such is the only nociceptor-specific TRP channel as yet identified.

Opening the TRPV4 channel pharmacologically increases the afferent response to mechanical stimuli. The endogenous arachidonic acid metabolite 5,6-EET is an agonist of TRPV4, which causes significant potentiation of mechanosensory responses in wild-type mice, but not in TRPV4 knockouts. Pharmacological blockade with the non-selective TRP channel blocker ruthenium red correspondingly reduces mechanosensitivity only in wild-type mice.[3][67] Consistent with effects of TRPV4 activation in colonic afferent endings, 4α-PDD, a synthetic TRPV4 agonist, caused significant TRPV4-mediated calcium influx in isolated colonic DRG neurons.[68] From these data it is clear that alterations in the pharmacology of splanchnic and pelvic colonic afferents parallel the changes in mechanosensitivity in TRPV4 knockouts, indicating that there may be potential for development of a nociceptor-specific analgesic.

The selective role of TRPV4 in high threshold afferents would be expected to translate into a role in pain perception in vivo, which was indeed the case. There were decreased abdominal electromyographic (EMG) responses to noxious colorectal distension in TRPV4 knockouts or in mice with downregulated TRPV4 expression (via intervertebral small interfering RNA (siRNA) delivery).[3][68] This was apparent particularly at higher distension pressures. Intracolonic administration of 4α-PDD in wild-type mice caused neuronal activation in the lumbosacral spinal cord and caused dose-dependent visceral hypersensitivity to colorectal distension.[68]

TRPA

TRPA1 was originally thought to play a role in hair cells of the inner ear, but TRPA1$^{-/-}$ mice have normal hearing.[36][69] One line of TRPA1-deficient mice has increased pain thresholds to somatic mechanical stimuli,[69] but another line had normal responses to noxious stimuli,[36] so the contribution of TRPA1 to somatosensory function is unresolved. Its role in the gut is becoming clearer, although results are still preliminary. TRPA1$^{-/-}$ mice have reduced mechanosensitivity of mucosal afferents in vagal and pelvic pathways. TRPA1 deletion also reduced the stimulus–response functions of high threshold colonic splanchnic and pelvic serosal and mesenteric afferents. However, the distension responses of vagal tension receptors and pelvic muscular and muscular–mucosal afferents were unaltered.[43] Taken together these data suggest paradoxically that TRPA1 contributes to mechanosensation in both tactile and nociceptive afferents, but not in others.

A nociceptive role for TRPA1 was also apparent in vivo; intrathecal administration of TRPA1 antisense oligodeoxynucleotide in rats (to reduce TRPA1 expression in DRGs) reduced the colitis-induced hyperalgesia to nociceptive colonic distension and intracolonic mustard oil.[70] Although TRPA1 may not be as specific in its role as TRPV4, it is clearly evident as a target for reducing signalling of pain from the colon. When its role in mucosal afferents emerges, this may provide important insight into not only the functional role of the channel, but also the role of this subtype of afferents in sensation from the lower gut.

TRPM

Evidence for or against TRPM8 as a mechanosensor is lacking. Activation of a subpopulation of cutaneous sensory neurons by TRPM8 agonists elicits analgesia in chronic pain models in rats, which is blocked by siRNA knockdown of TRPM8.[71] This analgesic effect of TRPM8-sensitive afferents is probably centrally mediated through activation of inhibitory interneurons in the spinal dorsal horn. This is similar to a somatosensory

process known as "gate control",[72] which underlies the analgesic effects of massage and transcutaneous electrical nerve stimulation. Although the exact mechanisms involved are unknown, the role of TRPM8 in gate control is potentially important. TRPM8 agonists are already known to activate non-nociceptive vagal afferent neurons innervating the gut.[34]

TRPP

TRPP1 and 2 are recent mechanosensory candidates in the primary cilium of kidney cells[73] and are suggested to be important in ciliated mechanosensory structures that detect very small forces. Therefore, this may be important in colonic mucosal afferents which are highly tactile. It was recently shown that PKD1L3 and PKD2L1 are activated by various acids at pH <3 when co-expressed in heterologous cells but not by other classes of tastants.[52 53] These results suggest that TRPPs may function as sour taste receptors, which begs the question as to whether they may be involved in the detection of refluxed acid in the oesophagus. Since knockouts of these channels are lethal, advances in the field may well depend on novel pharmacology in recombinant systems.

