TRP Channels in Visceral Pain

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Abstract: Visceral pain is both different and similar to somatic pain - different in being poorly localized and usually referred elsewhere to the body wall, but similar in many of the molecular mechanisms it employs (like TRP channels) and the specialization of afferent endings to detect painful stimuli. TRPV1 is sensitive to low pH. pH is lowest in gastric juice, which may cause severe pain when exposed to the oesophageal mucosa, and probably works via TRPV1. TRPV1 is found in afferent fibres throughout the viscera, and the TRPV1 agonist capsaicin can recapitulate symptoms experienced in disease. TRPV1 is also involved in normal mechanosensory function in the gut. Roles for TRPV4 and TRPA1 have also been described in visceral afferents, and TRPV4 is highly enriched in them, where it plays a major role in both mechanonociception and chemonociception. It may provide a visceral-specific nociceptor target for drug development. TRPA1 is also involved in mechano-and chemosensory function, but not as selectively as TRPV4. TRPA1 is colocalized with TRPV1 in visceral afferents, where they influence each other's function. Another modulator of TRPV1 is the cool/mint receptor TRPM8, which, when activated can abrogate responses mediated via TRPV1, suggesting that TRPM8 agonists may provide analgesia via this pathway. In all, the viscera are rich in TRP channel targets on nociceptive neurones which we hope will provide opportunities for therapeutic analgesia.

Keywords: Pain, mechanosensitivity, inflammation.

INTRODUCTION

This review will explore the TRP channel family for possible targets that could reduce visceral pain in the clinic. Chronic pain and discomfort from the viscera affect up to 10% of the general population, and therefore represent a large unmet need for treatment and consequent economic impact, but leading off the science behind visceral pain. To understand how pain is evoked in the viscera and how pain signals are transmitted to the central nervous system, we need to know what types of sensory fibres there are and what they signal. We must also have an idea about the molecular basis of sensory transduction, and how this system changes in disease. No systemically active drugs are yet available for clinical use that target TRP channels, although some have been through clinical trials that hold promise for use in treatment of visceral pain. These and other opportunities will be identified here.

Our group has focussed on the colon as a source of visceral pain, since this is one of the most common reasons for clinical consultation. However we expect many of the principles that apply in the large intestine will apply elsewhere. Instances where there are clear differences between viscera are identified specifically.

What Types of Sensory Fibres are there and what do they Signal?

Sensory afferent peripheral endings are classified into 5 functional subtypes in the mouse colon according to the location of their mechanoreceptive fields [1, 2]: mucosal, muscular (or tension receptor), muscular-mucosal (or tension-mucosal), serosal and mesenteric afferents Fig. (**1**) [1-4]. Mucosal afferents respond only to fine tactile stimulation of the epithelium., They appear anatomically as bare endings in the lamina propria [5]. Muscular afferents (a.k.a. tension receptors) respond to distension at physiological levels (<20mmHg), and have specialized terminals associated with myenteric ganglia [6-8]. Serosal and mesenteric afferents respond at painful levels of distension (>40mmHg) [1, 4, 9, 10] and appear as varicose branching axons apposed to blood vessels [11]. Muscular-mucosal afferents respond to both touch and distension stimuli, but their anatomy is not known. These classifications are based on functional observations, and we are still working on matching anatomy and physiology. Other classifications have been made in mouse and other species, which may be confusing, but there appears to be agreement that there are fibres with low thresholds to distension, those with high thresholds, fibres that are distension-insensitive (most likely mucosal afferents), and genuinely mechanically-insensitive fibres that respond normally only to chemical stimuli [12, 13]. It is probably wrong to name fibres based on the layer of the gut wall where their receptive field appears to be, and better to wait until their structural identity is confirmed. For example, high threshold afferents

