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Review

TRPV1 and the gut: from a tasty receptor for a painful vanilloid to a key player in hyperalgesia

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Abstract

Capsaicin, the pungent ingredient in red pepper, has been used since ancient times as a spice, despite the burning sensation associated with its intake. More than 50 years ago, Nikolaus Jancsó discovered that capsaicin can selectively stimulate nociceptive primary afferent neurons. The ensuing research established that the neuropharmacological properties of capsaicin are due to its activation of the transient receptor potential ion channel of the vanilloid type 1 (TRPV1). Expressed by primary afferent neurons innervating the gut and other organs, TRPV1 is gated not only by vanilloids such as capsaicin, but also by noxious heat, acidosis and intracellular lipid mediators such as anandamide and lipoxygenase products. Importantly, TRPV1 can be sensitized by acidosis and activation of various pro-algesic pathways. Upregulation of TRPV1 in inflammatory bowel disease and the beneficial effect of TRPV1 downregulation in functional dyspepsia and irritable bladder make this polymodal nociceptor an attractive target of novel therapies for chronic abdominal pain.

Keywords: TRPV1; Vanilloid; Hyperalgesia

Contents

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1. From *Drosophila* to man: capsaicin is not just a matter of taste

Few would object that seasoning heightens the joy of a meal, and history tells us that wars have been fought to ensure an unbroken supply of spices. One of the most unusual seasonings is the vanilloid derivative capsaicin, the pungent ingredient in red peppers of the genus *Capsicum* including chilli and jalapeño, given that the sensory experience associated with its intake ranges from pleasant to painful. This is probably a reason why mankind is divided into people who love and those who abhor red pepper, with a distinct geographical distribution. However, the great divide between pleasant and repellent sensations associated with capsaicin is rooted much deeper within the vertebrate kingdom. Individuals that have ever been exposed to capsaicin powder spread in the air know that, for a few milliseconds, the attractive smell/taste of vanilla precedes the repellent experience of severe irritation in the eyes, nose, mouth and airways that immediately follows. Birds, to the contrary, are not repelled by capsaicin at all, because the avian ortholog of the transient receptor potential (TRP) ion channel of the vanilloid type 1 (TRPV1), which represents the "capsaicin receptor" in mammals, lacks the vanilloid binding site (Jordt and Julius, 2002). It may be that capsaicin offers only a favourable vanilla flavour to birds, providing an incentive for these creatures to distribute the seeds of red pepper.

In the past years, TRP ion channels have become a hot spot in sensory physiology, pharmacology and pain research. An explosion of research has revealed that TRP ion channels represent an ancient sensory apparatus of the cell, responding to temperature, touch, sound, osmolarity, pheromones, taste, pain and other stimuli (Clapham, 2003). TRP ion channels were first described in *Drosophila*, but now are known to occur throughout the animal kingdom. Humans use TRP channels to appreciate sweet, bitter and umami tastes (Zhang et al., 2003) and to discriminate warmth, heat and cold (Clapham, 2003; Patapoutian et al., 2003). TRPV1 has attracted particular attention, because it is activated not only by capsaicin, but also by noxious heat, acidosis and other painful stimuli.

2. TRPV1 as a polymodal detector of painful physical and chemical stimuli

2.1. Milestones in the identification of the "capsaicin receptor"

The prime trace to the discovery of TRPV1 was laid more than 50 years ago by the Hungarian pharmacologist Nikolaus Jancsó who realized that the sensation of burning pain elicited by capsaicin is due to stimulation of nociceptive afferent neurons (Jancsó, 1960). Studies into the structure–activity relationship of capsaicin congeners led Szolcsányi and Jancsó-Gábor (1975) to propose that capsaicin excites afferent neurons via specific receptors for this vanilloid. This concept was corroborated by the development of a capsaicin antagonist, capsazepine (Bevan et al., 1992), and the identification of specific binding sites for resiniferatoxin (Szallasi and Blumberg, 1999), a compound sharing structural and pharmacological similarities with capsaicin. The final proof came in 1997 when the "capsaicin receptor" was cloned and, at that time, termed vanilloid receptor of type 1 (VR1; Caterina et al., 1997). Following the discovery of several related ion channels, all of which belong to the TRP