TRP channels as effectors

TRP channels can also function as effectors, mediating excitation of cells in response to activation of G-protein-coupled receptors and other channels (table 1). This is an important aspect of the biology of most TRP subfamilies, and in some cases it is their only identified role, for example in some members of the TRPC family.[74] The effector function of TRP channels is, however, important in sensory nerve function, such as inflammatory pain evoked by the mediators bradykinin[36] and mast cell proteases.[75] TRPV1 is not considered to be directly mechanically gated; therefore, the effects on mechanosensation may be mainly due to indirect effects on neuron excitability or via interactions with other receptors or TRP channels. For example, 5-hydroxytryptamine (5-HT) enhances sensitivity to heat in colonic DRG neurons via TRPV1[76], which leads to excitation at normal body temperature. Protease-activated receptor 2 (PAR$_2$) sensitises TRPV1 through defined intracellular pathways.[77] Cannabinoids modulate TRPV1 either by a direct interaction of the eicosanoid mediator anandamide with the channel itself, or by coupling through intracellular pathways after acting on G-protein-coupled cannabinoid receptors.[78 79]

In addition to its coupling with TRPV1, there is also evidence for a strong interaction of PAR$_2$ with TRPV4, which may contribute to visceral hypersensitivity.[67 68] TRPV4 and PAR$_2$ are co-expressed in a large proportion of colonic sensory neurons.[67 68] In isolated colonic DRG neurons, PAR$_2$-activating peptide (AP) sensitises TRPV4-mediated currents, whilst PAR$_2$ AP also activates splanchnic serosal colonic afferent endings, but not in TRPV4 knockouts.[67] Intracolonic administration of PAR$_2$ AP increases the behavioural response to noxious colorectal distension, an effect also lost in TRPV4$^{-/-}$ mice.[67 68]

PAR$_2$ interacts with TRPA1 via similar intracellular mechanisms to those involved with TRPV1.[80] TRPA1 can also be indirectly activated by bradykinin,[36 81] and mediates bradykinin-induced mechanical hypersensitivity in the guinea-pig oesophagus.[82] In the colon bradykinin induces mechanical hypersensitivity in splanchnic serosal afferents,[12] which is lost in fibres from TRPA1$^{-/-}$ mice.[43]

Other TRP channels are also associated with bradykinin activation, including TRPC1, whereby specific signalling from the BK2 receptor opens TRPC1.[83] Thus TRPC1, like TRPV4 and TRPA1, interacts with inflammatory G-protein-coupled receptors. However, in contrast to TRPV1, TRPA1 and TRPC1, which are all sensitised by BK2 receptor activation, TRPM8 function is inhibited by bradykinin via a reduction in intracellular phosphoinositide (PIP$_2$) levels.[21 84]

In addition to its role in neurons, there is emerging evidence for involvement of TRPA1 in mediator release from enteroendocrine cells. Enterochromaffin cells express TRPA1 and release serotonin cholecystikinin (CCK) in response to mustard oil,[85] which also releases CCK from the enteroendocrine cell line STC-1,[86] suggesting that dietary spices may augment release of mucosal mediators in response to nutrients.

Although the role of TRPM5 is best established in the tongue, as a channel that couples taste receptor activation with cation influx, via the G-protein–phospholipase C pathway,[46 47] it is also known to be expressed in the gut epithelium, where it may serve a similar "tasting" function. In keeping with this, its expression is regulated by changes in luminal or systemic glucose concentration.[49]

Although TRP channels function as effectors for many pathways, single TRP knockouts normally retain some response to the initial stimulus, for example in bradykinin-evoked excitation of airway afferents,[87] suggesting that there are parallel mechanisms—either other TRP channels or completely distinct pathways.

TRP channels may interact with one another, for example TRPA1 and TRPV1 are often co-localised in nociceptive DRG neurons, where a TRPA1 agonist causes cross-desensitisation of responses to capsaicin, and vice versa.[87] Whether or not TRP channels may couple together positively, and therefore act as effectors for one another, is not yet evident.

CHANGES IN SENSORY SIGNALLING IN DISEASE

The effects of inflammation on visceral afferent endings have been studied by several groups, with a view to finding a model for postinfectious irritable bowel syndrome (eg, Mayer and Gebhart[89]). The majority of electrophysiological studies in the literature have focused on the responses of afferents to colorectal distension and how this is altered by inflammation. A recent study by DeSchepper et al[90] showed that acute