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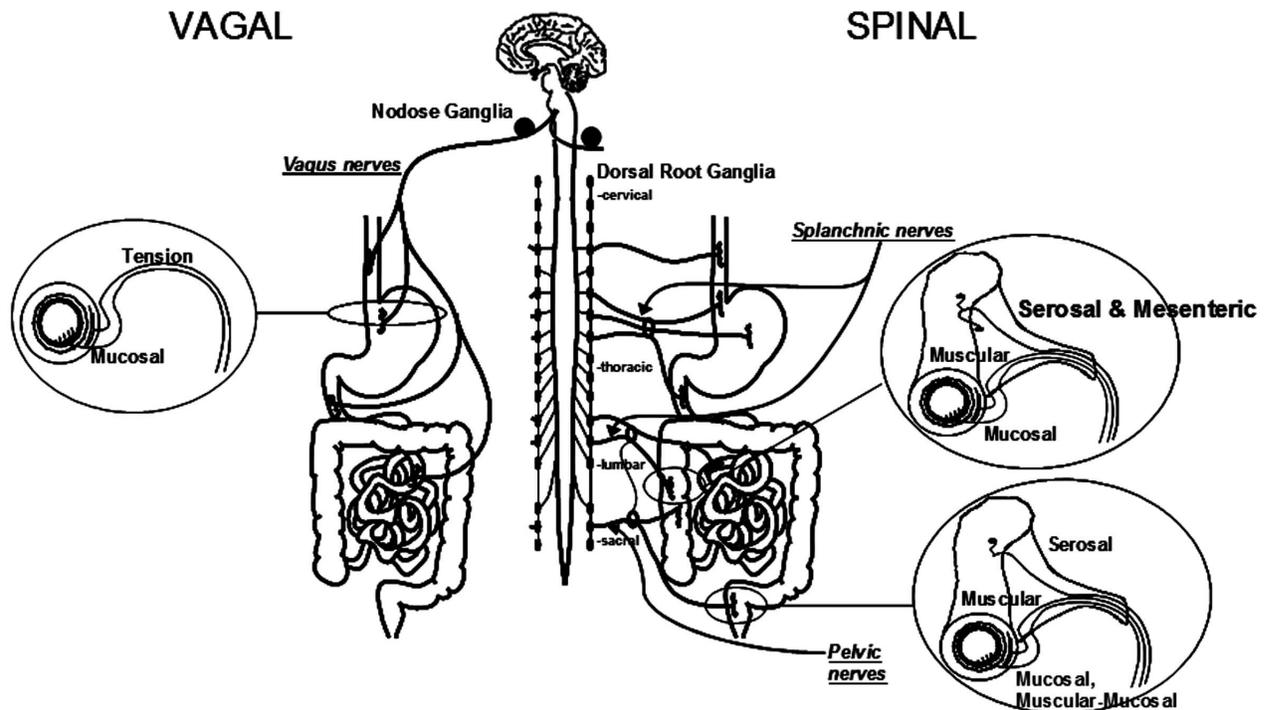
Fig. (1). Pathways and subtypes of gastrointestinal afferents, based mainly on our evidence from mouse experiments. The vagal and spinal pathways are shown on mirror images of the gut. The locations of endings are based on functional localization of mechanoreceptive fields, which in some cases has been confirmed by anatomical studies. The splanchnic and pelvic innervations of the colon overlap in the distal colon (not shown), otherwise they are separate. Tension-mucosal and muscular-mucosal afferents are not shown, but have properties consistent with a location of endings in both layers of the gut. Adapted from [101]

are not only in the serosa and mesentery, but also in the sub-mucosa [11].

Mucosal afferents are distributed throughout the gut, although they are rarely found in the mid-colon [1]. They are unlikely to contribute to direct conscious perception of events in the gut, except in the anal sphincter and pharynx, where conscious discrimination of solid, liquid and gas are required. It follows that in other locations in between they may be important in modulating perception of events detected by other afferents such as distension and contraction. Also they most likely contribute to subliminal autonomic reflexes controlling gut function. Stimulation of gastric and small intestinal mucosal afferents is commonly associated with satiety after a meal, and in more extreme cases with unpleasant sensations associated with nausea and vomiting. This follows their potent activation by hormones and mediators released from enteroendocrine cells and mucosal mast cells [14]. Their functions in the lower bowel are something of a mystery. Muscular-mucosal (a.k.a. tension-mucosal) receptors are found in the oesophagus and in the rectum. These afferents detect both touch and distension, and therefore function as both muscular and mucosal afferents. Their physiological role is undetermined, but it is possible they may play a specialized role in detecting passage of solid or semi-solid material. The functional roles of other classes of sensory fibres are more straightforward: muscular receptors provide perception of distension or contraction; serosal and mesenteric afferents detect high amplitude contraction, overdistension, and distortion of blood vessels [15, 16]. The structure and localization of afferent endings are clearly very

important in determining their function. However their molecular machinery in the form of ion channels, receptors and enzymes is also critical, and potentially supersedes their anatomical specialisations.