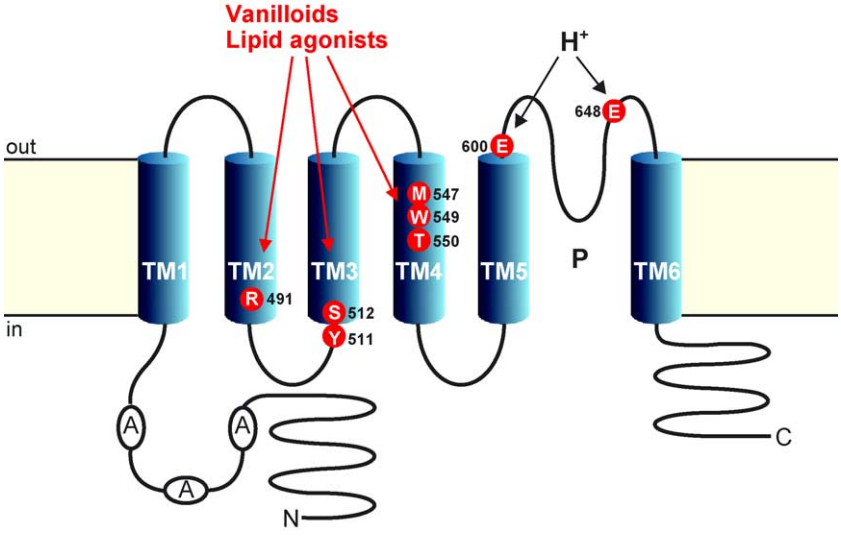

Fig. 1. Membrane topology of the rat TRPV1 showing amino acid positions critical for channel activation by vanilloids (capsaicin and resiniferatoxin) and lipid ligands, on the one hand, and H^+ ions, on the other hand. E-600 is important for TRPV1 sensitization by H^+ ions, whereas E-648 plays an important role in acidosis-induced gating of TRPV1.

channel superfamily, VR1 was renamed TRPV1 (Clapham et al., 2003).

2.2. TRPV1 as a member of a sensory ion channel superfamily

The mammalian TRP channels comprise six related protein families (TRPA, TRPC, TRPM, TRPML, TRPP, and TRPV), among which TRPV1 is the prototypical member of the TRPV subfamily which currently comprises six members, TRPV1–TRPV6 (Clapham et al., 2003). All members of the TRP superfamily are putative six transmembrane (TM) polypeptide subunits that assemble as tetramers to form cation-permeable pores (Clapham, 2003). Like many other TRP channels, TRPV1 is a nonselective cation channel with high permeability for Ca^{2+} (Caterina et al., 1997; Clapham, 2003). Cations are selected for permeation by the extracellular pore loop between TM5 and TM6 (Fig. 1), and in the tetrameric TRP structure the four TM5-pore loop-TM6 elements face the centre of the channel to form the gate and its selectivity filter (Clapham, 2003). TRPV1 is most likely a homotetramer (Kedei et al., 2001), although the existence of heteromultimers of TRPV1 with other members of the TRPV subfamily is possible (Gunthorpe et al., 2002; Smith et al., 2002).

Built into the cell membrane, TRP channels respond to a large variety of physical and chemical stimuli, acting from both within and outside the cell. One of the many remarkable properties is that TRPV1, TRPV2, TRPV3, TRPV4, TRPM8 and TRPA1 (ANKTM1) are thermosensors with different working ranges (Table 1), that enable sensory neurons to monitor a wide spectrum of temperatures from noxious cold to noxious heat (Patapoutian et al., 2003). With these properties, the so-called thermoTRP channels (Table 1; Patapoutian et al., 2003) are in a prime position to orchestrate thermosensation and thermoregulation.

Another striking property of TRP channels is that they function as receptor-gated ion channels (Fig. 1, Tables 1 and 2). This is true for the mammalian TRPV1 which, unlike the avian ortholog, responds to capsaicin and related vanilloids such as resiniferatoxin, because it contains a vanilloid binding site which involves several amino acids in TM2 (R-49), TM3 (Y-511, S-512) and TM4 (M-547, W-549, T-550 in rat; Jordt and Julius, 2002; Chou et al., 2004; Gavva et al., 2004). Amino acid substitutions at positions 547 and 550 determine the differential vanilloid sensitivity of the human, rat, rabbit and avian TRPV1 (Jordt and Julius, 2002; Chou et al., 2004; Gavva et al., 2004). Much as TRPV1 is the receptor for capsaicin, the hot ingredient in red peppers of the genus *Capsicum* (Caterina et al., 1997), TRPA1 is the receptor for isothiocyanate (mustard oil), the spicy and irritating ingredient in plants of the genus *Brassica* such as mustard, horseradish and wasabi (Jordt et al., 2004). In contrast, the pleasant cooling sensation caused by menthol is mediated by TRPM8 which is a thermoTRP channel operating in a cool temperature range (McKemy et al., 2002; Peier et al., 2002).