trinitrobenzene sulfonic acid (TNBS) colitis in rats increased the response to colorectal distension of pelvic afferent C-fibres in vivo; the increased sensitivity to distension was reduced by a TRPV1 antagonist. An earlier study by Sengupta et al[91] using an identical in vivo rat TNBS protocol recording from the same population of afferents did not reveal any changes in mechanosensitivity, so there is clearly controversy in this area. In agreement with Sengupta's[91] findings in rat, Jones et al[92] saw no change in mechanosensitivity of pelvic muscular or muscular–mucosal afferents in a mouse zymosan colonic inflammation model. The behavioural response to colorectal distension was, however, increased after zymosan, and this remained to an extent in TRPV1 knockouts, so the mechanism underlying pain hypersensitivity was not revealed. In a model of colonic hypersensitivity induced by colonic irritation in neonatal rats,[93] TRPV1 inhibitors were effective in reducing pain responses to colorectal distension. Increased expression of TRPV1 in DRGs is evident in this model, as well as in a TNBS colitis model,[94] suggesting that TRPV1 upregulation may be a mechanism by which the effect of a TRPV1 antagonist becomes manifest. In a model of pancreatic inflammation this mechanism was confirmed.[95] The upregulation of function via TRPV1 can be long lasting, and may initiate other events leading to hypersensitivity.[93][94] Alternatively, the translocation of TRPV1 to the cell membrane may have an important influence on its function independent of changes in expression.[96] Studies of biopsies from patients with visceral hypersensitivity, either in irritable bowel syndrome (IBS)[97] (fig 3) or in non-erosive reflux disease,[63] show that mucosal fibres containing TRPV1 may be increased in number up to 3.5-fold, and that this increase may correlate with symptoms. Chan et al[98] showed that increased rectal sensitivity was associated with increased TRPV1 fibres in all layers of the gut wall.

Mustard oil, which we now know to be a selective TRPA1 agonist, has long been used as a visceral inflammatory model to sensitise nociceptors and provoke tissue damage.[54] This suggests that TRPA1 has a role not only in activation of sensory pathways, but also in local neurogenic inflammation, presumably after evoking release of peptides such as substance P from peripheral endings. Studies are ongoing to determine if TRPA1 function or expression is increased in inflammatory models or patients with IBS.

From the perspective of active inhibition of visceral pain the observation is worth noting that a combination of peppermint oil (a TRPM8 agonist) and caraway oil attenuates postinflammatory visceral hyperalgesia in rats,[99] which may correlate with its therapeutic effects in patients described below.

THERAPEUTIC OPPORTUNITIES

A hallmark of functional gastrointestinal disorders is allodynia and hyperalgesia to mechanical events,[100–102] and low-grade inflammatory status.[103–105] Therefore, treatments are needed that reduce signalling of
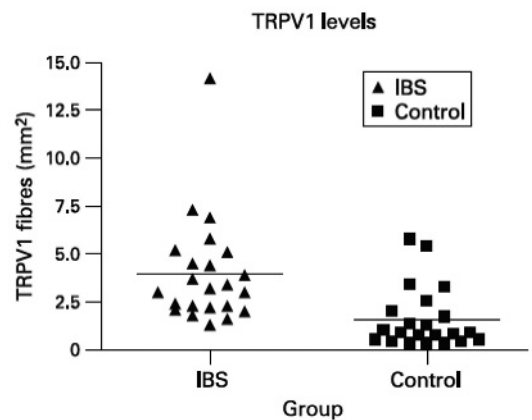
Figure 3 Number of transient receptor potential V1 (TRPV1)-immunoreactive fibres/mm² in rectosigmoid biopsies from patients with irritable bowel syndrome (IBS) and control groups; p = 0.001. From Akbar et al[97], with permission.

nociceptive mechanosensory and inflammatory events. TRP channels are clearly involved in both of these processes. Normally, there is a constant stream of subliminal information from the gut, which is involved in autonomic reflexes controlling motor and secretory function. It is therefore important to distinguish this information from nociceptive signals in targeting visceral pain to avoid altering normal gut function. So far, TRPV4 is the only TRP channel that appears to be nociceptor specific, but ironically is the least well served pharmacologically. As with many other TRP channels, its localisation is not, however, confined to sensory neurons,[105] so the potential exists for off-target adverse effects. Such effects have applied powerful brakes to the progress of other types of treatments for visceral pain, but it could be argued that in the case of TRP channels, there are fewer other target tissues to be concerned about. We hope this article may provide a stimulus for further development of selective drugs, either as pharmacological treatments or as tools to investigate the roles of TRP channels more effectively. Another interesting application of TRP channel pharmacology is in diagnostic testing for functional gastrointestinal disorders. Administration of a capsaicin capsule produces more symptoms including pain, warmth and pressure in patients with functional dyspepsia compared with controls.[107] Although the predictive value is far from ideal—only half the patient cohort were responsive—there is promise for development of better provocative tests for functional disorders, considering we have very few options currently.