Sensory nerves follow 3 main pathways from the gut to the CNS - vagal, splanchnic and pelvic nerves. Cell bodies of vagal afferent fibres are in the nodose and jugular ganglia; splanchnic afferent cell bodies are in the spinal thoracolumbar dorsal root ganglia (DRG); and pelvic afferent cell bodies are in the lumbosacral DRG. Abdominal vagal afferents are associated with non-nociceptive responses such as satiety and nausea, although a subpopulation of oesophageal vagal afferents responds at relatively high thresholds to intra-luminal pressure suggesting a role in pain [17]. All the viscera are innervated by spinal pathways, which are associated with sensations of pain, discomfort, bloating, and urgency to void [15]. Correspondingly, most muscular vagal afferents respond over a narrow range of distension pressures, whereas spinal afferents have either a wide dynamic range or a narrow range with high thresholds [4, 18, 19]. Not all spinal afferents are the same, such that the pelvic pathway contains both non-nociceptive and nociceptive afferents, whilst splanchnic afferents are almost exclusively nociceptive, with few mucosal and muscular afferents, [1] and are therefore useful for studies exclusively of pain. Understanding the specialized roles of TRP channels in visceral pain depends on determining which of the afferent subtypes and pathways express which TRP channels, and what happens when we interfere with their function in each subtype.

Roles of TRP Channels in Visceral Sensory Signalling

As outlined elsewhere in this volume, the TRP family comprises 5 sub-families (TRPA, TRPC, TRPM, TRPP, TRPV) in mammals, which share several key properties: they are non-selective cation channels and most have six trans-membrane domains. They were first identified as channels mediating brief excitatory events in non-mammalian sensory systems, although their roles extend well beyond this initial association as we shall describe. They have been grouped according to structural similarities, although we discuss them below in order of the focus on visceral sensory pathways. The reader is referred also to reviews by Clapham [20], Dhaka *et al.* [21] and Christensen & Corey [22]. TRPs been studied intensively in a number of fields, including pain [23], respiratory and cardiac function [24, 25], ion metabolism and absorption [26].

TRPV1 is activated by the pungent extract of chillies, capsaicin. TRPV1 is more highly expressed in gut innervating afferents than skin innervating afferents [27], with up to 60% of lumbosacral and 82% of thoracolumbar colonic DRG neurones immunoreactive for TRPV1 [13, 27, 28], which is similar to the proportion of thoracic gastric DRG neurones [29]. TRPV1 is found correspondingly in peripheral terminals of gut afferents [30], and in 40-80% of gastric vagal afferent neurones [29, 31].

TRPV4 responds to extracts of the herb Andrographis Paniculata [32, 33], and cooresponds to the mammalian homologue of the C-elegans osmosensory gene Osm-9 [32]. TRPV4 has been localized at sites of mechanotransduction including inner-ear hair cells, sensory neurones, and endings [32]. TRPV4 is enriched in sub-populations of DRG sensory neurones. There is twenty times more TRPV4 mRNA in retrogradely labelled colonic sensory neurones than in the rest of the DRG within the thoracolumbar (splanchnic) DRG. and 3-8 times the levels of TRPV4 in retrogradely labelled gastric vagal sensory neurones. TRPV4 is expressed in 38% of gastro-oesophageal vagal afferents, 65-76% of splanchnic colonic DRG neurones and 58% of pelvic colorectal DRG neurones [3]. In the periphery TRPV4 protein is found to co-localize with CGRP in serosal and mesenteric colonic nerve fibres, but it is scarce in intramuscular or mucosal endings. This distribution is seen in both mouse and human tissue [3]; it correlates well with the functional role of TRPV4 (see below). Other vanilloid TRP channels include ***TRPV2,3,5*** and ***6***, whose function in the gut remains to be investigated. TRPV2, but not TRPV3 is expressed in gastric vagal afferent neurones [34].