Table 1
Key properties of thermoTRP channels

TRP channel	Temperature sensitivity (°C)	Characteristic chemical agonist
TRPA1 (ANKTM1)	<17	Isothiocyanate
TRPM8	<25	Menthol
TRPV4	>25–42	
TRPV3	>33–>42	
TRPV1	>42	Capsaicin
TRPV2	>52	

For a detailed review and specific references, see Patapoutian et al. (2003).

Table 2
Activators and sensitizers of TRPV1

Stimulus	Site/mechanism of action	Net effect on TRPV1
Noxious heat		Channel gating
Vanilloids (capsaicin, resiniferatoxin)	Intracellularly on TM3/TM4 of TRPV1	Channel gating
Anandamide, *N*-arachidonoyl-dopamine (NADA) and *N*-oleoyl-dopamine	Intracellularly on TM3/TM4 of TRPV1	Channel gating
Lipoxygenase products (12-HPETE, 15-HPETE)	Intracellularly	Channel gating
Acidosis (pH<6)	Extracellularly on E-648 of TRPV1	Channel gating
Ethanol (0.3–3%)		Channel gating
Acidosis (pH 7–6)	Extracellularly on E-600 of TRPV1	Sensitization
Ethanol (0.3–3 %)		Sensitization
Anandamide, bradykinin acting via B_2 receptors, and nerve growth factor	Intracellularly via PLC-mediated displacement of PIP_2 from TRPV1	Sensitization
Adenosine triphosphate acting via $P2Y_2$ receptors, bradykinin acting via B_2 receptors, and *N*-arachidonoyl-dopamine (NADA)	Intracellularly via PKC-mediated phosphorylation of S-502 and S-800 on TRPV1	Sensitization
Prostaglandin E_2	Intracellularly via PKA-mediated phosphorylation of S-116 on TRPV1	Sensitization

For details and references, see text.

2.3. TRPV1 as a sensor relevant to nociception

The observation that capsaicin elicits burning pain and neurogenic inflammation (Jancsó, 1960) was an early hint that the cellular mechanisms triggered by this vanilloid may be fundamentally relevant to nociception. This conjecture is fully borne out by the unique biological properties of TRPV1 (Fig. 1, Table 2; Caterina and Julius, 2001; Di Marzo et al., 2002; Gunthorpe et al., 2002; Hwang and Oh, 2002). Thus, human, rat, guinea pig and rabbit TRPV1 is

not only activated by capsaicin, resiniferatoxin and noxious heat, but also by acidosis (Caterina et al., 1997; Tominaga et al., 1998; Cortright et al., 2001; Smart et al., 2001; Savidge et al., 2002; Gavva et al., 2004), ethanol (Trevisani et al., 2002) and lipid mediators such as anandamide (Zygmunt et al., 1999; Craib et al., 2001), *N*-arachidonoyl-dopamine (NADA; Huang et al., 2002; Premkumar et al., 2004), *N*-oleoyl-dopamine (Chu et al., 2003) as well as 12-, 15-, and 5-lipoxygenase products including 12-(*S*)-hydroperoxy eicosatetraenoic acid (12-HPETE), 15-HPETE and leukotriene B_4 (Hwang et al., 2000).

The vanilloid and fatty acid agonists bind to an intracellular site of TRPV1 (Hwang et al., 2000; Jordt et al., 2000; Welch et al., 2000; Premkumar and Ahern, 2000; McLatchie and Bevan, 2001; De Petrocellis et al., 2001; Jung et al., 2002; Chou et al., 2004; Gavva et al., 2004), and anandamide targets the same recognition site as capsaicin (Jordt and Julius, 2002). The intracellular location of the lipid ligand-binding site suggests that endogenous TRPV1 agonists may come from within the cell (Hwang and Oh, 2002) following noxious stimulation, and the relatively low potency with which extracellularly administered anandamide or NADA activates TRPV1 may be due to their limited access to the intracellular recognition domain (Premkumar et al., 2004). In addition, the pharmacology of anandamide is complicated by its agonism at cannabinoid CB_1 receptors (Ross, 2003).