Herbal preparations containing peppermint have been successful in the treatment of functional dyspepsia,[108] although whether this is a sensory or motor effect and whether it is mediated via TRPM8 remain to be seen. Several clinical trials have been conducted with selective TRP channel antagonists for pain,[109] such as the TRPV1 antagonist, AMG-517, which was discontinued due to causing hyperthermia after systemic administration. Pharmaceutical companies are currently

determining whether this liability for TRPV1 antagonists can be managed. Site-specific administration of TRPV1 desensitisation gets around this issue, and has shown promise in other visceral neurological disease, reviewed elsewhere,[110 111] but whether the gut is an appropriate place for site-specific interventions remains a difficult question. By far the greatest attention has been given to TRPV1 as a therapeutic target, and there is still potential for its successful exploitation despite the current problems, not only in visceral pain, but also in neurogenic inflammation.[112] Hopefully it is clear from this review that there are many other emerging candidates within the TRP family. We discussed earlier evidence that the role of TRP channels may be increased in pathological conditions such as IBS; this suggests that normalising their function may be sufficient for therapeutic benefit without blocking their function totally, and may provide more scope for entry of compounds into the market. It is also possible that the role of TRP channels as effectors for other receptors associated with pain may provide a bonus in the antinociceptive actions of anti-TRP treatment.