TRPA1 responds to a range of environmental irritants [35-37] and extracts of herbes and spices, including mustard, cinnamon, garlic, and oregano [38-41] (Table **1**). TRPA1 is localized in 55% of gastric vagal afferents, 54% of splanchnic colonic afferents and 58% of pelvic colonic afferents [42].

TRPM8 responds to menthol, icilin and eucalyptol, and probably mediates a cooling and soothing sensation [21, 43]. Therefore TRPM8 may be important in *alleviating* pain. TRPM8 is localized in DRG neurones that do not co-localize with the "algesic" TRPs V1 and A1 [44]. It will be important to know about TRPM8 expression and function in specific subpopulations of visceral afferents, which, like in skin, may

have an anti-nociceptive function. The ***TRPC*** family has 6 members, most of which operate as classical calcium channels, rather than sensory channels. Their sensory role in the gut has not yet been published.

Other TRP channels shown to have potential sensory roles elsewhere, including TRPC and TRPP channels have not been investigated in visceral sensation and will not be considered further here.

The Molecular Basis of Visceral Sensory Transduction

TRPs are primary transducers of thermal, mechanical and chemical stimuli. Thermal transduction is unlikely to be important in the viscera apart from in sensitized sensory neurons (see later) and so will not be discussed in detail here. There are several mechano- and chemo-sensory properties (outlined below) that suggest TRPs are important targets in visceral sensory pathways. Despite their established roles as chemosensors, there is little conclusive evidence that TRPs function as mechanosensors. This has been elusive because it demands mechanosensory function studies in isolated channels, intact sensory fibres and in intact animals.

TRPV1 is activated by a range of herb and spice extracts including capsaicin; also by noxious heat and low pH. This produces the characteristic burning feeling evoked by chillies in the mouth. When administered intracolonically capsaicin causes pronounced pain [45]. However capsaicin also activates non-nociceptive upper gastrointestinal vagal afferents [46],.. TRPV1 knockout mice have no significant deficit in mechanosensory function of somatic nociceptors [47], but they have deficits in TRPV1-/- visceral mechanoreceptors (Table **2**). TRPV1 knockouts had reduced vagal afferent responses to distension of the stomach and oesophagus [48]. They also have reduced responses to distension of jejunal wide-dynamic range afferents, but they had normal function of low threshold and high threshold afferent populations [49]. TRPV1 deletion significantly reduced the distension responses of pelvic muscular and muscular/mucosal afferents of the distal colon/rectum [50], but did not affect responses to mucosal stroking. We don't know about effects on serosal afferents. Therefore, TRPV1 contributes to the mechanosensitivity of distension sensitive gastro-oesophageal, jejunal and pelvic colonic afferents. Similar roles were suggested in bladder afferents [51]. Capsaicin potently activates splanchnic and pelvic colonic serosal afferents, which is followed by pronounced mechanical desensitization exclusively in splanchnic afferents [13]. This suggests that the coupling of TRPV1 may differ between splanchnic and pelvic pathways. Since TRPV1 -/- mice had normal somatic mechanical pain sensitivity [47], and their behavioural responses to colorectal distension were reduced [50], it follows that TRPV1 is important in the signalling of mechanical stimuli specifically from the viscera.

Because TRPV1 responds to low pH [52], this places it as a prime candidate for detecting refluxed acid in the oesophagus, and thus giving rise to sensations like heartburn. Indeed it has been localized to fibres in the human esophageal mucosa [53, 54]. TRPV1 knockout mice develop significantly less inflammation after esophageal acid exposure compared with wild-types [55], suggesting a role perhaps in neurogenic inflammation. In the guinea-pig,

'nociceptive-like' esophageal tension sensitive vagal afferents are distinguishable from 'non -nociceptive-like' afferents because they respond to capsaicin [17]. 'Nociceptive-like' tension receptors in the esophagus are stimulated by acid [56]. However, responses of 'non-nociceptive' tension receptors to acid are less well-defined. Rong *et al.* [49] showed that responses of jejunal afferents to acid were reduced by up to 50% in TRPV1 knockouts, indicating TRPV1 has a major, but not exclusive role in detecting low pH.