H^+ ions have long been suspected to be the endogenous activators of the "capsaicin receptor" (Bevan and Geppetti, 1994). Both the capsaicin-sensitive TRPV1 (Caterina et al., 1997; Tominaga et al., 1998) and the capsaicin-insensitive TRPV4 (Suzuki et al., 2003) are gated by a drop in the extracellular pH below 6 (Caterina et al., 1997; Tominaga et al., 1998; Jordt et al., 2000; Welch et al., 2000; McLatchie and Bevan, 2001). However, genetic deletion of TRPV1 fails to modify the excitatory effect of acidosis on nodose ganglion neurons (Kollarik and Undem, 2004), which is in keeping with the concept that the acid sensitivity of afferent neurons involves many H^+-sensitive ion channels (Holzer, 2003).

2.4. TRPV1 as a polymodal nociceptor that can be sensitized

An exceptional property of TRPV1 is its sensitization by H^+ ions and various pro-algesic pathways (Table 2). Thus, mild acidosis (pH 7–6) which does not gate TRPV1 sensitizes this channel to other stimuli such as capsaicin and heat (Tominaga et al., 1998; Cortright et al., 2001; McLatchie and Bevan, 2001). Unlike the lipid ligands, H^+ ions target an extracellular domain of TRPV1 (Jordt et al., 2000). While the ability of H^+ ions to sensitize TRPV1 to heat and other stimuli depends critically on E-600, the ability of acidosis to gate TRPV1 is mediated by E-648 (Fig. 1; Jordt et al., 2000). Acid-induced sensitization of TRPV1 lowers the temperature threshold for TRPV1 activation so that the channel becomes active at normal body temperature (Tominaga et al., 1998). This finding has led to the hypothesis that TRPV1 is a central factor in hyperalgesia (Reeh and Pethö, 2000) and prompted a series of studies into the regulation of TRPV1 activity by other pro-algesic pathways.

TRPV1 has a number of consensus phosphorylation sites that can be targeted by protein kinase (PK) A (PKA), PKC and other kinases. Thus, activation of prostaglandin E_2 receptors enhances TRPV1 currents via the cyclic adenosine monophosphate–PKA pathway (Lopshire and Nicol, 1998), PKA phosphorylating the cation channel at S-116 and thus preventing its rapid desensitization (Bhave et al., 2002). Phorbol esters, oleoylethanolamide, NADA and stimulation of bradykinin B_2 receptors or metabotropic $P2Y_2$ purinoceptors lead to PKC-mediated phosphorylation of TRPV1 at S-502 and S-800, which enhances the probability of channel gating by protons, capsaicin, anandamide and/or heat (Premkumar and Ahern, 2000; Vellani et al., 2001; Crandall et al., 2002; Kagaya et al., 2002; Numazaki et al., 2002; Olah et al., 2002; Ahern, 2003; Bhave et al., 2003; Moriyama et al., 2003; Premkumar et al., 2004). Adenosine triphosphate can also directly interact with nucleotide-binding domains of TRPV1 to augment the channel response to capsaicin (Kwak et al., 2000).

Another mechanism whereby bradykinin, nerve growth factor and anandamide sensitize TRPV1 involves phospholipase C-mediated hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP_2) which normally inhibits TRPV1 gating by agonists (Prescott and Julius, 2003). PIP_2 binds to a site within the C-terminal domain of TRPV1, and intracellular lipid agonists can activate TRPV1 by cleaving PIP_2. Indeed, TRPV1 activation by lipoxygenase products generated through stimulation of phospholipase A_2 seems to contribute to the excitatory action of bradykinin on spinal and vagal afferents (Shin et al., 2002; Carr et al., 2003). A similar situation applies to the TRPV1-mediated excitation of vagal afferents by anandamide, which is likewise inhibited by a lipoxygenase inhibitor (Kagaya et al., 2002).