REFERENCES

1. **Brierley SM,** Jones RCW III, Gebhart GF, et al. Splanchnic and pelvic mechanosensory afferents signal different qualities of colonic stimuli in mice. Gastroenterology 2004;**127**:166–78.
2. **Page AJ,** Martin CM, Blackshaw LA. Vagal mechanoreceptors and chemoreceptors in mouse stomach and esophagus. J Neurophysiol 2002;**87**:2095–103.
3. **Brierley SM,** Page AJ, Hughes PA, et al. Selective role for TRPV4 ion channels in visceral sensory pathways. Gastroenterology 2008;**134**:2059–69.
4. **Hughes PA,** Brierley SM, Martin CM, et al. Post-inflammatory colonic afferent sensitization: different subtypes, different pathways, and different time-courses. Gut 2009;**58**:1333–41.
5. **Berthoud HR,** Kressel M, Raybould HE, et al. Vagal sensors in the rat duodenal mucosa: distribution and structure as revealed by in vivo DiI-tracing. Anat Embryol (Berl) 1995;**191**:203–12.
6. **Berthoud HR,** Powley TL. Vagal afferent innervation of the rat fundic stomach: morphological characterization of the gastric tension receptor. J Comp Neurol 1992;**319**:261–76.
7. **Lynn PA,** Olsson C, Zagorodnyuk V, et al. Rectal intraganglionic laminar endings are transduction sites of extrinsic mechanoreceptors in the guinea pig rectum. Gastroenterology 2003;**125**:786–94.
8. **Zagorodnyuk VP,** Brookes SJ. Transduction sites of vagal mechanoreceptors in the guinea pig esophagus. J Neurosci 2000;**20**:6249–55.
9. **Blumberg H,** Haupt P, Janig W, et al. Encoding of visceral noxious stimuli in the discharge patterns of visceral afferent fibres from the colon. Pflugers Arch 1983;**398**:33–40.
10. **Morrison JFB.** Splanchnic slowly adapting mechanoreceptors with punctate receptive fields in the mesentery and the gastrointestinal tract of the cat. J Physiol 1973;**233**:349–61.
11. **Song X,** Chen BN, Zagorodnyuk VP, et al. Identification of medium/high threshold extrinsic mechanosensitive afferent nerves to the gastrointestinal tract. Gastroenterology 2009;**137**:274–84.
12. **Brierley SM,** Jones III RCW, Xu L, et al. Activation of splanchnic and pelvic colonic afferents by bradykinin in mice. Neurogastroenterol Motil 2005;**17**:854–62.
13. **Brierley SM,** Jones III RCW, Xu L, et al. Differential chemosensory function and receptor expression of splanchnic and pelvic colonic afferents in mice. J Physiol 2005;**567**:267–81.
14. **Andrews PL,** Sanger GJ. Abdominal vagal afferent neurones: an important target for the treatment of gastrointestinal dysfunction. Curr Opin Pharmacol 2002;**2**:650–6.
15. **Blackshaw LA,** Gebhart GF. The pharmacology of gastrointestinal nociceptive pathways. Curr Opin Pharmacol 2002;**2**:642–9.
16. **Brunsden AM,** Brookes SJ, Bardhan KD, et al. Mechanisms underlying mechanosensitivity of mesenteric afferent fibers to vascular flow. Am J Physiol Gastrointest Liver Physiol 2007;**293**:G422–8.
17. **Yu S,** Undem BJ, Kollarik M. Vagal afferent nerves with nociceptive properties in guinea-pig oesophagus. J Physiol 2005;**563**:831–42.
18. **Booth CE,** Kirkup AJ, Hicks GA, et al. Somatostatin sst(2) receptor-mediated inhibition of mesenteric afferent nerves of the jejunum in the anesthetized rat. Gastroenterology 2001;**121**:358–69.
19. **Sengupta JN,** Saha JK, Goyal RK. Stimulus–response function studies of esophageal mechanosensitive nociceptors in sympathetic afferents of opossum. J Neurophysiol 1990;**64**:796–812.
20. **Clapham DE.** TRP channels as cellular sensors. Nature 2003;**426**:517–24.
21. **Dhaka A,** Viswanath V, Patapoutian A. TRP ion channels and temperature sensation. Annu Rev Neurosci 2006;**29**:135–61.
22. **Christensen AP,** Corey DP. TRP channels in mechanosensation: direct or indirect activation? Nat Rev Neurosci 2007;**8**:510–21.
23. **Broad LM,** Mogg AJ, Beattie RE, et al. TRP channels as emerging targets for pain therapeutics. Expert Opin Ther Targets 2009;**13**:69–81.
24. **Bessac BF,** Jordt SE. Breathtaking TRP channels: TRPA1 and TRPV1 in airway chemosensation and reflex control. Physiology (Bethesda) 2008;**23**:360–70.
25. **Nishida M,** Kurose H. Roles of TRP channels in the development of cardiac hypertrophy. Naunyn Schmiedebergs Arch Pharmacol 2008;**378**:395–406.
26. **Hoenderop JG,** Bindels RJ. Calciotropic and magnesiotropic TRP channels. Physiology (Bethesda) 2008;**23**:32–40.
27. **Christianson JA,** Traub RJ, Davis BM. Differences in spinal distribution and neurochemical phenotype of colonic afferents in mouse and rat. J Comp Neurol 2006;**494**:246–59.
28. **Robinson DR,** McNaughton PA, Evans ML, et al. Characterization of the primary spinal afferent innervation of the mouse colon using retrograde labelling. Neurogastroenterol Motil 2004;**16**:113–24.
29. **Schicho R,** Florian W, Liebmann I, et al. Increased expression of TRPV1 receptor in dorsal root ganglia by acid insult of the rat gastric mucosa. Eur J Neurosci 2004;**19**:1811–8.
30. **Ward S,** Bayguinov J, Won K, et al. Distribution of the vanilloid receptor (VR1) in the gastrointestinal tract. J Comp Neurol 2003;**465**:121–35.
31. **Patterson LM,** Zheng H, Ward SM, et al. Vanilloid receptor (VR1) expression in vagal afferent neurons innervating the gastrointestinal tract. Cell Tissue Res 2003;**311**:277–87.
32. **Liedtke W,** Friedman JM. Abnormal osmotic regulation in TRPV4−/− mice. Proc Natl Acad Sci USA 2003;**100**:13698–703.
33. **Smith PL,** Maloney KN, Pothen RG, et al. Bisandrographolide from Andrographis paniculata activates TRPV4 channels. J Biol Chem 2006;**281**:29897–904.
34. **Zhang L,** Jones S, Brody K, et al. Thermosensitive transient receptor potential channels in vagal afferent neurons of the mouse. Am J Physiol Gastrointest Liver Physiol 2004;**286**:G983–91.
35. **Vollrath MA,** Kwan KY, Corey DP. The micromachinery of mechanotransduction in hair cells. Annu Rev Neurosci 2007;**30**:339–65.
36. **Bautista DM,** Jordt S-E, Nikai T, et al. TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. Cell 2006;**124**:1269–82.
37. **Macpherson L,** Dubin A, Evans M, et al. Noxious compounds activate TRPA1 ion channels through covalent modification of cysteines. Nature 2007;**445**:541–5.
38. **McNamara CR,** Mandel-Brehm J, Bautista DM, et al. TRPA1 mediates formalin-induced pain. Proc Natl Acad Sci USA 2007;**104**:13525–30.
39. **Bandell M,** Story GM, Hwang SW, et al. Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin. Neuron 2004;**41**:849–57.
40. **Bautista DM,** Movahed P, Hinman A, et al. Pungent products from garlic activate the sensory ion channel TRPA1. Proc Natl Acad Sci USA 2005;**102**:12248–52.

41. **Jordt S-E,** Bautista DM, Chuang H-h, et al. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. *Nature* 2004;**427**:260–5.

42. **Xu H,** Delling M, Jun J, et al. Oregano, thyme and clove-derived flavors and skin sensitizers activate specific TRP channels. *Nat Neurosci* 2006;**9**:628–35.