TRPV4 is implicated in mechanotransduction, since TRPV4 knockout mice have reduced behavioural responses to painful mechanical stimuli to the skin [32, 57]. However, deletion of TRPV4 has no effect on vagal afferent function [3], which correlates with low levels of TRPV4 expression in gastric vagal afferents. In contrast, in colonic afferents TRPV4 is enriched, and mechanosensory responses are greatly reduced in TRPV4 knockouts, and mechanosensory thresholds are increased. This is the case for both splanchnic and pelvic high threshold (serosal and mesenteric) afferents, consistent with TRPV4 expression in their peripheral endings The excitability of afferent endings, their electrical thresholds and conduction velocities were identical in wild type and knockout mice, indicating TRPV4 has a specific role. However, as was the case in the vagal pathway in this study, pelvic mucosal and muscular afferents were normal. Therefore, we concluded that TRPV4 makes a highly specific contribution to mechanosensory function of colonic high threshold afferents; as such it is the only nociceptor-specific TRP channel so far identified.

Afferent responses to mechanical stimuli can be augmented by pharmacological agents that induce opening of the TRPV4 channel. The endogenous arachidonic acid metabolite 5,6-EET is a TRPV4agonist,, which causes potentiation of mechanosensory responses in wild-type mice, but not in TRPV4 knockouts. Ruthenium red, a non-selective TRP channel blocker, correspondingly reduces mechanosensitivity only in wild-type mice [3, 58]. In isolated colonic DRG neurones 4α-PDD, a synthetic TRPV4 agonist, caused significant TRPV4-mediated calcium influx [59], which is consistent with effects of TRPV4 activation in colonic afferent endings. Therefore it is clear that alterations in the pharmacology of splanchnic and pelvic colonic afferents parallel the changes in mechanosensitivity in TRPV4 knockouts, indicating there may be potential for development of a nociceptor-specific analgesic.

The selective role of TRPV4 in high-threshold afferents translates to a role in pain perception *in vivo*,. Visceromotor responses to noxious colorectal distension were decreased in TRPV4 knockouts or in mice with down-regulated TRPV4 expression (via intervertebral siRNA delivery) [3, 59]. This was apparent only at higher distension pressures. Intracolonic administration of 4α-PDD in wild-type mice caused activation of second-order neurones in the lumbosacral spinal cord and caused visceral hypersensitivity to colorectal distension [59].

TRPA1 knockout mice have reduced mechanosensitivity of colonic splanchnic and pelvic serosal and mesenteric afferents, and responses of vagal and pelvic mucosal afferents to mucosal stroking, In contrast, the distension responses of vagal tension receptors and pelvic muscular and muscular/mucosal afferents are similar to wild-types [42]. Therefore TRPA1 contributes to mechanosensation in both tactile and nociceptive afferents, but not in others. Correspondingly a TRPA1 antagonist reduces mechanosensory responses of sensory neurites of DRG neurons [60]. In conscious rats, TRPA1 antisense oligodeoxynucleotide intrathecally reduced colitis-induced hypersensitivity to colonic distension and mustard oil [61]. Although TRPA1 may not be specific to one afferent population like TRPV4, it is clearly evident as a target for reducing signaling of pain from the colon. When its role in mucosal afferents becomes clearer, this may provide important knowledge about the functional role of the channel, and the role of mucosal afferents in visceral sensation.

TRPM8 agonists are already known to activate non-nociceptive vagal afferent neurones innervating the gut [34]. Our recent study provided anatomical and molecular evidence for the expression of TRPM8 in a sub-population of colonic afferent neurons, and showed direct activation of high-threshold colonic afferent fibres through TRPM8 and an interaction of TRPM8 with both TRPV1 and TRPA1, which alters the properties of mechanoreceptive colonic afferent endings [62]. Our major findings were that pro-and anti-nociceptive roles may exist for TRPM8 in high-threshold colonic afferents, since it produces initial activation followed by mechanical desensitisation. TRPM8 activation also influences TRPV1 and TRPA1 sensitivity, resulting in diminished agonist-evoked responses.