A further aspect relevant to TRPV1 activity is its property to desensitize in the presence of capsaicin, which depends on extracellular Ca^{2+} and involves binding of calmodulin to a domain in the C-terminus of TRPV1 (Numazaki et al., 2003; Rosenbaum et al., 2004). It appears as if a dynamic balance between phosphorylation and dephosphorylation of TRPV1 by Ca^{2+}-calmodulin-dependent kinase II and calcineurin, respectively, controls the activation/desensitization state of the channel (Jung et al., 2004). Furthermore, Y-671 which is critical for the high Ca^{2+} permeability of TRPV1 participates in the rearrangement of the channel protein leading to desensitization (Mohapatra et al., 2003). Phosphorylation of TRPV1 at S-116 and possibly T-370 by PKA likewise prevents its rapid desensitization and thus increases channel activity (Bhave et al., 2002; Mohapatra and Nau, 2003).

From these findings, it is emerging that TRPV1 integrates many noxious stimuli and thus plays a significant

role in setting the gain of nociceptors. As acidosis, prostaglandins, bradykinin, adenosine triphosphate and nerve growth factor are formed under conditions of injury and inflammation, they could bring about hyperalgesisa by lowering the temperature threshold of TRPV1 to a level permissive for channel gating at normal body temperature (Reeh and Pethö, 2000). The relevance of TRPV1 to inflammatory hyperalgesia is borne out by the finding that TRPV1 knockout mice do not develop thermal hyperalgesia in response to experimental inflammation or adenosine triphosphate stimulation (Caterina et al., 2000; Davis et al., 2000; Moriyama et al., 2003).

3. Contribution of TRPV1 to gastrointestinal function in health and disease

3.1. Capsaicin as a neuropharmacological tool: demonstration that sensory neurons are important for gut function

Capsaicin has been used since ancient times both as a spice and a traditional treatment for gastrointestinal disease. The biological effects of capsaicin were little understood until it was discovered that capsaicin exerts two distinct actions on sensory neurons, an immediate but transient excitation followed by a long-lasting desensitization to capsaicin and other sensory nerve stimuli (Jancsó, 1960). Both actions were subsequently employed to probe sensory neuron functions in many organs including the gut (Holzer and Barthó, 1996; Holzer, 1998). These studies had an important impact on gastrointestinal physiology and pathophysiology as they brought to light that afferent neurons participate in the control of gastrointestinal blood flow, mucosal ion transport, mucosal inflammation, mucosal protection, mucosal repair, motor activity and nociception (Holzer and Barthó, 1996; Holzer, 1998). There is now increasing awareness that hypersensitivity of sensory neurons and a disturbed gut–brain axis contribute to functional bowel disorders such as dyspepsia and irritable bowel syndrome (Holzer, 2002).

3.2. Capsaicin-sensitive afferent neurons in the gut: an incomplete match with neurons expressing TRPV1

It was long before TRPV1 was identified that a subgroup of primary sensory neurons had been classified as "capsaicin-sensitive afferent neurons" on the basis of their susceptibility to the excitatory and desensitizing action of capsaicin (Szolcsányi, 1982). Typically, capsaicin-sensitive afferents have small to medium-sized cell bodies with mostly unmyelinated fibres and contain peptide transmitters among which calcitonin gene-related peptide and substance P are the most prominent (Holzer, 1991). After the identification of TRPV1, it has become possible to study the distribution of the "capsaicin receptor" by immunocytochemistry and in situ hybridization. As expected, TRPV1 has been localized to sensory neurons originating from the trigeminal, nodose and dorsal root ganglia in which TRPV1 is preferentially expressed by small somata that give rise to unmyelinated fibres (Caterina et al., 1997; Helliwell et al., 1998; Guo et al., 1999; Michael and Priestley, 1999; Ichikawa and Sugimoto, 2003; Patterson et al., 2003; Ward et al., 2003; Robinson et al., 2004; Schicho et al., 2004; Zhang et al., 2004). However, it turned out that the group of capsaicin-sensitive afferent neurons, as defined in neurochemical, neurophysiological and neuropharmacological terms, does not completely match with the population of neurons that express TRPV1-like immunoreactivity (TRPV1-LI) or TRPV1 messenger ribonucleic acid (mRNA). A remarkable aspect of this mismatch is that TRPV1 is much wider distributed than envisaged from the functional studies.

One instance of mismatch relates to the brain. While sensitivity to capsaicin is thought to be a rather exclusive property of primary afferent neurons (Holzer, 1991; Szallasi and Blumberg, 1999), TRPV1 mRNA and TRPV1-like binding sites are widely distributed in the brain (Mezey et al., 2000), albeit at a lower level than in the spinal ganglia (Sanchez et al., 2001). The presence of TRPV1 in the brain fits with previous findings that neurons in discrete fore- and hindbrain areas including the preoptic area of the hypothalamus are susceptible to the neurotoxic action of capsaicin (Szolcsányi, 1982; Ritter and Dinh, 1988).