43. **Brierley SM,** Hughes PA, Page AJ, et al. Novel and specific roles for the ion channel TRPA1 in visceral sensory transduction. *Gastroenterology* 2008;**134**:32.

44. **Chuang H-h,** Neuhausser WM, Julius D. The super-cooling agent icilin reveals a mechanism of coincidence detection by a temperature-sensitive TRP channel. *Neuron* 2004;**43**:859–69.

45. **Story GM,** Peier AM, Reeve AJ, et al. ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell* 2003;**112**:819–29.

46. **Perez CA,** Huang L, Rong M, et al. A transient receptor potential channel expressed in taste receptor cells. *Nat Neurosci* 2002;**5**:1169–76.

47. **Zhang Y,** Hoon MA, Chandrashekar J, et al. Coding of sweet, bitter, and umami tastes: different receptor cells sharing similar signaling pathways. *Cell* 2003;**112**:293–301.

48. **Bezencon C,** le Coutre J, Damak S. Taste-Signaling proteins are coexpressed in solitary intestinal epithelial cells. *Chem Senses* 2007;**32**:41–9.

49. **Young RL,** Sutherland K, Pezos N, et al. Expression of taste molecules in the upper gastrointestinal tract in humans with and without type 2 diabetes. *Gut* 2009;**58**:337–46.

50. **Maroto R,** Raso A, Wood T, et al. TRPC1 forms the stretch-activated cation channel in vertebrate cells. *Nat Cell Biol* 2005;**7**:179–85.

51. **Gottlieb P,** Folgering J, Maroto R, et al. Revisiting TRPC1 and TRPC6 mechanosensitivity. *Pflugers Arch* 2008;**455**:1097–103.

52. **Huang AL,** Chen X, Hoon MA, et al. The cells and logic for mammalian sour taste detection. *Nature* 2006;**442**:934–8.

53. **Ishimaru Y,** Inada H, Kubota M, et al. Transient receptor potential family members PKD1L3 and PKD2L1 form a candidate sour taste receptor. *Proc Natl Acad Sci USA* 2006;**103**:12569–74.

54. **Laird J,** Martinez-Caro L, Garcia-Nicas E, et al. A new model of visceral pain and referred hyperalgesia in the mouse. *Pain* 2001;**92**:335–42.

55. **Blackshaw LA,** Page AJ, Partosoedarso ER. Acute effects of capsaicin on gastrointestinal vagal afferents. *Neuroscience* 2000;**96**:407–16.

56. **Caterina MJ,** Leffler A, Malmberg AB, et al. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* 2000;**288**:306–13.

57. **Bielefeldt K,** Davis BM. Differential effects of ASIC3 and TRPV1 deletion on gastroesophageal sensation in mice. *Am J Physiol Gastrointest Liver Physiol* 2008;**294**:G130–4.

58. **Rong W,** Hillsley K, Davis JB, et al. Jejunal afferent nerve sensitivity in wild-type and TRPV1 knockout mice. *J Physiol* 2004;**560**:867–81.

59. **Jones RCW III,** 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**:10981–9.

60. **Birder LA,** Nakamura Y, Kiss S, et al. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. *Nat Neurosci* 2002;**5**:856–60.

61. **Caterina MJ,** Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. *Annu Rev Neurosci* 2001;**24**:487–517.

62. **Matthews PJ,** Aziz Q, Facer P, et al. Increased capsaicin receptor TRPV1 nerve fibres in the inflamed human oesophagus. *Eur J Gastroenterol Hepatol* 2004;**16**:897–902.

63. **Bhat YM,** Bielefeldt K. Capsaicin receptor (TRPV1) and non-erosive reflux disease. *Eur J Gastroenterol Hepatol* 2006;**18**:263–70.

64. **Fujino K,** de la Fuente SG, Takami Y, et al. Attenuation of acid induced oesophagitis in VR-1 deficient mice. *Gut* 2006;**55**:34–40.

65. **Kollarik M,** Ru F, Undem BJ. Acid-sensitive vagal sensory pathways and cough. *Pulm Pharmacol Ther* 2007;**20**:402–11.

66. **Suzuki M,** Mizuno A, Kodaira K, et al. Impaired pressure sensation in mice lacking TRPV4. *J Biol Chem* 2003;**278**:22664–8.

67. **Sipe W,** Brierley SM, Martin CM, 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**:G1288–98.

68. **Cenac N,** Altier C, Chapman K, et al. Transient receptor potential vanilloid-4 has a major role in visceral hypersensitivity symptoms. *Gastroenterology* 2008;**135**:937–46.