TRPs in Effector Systems

TRPs can also function as effector channels, providing a means of excitation of cells in response to activation of G-protein coupled receptors and other types of channel. This is an important function of most TRP sub-families, and in some cases it is their only identified role, for example in some members of the TRPC family [63]. The effector function of TRPs is important in sensory nerve function, such as inflammatory pain evoked by the mediators bradykinin [35] and mast cell proteases [64]. TRPV1 is not thought to be directly mechanically gated; therefore its apparent role in mechanosensation may be attributable to indirect effects on neurone excitability or via interactions with other receptors or TRP channels. For example, 5-HT enhances sensitivity to heat in colonic DRG neurones via TRPV1 (Sugiura *et al.*, 2004), so that they are activated at normal body temperature. Cannabinoids modulate TRPV1 either directly by a direct interaction with the eicosanoid mediator anandamide with the channel itself, or by coupling through intracellular pathways after acting on G-protein coupled cannabinoid receptors [65-67]. The protease receptor PAR2 sensitizes TRPV1 through specific intracellular pathways [65].

In addition to PAR2 coupling with TRPV1, there is also evidence for interaction with TRPV4, which may contribute to visceral hypersensitivity [58, 59]. TRPV4 and PAR$_2$ are often co-expressed in colonic sensory neurones [58, 59]. In isolated colonic DRG neurones PAR$_2$- activating peptide (AP), sensitizes TRPV4-induced currents, whilst PAR2-AP also directly activates splanchnic serosal colonic afferent endings in wild-types, but not in TRPV4 knockouts [58]. Intra-colonic administration of PAR$_2$-AP increases the

behavioural response to noxious colorectal distension, an effect also lost in TRPV4 -/- mice [58, 59].

There is evidence that PAR$_2$ interacts with TRPA1 via similar intracellular mechanisms to those involved with TRPV1 [68]. TRPA1 can also be indirectly activated via bradykinin B2 receptors [35, 69], which mediates bradykinin-induced mechanical hypersensitivity in guinea-pig oesophageal afferents [70]. In the colon bradykini selectively induces mechanical hypersensitivity of splanchnic serosal afferents but not pelvic afferents [12], an effect that is lost in TRPA1 knockouts [42].

Other TRPs are also associated with effects of bradykinin, including TRPC1, whereby activation via the B2 receptor opens TRPC1 [71]. It appears that TRPC1, TRPV4 and TRPA1 all interact with inflammatory G-protein coupled receptors. In contrast to these channels, TRPM8 function is inhibited by BK via a reduction in intracellular phosphoinositide (PIP2) levels [21, 72].

In addition to these roles in neurones, TRPA1 is also involved in mediator release from enteroendocrine cells. Enterochromaffin cells express TRPA1 and release serotonin in response to the TRPA1 agonist AITCl [73], which also releases CCK from other enteroendocrine (STC-1) cells [74]. These data suggest that dietary spices may augment release of mucosal mediators in response to nutrients.

There appears to be great redundancy amongst TRP channels. Although they 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 [75], suggesting there are parallel mechanisms – either other TRPs or completely distinct pathways.

TRPs may interact with one another, such as TRPA1 and TRPV1, which are co-localized in nociceptive DRG neurons. Thus, TRPA1 activation causes cross-desensitization of responses to capsaicin and vice versa [76]. Whether or not TRP channels may couple together positively, and therefore act as effectors for one another, is yet to be determined.

Changes in Sensory Signalling in Disease

Studying the effects of inflammation on visceral afferent endings is important not only to determine mechanisms of inflammatory pain, but also to find a model for chronic visceral pain in humans (eg. [77]). Most published electrophysiological studies have focused on the mechanosensory responses of afferents, in particular to colorectal distension, and how this response is altered by inflammation. For example, a recent study [78] showed that acute colitis in rats induced by TNBS resulted in increased responses of pelvic afferent C-fibers to colorectal distension *in vivo*. This increased sensitivity was reduced by a TRPV1 antagonist. On the other hand, an earlier study by Sengupta *et al.* [79] using an identical *in vivo* protocol, recording from the same population of afferents did not reveal any sensitization, so there is clearly controversy in this area. Similar to Sengupta's [79] findings in rat, Jones *et al.* [80] in a mouse zymosan colonic inflammation model saw no change in mechanosensitivity of pelvic muscular or muscular-mucosal afferents. The behavioural response to colorectal distension was, however, increased after zymosan,