Another example of mismatch concerns the chemical coding of TRPV1-expressing sensory neurons. Capsaicin-sensitive afferents abound with calcitonin gene-related peptide and substance P (Green and Dockray, 1988; Holzer, 1991), whereas these neuropeptides are, in general, rare in TRPV1-positive dorsal root ganglion neurons (Guo et al., 1999). There is, however, a substantial coexpression of calcitonin gene-related peptide and TRPV1 in visceral sensory neurons (Green and Dockray, 1988; Perry and Lawson, 1998; Ward et al., 2003; Robinson et al., 2004).

A third instance of mismatch is found in the gut. Functional studies have indicated that the population of gastrointestinal capsaicin-sensitive neurons is constituted by extrinsic primary afferents, whereas intrinsic enteric and extrinsic autonomic neurons do not directly respond to capsaicin (Holzer, 1991, 1998; Holzer and Barthó, 1996). Indeed, Patterson et al. (2003), Ward et al. (2003) and Schicho et al. (2004) have failed to detect TRPV1-LI in enteric neurons of the rat, guinea pig and mouse gastrointestinal tract, which implies that the numerous TRPV1-positive nerve fibres that occur in the enteric nerve plexuses, musculature and mucosa represent processes of spinal afferents and, in the stomach, of some vagal afferents. This conjecture is strongly supported by the disappearance of TRPV1 mRNA from the rat stomach following extrinsic denervation (Schicho et al., 2004). Other investigators, though, report that TRPV1-LI is expressed by enteric neurons of the guinea pig, porcine

and human intestine (Poonyachoti et al., 2002; Anavi-Goffer and Coutts, 2003; Chan et al., 2003). In addition, TRPV1 mRNA, TRPV1 protein and TRPV1-like binding sites have been found on rat gastric epithelial cells (Nozawa et al., 2001; Kato et al., 2003), which is reminiscent of the presence of TRPV1 on epithelial cells of the urinary bladder where this ion channel acts as a sensor relevant to bladder function (Birder et al., 2001). Capsaicin has been reported to excite enteric neurons (Takaki and Nakayama, 1989), and it appears worth re-investigating this effect which previously was thought to be due to transmitter release from extrinsic afferents.

3.3. Implications of TRPV1 in gastrointestinal mucosal functions

Extensive studies involving capsaicin have demonstrated that capsaicin-sensitive afferent neurons participate in the regulation of gastrointestinal circulation, secretion, mucosal homeostasis, motility and nociception (Holzer and Barthó, 1996; Holzer, 1998). These tasks are brought about by two different modes of operation: an afferent and an efferent-like function (Maggi, 1995; Holzer and Maggi, 1998). By conveying information from the gut to the spinal cord and brainstem, capsaicin-sensitive afferents contribute to gastrointestinal sensation and constitute the afferent arm of autonomic and neuroendocrine reflex circuits relevant to digestion. Other afferents subserve a local efferent-like function, which is mediated by release of calcitonin gene-related peptide, substance P and other mediators from their peripheral fibres, these transmitters in turn acting on gastrointestinal effector systems (Maggi, 1995; Holzer, 1998).

The efferent-like mode of operation is exemplified by the reactions of the rat gastric mucosa to luminal capsaicin exposure or acid backdiffusion (Holzer, 1998). Both stimuli increase mucosal blood flow through a peripheral circuitry and initiate other mechanisms of defence such as bicarbonate and mucus secretion (Holzer, 1998, 2002). In addition, capsaicin-sensitive neurons participate in the feedback regulation of gastric acid secretion: as they are activated by secreted acid, they release calcitonin gene-related peptide which, via somatostatin release, halts further acid secretion (Manela et al., 1995; Holzer, 1998). While the gastric hyperaemic response to luminal acid backdiffusion is mediated by spinal afferents, the afferent signalling of gastric acid challenge to the brain is carried by vagal afferents (Schuligoi et al., 1998; Lamb et al., 2003). Thus, the local efferent-like and afferent functions are subserved by different populations of sensory neurons (Holzer and Maggi, 1998).