69. **Kwan KY,** Allchorne AJ, Vollrath MA, et al. TRPA1 contributes to cold, mechanical, and chemical nociception but is not essential for hair-cell transduction. *Neuron* 2006;**50**:277–89.

70. **Yang J,** Li Y, Zuo X, et al. Transient receptor potential ankyrin-1 participates in visceral hyperalgesia following experimental colitis. *Neurosci Lett* 2008;**440**:237–41.

71. **Proudfoot CJ,** Garry EM, Cottrell DF, et al. Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. *Curr Biol* 2006;**16**:1591–605.

72. **Melzack R,** Wall PD. Pain mechanisms: a new theory. *Science* 1965;**150**:971–9.

73. **Nauli S,** Alenghat F, Luo Y, et al. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat Genet* 2003;**33**:129–37.

74. **Soboloff J,** Spassova M, Hewavitharana T, et al. TRPC channels: integrators of multiple cellular signals. *Handb Exp Pharmacol* 2007;(179)575–91.

75. **Grant AD,** Cottrell GS, Amadesi S, et al. Protease-activated receptor 2 sensitizes the transient receptor potential vanilloid 4 ion channel to cause mechanical hyperalgesia. *J Physiol* 2006;**578**:715–33.

76. **Sugiura T,** Bielefeldt K, Gebhart GF. TRPV1 function in mouse colon sensory neurons is enhanced by metabotropic 5-hydroxytryptamine receptor activation. *J Neurosci* 2004;**24**:9521–30.

77. **Amadesi S,** Nie J, Vergnolle N, et al. Protease-activated receptor 2 sensitizes the capsaicin receptor transient receptor potential vanilloid receptor 1 to induce hyperalgesia. *J Neurosci* 2004;**24**:4300–12.

78. **Jeske NA,** Patwardhan AM, Gamper N, et al. Cannabinoid WIN 55,212-2 regulates TRPV1 phosphorylation in sensory neurons. *J Biol Chem* 2006;**281**:32879–90.

79. **Levine JD,** Alessandri-Haber N. TRP channels: targets for the relief of pain. *Biochim Biophys Acta* 2007;**1772**:989–1003.

80. **Dai Y,** Wang S, M T, et al. Sensitization of TRPA1 by PAR2 contributes to the sensation of inflammatory pain. *J Clin Invest* 2007;**117**:1979–87.

81. **Wang S,** Dai Y, Fukuoka T, et al. Phospholipase C and protein kinase A mediate bradykinin sensitization of TRPA1: a molecular mechanism of inflammatory pain. *Brain* 2008;**131**:1241–51.

82. **Yu S,** Ouyang A. TRPA1 in bradykinin-induced mechanical hypersensitivity of vagal C fibers in guinea pig esophagus. *Am J Physiol Gastrointest Liver Physiol* 2009;**296**:G255–65.

83. **Delmas P,** Wanaverbecq N, Abogadie FC, et al. Signaling microdomains define the specificity of receptor-mediated InsP(3) pathways in neurons. *Neuron* 2002;**34**:209–20.

84. **Prescott ED,** Julius D. A modular PIP2 binding site as a determinant of capsaicin receptor sensitivity. *Science* 2003;**300**:1284–8.

85. **Nozawa K,** Kawabata-Shoda E, Doihara H, et al. TRPA1 regulates gastrointestinal motility through serotonin release from enterochromaffin cells. *Proc Natl Acad Sci USA* 2009;**106**:3408–13.

86. **Purhonen AK,** Louhivuori LM, Kiehne K, et al. TRPA1 channel activation induces cholecystokinin release via extracellular calcium. *FEBS Lett* 2008;**582**:229–32.

87. **Kollarik M,** Undem BJ. Activation of bronchopulmonary vagal afferent nerves with bradykinin, acid and vanilloid receptor agonists in wild-type and TRPV1−/− mice. *J Physiol* 2004;**555**:115–23.

88. **Akopian AN,** Ruparel NB, Jeske NA, et al. Transient receptor potential TRPA1 channel desensitization in sensory neurons is agonist dependent and regulated by TRPV1-directed internalization. *J Physiol* 2007;**583**:175–93.

89. **Mayer EA,** Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology* 1994;**107**:271–93.

90. **De Schepper HU,** De Winter BY, Van Nassauw L, et al. TRPV1 receptors on unmyelinated C-fibres mediate colitis-induced sensitization of pelvic afferent nerve fibres in rats. *J Physiol* 2008;**586**:5247–58.

91. **Sengupta JN,** Snider A, Su X, et al. Effects of kappa opioids in the inflamed rat colon. *Pain* 1999;**79**:175–85.