and this persisted in TRPV1 knockouts, so the mechanism underlying pain hypersensitivity was not revealed. In a model of colonic hypersensitivity induced by neonatal colonic irritation in rats [81], TRPV1 inhibitors were effective in reducing pain responses to colorectal distension. Increased expression of TRPV1 in DRG is evident in this model, as well as in a TNBS colitis model [82], suggesting that TRPV1 up-regulation may be a mechanism by which the effect of a TRPV1 antagonist becomes manifest. This mechanism was also evident In a model of pancreatic inflammation [83]. The up-regulation of function via TRPV1 can be long-term, and may lead to cascades of events resulting in hypersensitivity [81, 82]. Alternatively, the translocation of TRPV1 to the cell membrane may have an important influence on its function without changes in mRNA expression [84]. Studies of biopsies from patients with visceral hypersensitivity, either in IBS [85] or in non-erosive reflux disease [54], show that there may be more than three times the mucosal fibres containing TRPV1 compared to asymptomatic controls, and that expression correlates with symptoms. Furthermore, Chan *et al.* [86] showed that increased rectal sensitivity was associated with increased TRPV1 fibres throughout the gut wall.

Mustard oil, a selective TRPA1 agonist, has long been used as a visceral inflammatory model to sensitize nociceptors and provoke tissue damage [45]. Therefore TRPA1 has a role not only in activation of sensory pathways, but also in local neurogenic inflammation, presumably by evoking release of peptides like substance P from peripheral endings. Studies from our laboratory are nearing completion to determine if TRPA1 function and/or expression are increased in chronic visceral pain in animal models or IBS patients.

A combination of peppermint oil (a TRPM8 agonist) and caraway oil attenuates post-inflammatory visceral hyperalgesia in rats [87], which may correlate with its therapeutic effects in patients described below. TRPM8 activation can interfere with transduction via TRPV1 and TRPA1 [62], which is a possible mechanism for this effect.

Therapeutic Opportunities

Allodynia and hyperalgesia to mechanical events like distension and contraction are hallmarks of chronic visceral pains [88-90], along with inflammation, which may be very low-grade histologically [91-93]. Therefore, it is clear that therapies are needed that reduce signalling of nociceptive mechanosensory and inflammatory events. From the discussion above TRPs are closely involved in both of these processes. Normally, there is a constant stream of unperceived signals from the gut, which is involved in autonomic reflexes controlling physiological gut function. We must therefore avoid interfrerence with this information and focus on nociceptive signals in targeting visceral pain to avoid altering normal 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 TRPs, its localization is not, however, confined to sensory neurones [94], so the potential exists for off-target adverse effects. Such effects have hampered the progress of other types of treatments for visceral pain, but it could be argued that in the case of TRPs, there are fewer other target tissues to be con-

cerned about. We hope this chapter may rencourage further development of selective drugs, either as pharmacological treatments, or tools to investigate the roles of TRPs more effectively. Another interesting application of TRP pharmacology is in diagnostic testing for functional gastrointestinal disorders. Administration of capsaicin produces more symptoms including pain, warmth and pressure in functional dyspepsia patients compared with controls [95]. Although the predictive value is far from ideal at around 50%, 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 [96], 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 antagonists for pain [97], such as the TRPV1 antagonist, AMG-517, which was discontinued due to hyperthermia after systemic administration. Pharmaceutical companies are currently determining whether this liability for TRPV1 antagonists can be managed. Site-specific administration of TRPV1 desensitization or targeting non-thermosensitive regions of the TRPV1 molecule would circumvent this issue, and such approaches have shown promise in other visceral neurological disease, reviewed elsewhere [98, 99]. Whether or not the gut is an appropriate place for site-specific interventions remains a difficult question. Within the TRP family, 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 [100]. Hopefully there are also many other 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 normalizing 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 TRPs as effectors for other receptors associated with pain may provide a bonus in the antinociceptive actions of anti-TRP therapy.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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