The *capsaicin*-evoked gastric hyperaemia, gastric mucosal protection and duodenal bicarbonate secretion in the rat are mediated by TRPV1 because they are antagonized by the TRPV1 blocker capsazepine (Tashima et al., 2002; Kagawa et al., 2003; Kato et al., 2003; Horie et al., 2004). The gastric mucus secretion evoked by stimulation of protease-activated receptor-2 (PAR-2) is likewise blunted by capsazepine (Kawabata et al., 2002), which suggests a link between PAR-2 and TRPV1 (Table 3). In contrast, the *acid*-induced mucosal hyperaemia in the stomach remains unaltered by capsazepine (Tashima et al., 2002), while the acid-induced vasodilatation in the duodenum is blunted by this TRPV1 blocker (Table 3; Akiba et al., 1999). Since, however, the acid-evoked secretion of duodenal bicarbonate is left unchanged by capsazepine (Kagawa et al., 2003), it appears as if there are regional differences in the receptor mechanisms whereby acid challenge activates afferent neurons in the foregut.

While TRPV1 in the foregut mediates reactions that support mucosal homeostasis, TRPV1 in the pancreas, ileum and colon facilitates processes of inflammation and tissue damage (Table 3). For instance, experimental pancreatitis induced by caerulein (Nathan et al., 2001), ileitis induced by *Clostridium difficile* toxin A (McVey and Vigna, 2001) and colitis induced by dextrane sulphate (Kihara et al., 2003) are significantly ameliorated by capsazepine. Albeit it awaits to be disclosed how these inflammatory stimuli are linked to TRPV1, there is upcoming evidence that *C. difficile* toxin A enhances the formation of anandamide and 2-arachidonoyl glycerol in the mucosa and that these mediators, in turn, activate TRPV1 (McVey et al., 2003). TRPV1-mediated excitation of sensory nerve terminals releases substance P which activates enteric neurons, mast cell and other immune cells and thus leads to hypersecretion, inflammation and mucosal damage (McVey and Vigna, 2001).

3.4. Participation of TRPV1 in gastrointestinal nociception

The molecular characteristics of TRPV1 as a polymodal nociceptor and its association with nociceptive afferent

Table 3
Implications of TRPV1 in gastrointestinal functions

Gastrointestinal function	Type of evidence	References
Mucus secretion in the rat stomach evoked by stimulation of protease-activated receptor-2	Inhibition by capsazepine	Kawabata et al., 2002
Vasodilatation in the rat duodenum caused by exposure to luminal acid	Inhibition by capsazepine	Akiba et al., 1999
Inflammation of mouse pancreas induced by caerulein	Inhibition by capsazepine	Nathan et al., 2001
Inflammation of rat ileum caused by *Clostridium difficile* toxin A	Inhibition by capsazepine	McVey and Vigna, 2001
Inflammation of rat ileum caused by anandamide	Inhibition by capsazepine	McVey et al., 2003
Inflammation of rat colon caused by dextrane sulphate sodium	Inhibition by capsazepine	Kihara et al., 2003

nerve fibres attribute this ion channel a particular role in pain and hyperalgesia. The gut is innervated by two populations of extrinsic afferents, vagal and spinal, both of which express TRPV1 (Caterina et al., 1997; Helliwell et al., 1998; Guo et al., 1999; Michael and Priestley, 1999; Ichikawa and Sugimoto, 2003; Patterson et al., 2003; Robinson et al., 2004; Ward et al., 2003; Schicho et al., 2004; Zhang et al., 2004). Of the nodose ganglion neurons that innervate the rat stomach, 42–80% stain for TRPV1, whereas 71–82% of the dorsal root ganglion neurons projecting to the rat stomach and mouse colon, respectively, express TRPV1 (Patterson et al., 2003; Robinson et al., 2004; Schicho et al., 2004). Most TRPV1-positive nerve fibres in the gut appear to be processes of spinal afferents, since the level of TRPV1-LI in gastrointestinal terminals of nodose ganglion neurons is very low (Patterson et al., 2003; Ward et al., 2003; Schicho et al., 2004). This may explain why the proportion of capsaicin-sensitive fibres among vagal afferents supplying the oesophagus and stomach is ≤30% (Berthoud et al., 1997; Blackshaw et al., 2000).