92. **Jones RC 3rd,** Otsuka E, Wagstrom E, et al. Short-term sensitization of colon mechanoreceptors is associated with long-term hypersensitivity to colon distention in the mouse. *Gastroenterology* 2007;**133**:184–94.

93. **Winston J,** Shenoy M, Medley D, et al. The vanilloid receptor initiates and maintains colonic hypersensitivity induced by neonatal colon irritation in rats. *Gastroenterology* 2007;**132**:615–27.

94. **Miranda A,** Nordstrom E, Mannem A, et al. The role of transient receptor potential vanilloid 1 in mechanical and chemical visceral hyperalgesia following experimental colitis. *Neuroscience* 2007;**148**:1021–32.

95. **Xu GY,** Winston JH, Shenoy M, et al. Transient receptor potential vanilloid 1 mediates hyperalgesia and is up-regulated in rats with chronic pancreatitis. Gastroenterology 2007;**133**:1282–92.

96. **Morenilla-Palao C,** Planells-Cases R, Garcia-Sanz N, et al. Regulated exocytosis contributes to protein kinase C potentiation of vanilloid receptor activity. J Biol Chem 2004;**279**:25665–72.

97. **Akbar A,** Yiangou Y, Facer P, et al. Increased capsaicin receptor TRPV1-expressing sensory fibres in irritable bowel syndrome and their correlation with abdominal pain. Gut 2008;**57**:923–9.

98. **Chan CL,** Facer P, Davis JB, et al. Sensory fibres expressing capsaicin receptor TRPV1 in patients with rectal hypersensitivity and faecal urgency. Lancet 2003;**361**:385–91.

99. **Adam B,** Liebregts T, Best J, et al. A combination of peppermint oil and caraway oil attenuates the post-inflammatory visceral hyperalgesia in a rat model. Scand J Gastroenterol 2006;**41**:155–60.

100. **Lembo T,** Munakata J, Mertz H, et al. Evidence for the hypersensitivity of lumbar splanchnic afferents in irritable bowel syndrome. Gastroenterology 1994;**107**:1686–96.

101. **Ritchie J.** Pain from distention of the pelvic colon by inflating a balloon in the irritable bowel syndrome. Gut 1973;**6**:105–12.

102. **Azpiroz F,** Bouin M, Camilleri M, et al. Mechanisms of hypersensitivity in IBS and functional disorders. Neurogastroenterol Motil 2007;**19**:62–88.

103. **Barbara G,** Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004;**126**:693–702.

104. **Dunlop SP,** Jenkins D, Spiller RC. Distinctive clinical, psychological, and histological features of postinfective irritable bowel syndrome. Am J Gastroenterol 2003;**98**:1578–83.

105. **Spiller RC,** Jenkins D, Thornley JP, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut 2000;**47**:804–11.

106. **Alvarez DF,** King JA, Weber D, et al. Transient receptor potential vanilloid 4-mediated disruption of the alveolar septal barrier: a novel mechanism of acute lung injury. Circ Res 2006;**99**:988–95.

107. **Hammer J,** Fuhrer M, Pipal L, et al. Hypersensitivity for capsaicin in patients with functional dyspepsia. Neurogastroenterol Motil 2008;**20**:125–33.

108. **Rosch W,** Liebregts T, Gundermann KJ, et al. Phytotherapy for functional dyspepsia: a review of the clinical evidence for the herbal preparation STW 5. Phytomedicine 2006;**13**(Suppl 5):114–21.

109. **Wong GY,** Gavva NR. Therapeutic potential of vanilloid receptor TRPV1 agonists and antagonists as analgesics: recent advances and setbacks. Brain Res Rev 2009;**60**:267–77.

110. **Hicks GA.** TRP channels as therapeutic targets: hot property, or time to cool down? Neurogastroenterol Motil 2006;**18**:590–4.

111. **Holzer P.** TRPV1: a new target for treatment of visceral pain in IBS? Gut 2008;**57**:882–4.

112. **Storr M.** TRPV1 in colitis: is it a good or a bad receptor?—a viewpoint. Neurogastroenterol Motil 2007;**19**:625–9.

TRP channels: new targets for visceral pain

L A Blackshaw, S M Brierley and P A Hughes

Updated information and services can be found at:

http://gut.bmj.com/content/59/01/126.full.html

These include:

References
This article cites 111 articles, 41 of which can be accessed free at:
http://gut.bmj.com/content/59/01/126.full.html#ref-list-1

Article cited in:
http://gut.bmj.com/content/59/01/126.full.html#related-urls

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

GUT Recent advances in basic science (59 articles)

Notes