Capsaicin stimulates, most likely via TRPV1, extrinsic afferents of the gut (Maubach and Grundy, 1999; Su et al., 1999; Blackshaw et al., 2000), and administration of capsaicin into the lumen of the alimentary canal evokes pain in humans (Hammer et al., 1998; Drewes et al., 2003; Schmidt et al., 2004) and mice (Laird et al., 2001; Kawao et al., 2004). For instance, application of capsaicin to the human jejunum induces pain whose abdominal localization and perceptional quality are similar to distension-induced pain. Since it does not stimulate jejunal motility and does not alter jejunal mechanosensitivity, capsaicin is thought to evoke pain by stimulation of jejunal chemoreceptors, presumably TRPV1 (Schmidt et al., 2004).

Direct evidence for a role of TRPV1 in the pain associated with gastrointestinal disease has not yet been provided, but there are accumulating hints at such an implication. The observation that TRPV1 is relevant to sensitization of dermal afferents (Caterina et al., 2000; Davis et al., 2000) is matched by indirect evidence that TRPV1 contributes to gastrointestinal hyperalgesia. Thus, administration of capsaicin into the ileum of patients with an ileal stoma has been reported to cause mechanical hypersensitivity (Drewes et al., 2003). Vice versa, application of a PAR-2 agonist into the rat pancreatic duct sensitizes spinal afferents to capsaicin (Hoogerwerf et al., 2001), and nociception caused by intracolonic capsaicin is facilitated after intraperitoneal administration of a PAR-2 agonist to mice (Kawao et al., 2004). The molecular mechanism behind the interaction between PAR-2 and TRPV1 (Hoogerwerf et al., 2001; Kawabata et al., 2002; Kawao et al., 2004) involves PKC which phosphorylates TRPV1 and thereby sensitizes it to activation by other stimuli (Amadesi et al., 2004; Dai et al., 2004). Since trypsin and tryptase are released during tissue inflammation, it would appear that PAR-2-mediated sensitization of TRPV1 could be an important mechanism underlying inflammatory hyperalgesia.

Further indirect evidence for a role of TRPV1 in abdominal hyperalgesia comes from reports that capsaicin desensitization is beneficial in patients with functional dyspepsia or irritable bladder. This approach is based on the ability of capsaicin to induce a state of sensory refractoriness (Holzer, 1991) which, depending on the dose of capsaicin, may be due to desensitization/inactivation of TRPV1, downregulation of TRPV1 (Szallasi and Blumberg, 1999), loss of sensory neuron excitability or overt neurotoxicity (Holzer, 1991; Szallasi and Blumberg, 1999). Capsaicin pretreatment of rats prevents the behavioural pain reaction to gastric acid challenge (Lamb et al., 2003) and the inflammation-induced hypersensitivity to colonic distension (Plourde et al., 1997; Delafoy et al., 2003). Pretreatment of rats with SDZ 249-665, a vanilloid compound reproducing capsaicin desensitization, attenuates inflammatory bladder hyperreflexia, referred hyperalgesia (Jaggar et al., 2001) and behavioural pain responses to intraperitoneal acetic acid in rats (Urban et al., 2000).

Chronic administration of capsaicin is likewise beneficial in patients with abdominal pain. For instance, intravesical administration of capsaicin or resiniferatoxin ameliorates the symptoms of irritable bladder (Cruz, 2004). Intractable idiopathic pruritus ani is relieved by a 4-week treatment course with topical capsaicin (Lysy et al., 2003), and daily intragastric administration of red pepper containing 1.75 mg capsaicin for 5 weeks significantly reduces epigastric pain and other symptoms of functional dyspepsia (Bortolotti et al., 2002). It would hence appear conceivable that gastric acid-related pain syndromes in the oesophagus and upper gut are due to acid-induced TRPV1 sensitization.

4. Alterations of TRPV1 expression in gastrointestinal disease

Acute exposure of the rat gastric mucosa to a noxious HCl concentration leads to a rise of TRPV1-LI, but not

Table 4
TRPV1 channel blockers

Blocker (source)	References
Capsazepine (Novartis)	Bevan et al., 1992
5-Iodo-resiniferatoxin	Wahl et al., 2001
6-Iodo-nordihydrocapsaicin (DiSCAFF)	Appendino et al., 2003
N-alkyl glycine trimers	Garcia-Martinez et al., 2002
Arginine-rich hexapeptide R4W2	Himmel et al., 2002
N-(3-acyloxy-2-benzylpropyl)-*N*′-[4-(methylsulfonylamino) benzyl]thiourea and related vanilloid analogues	Lee et al., 2003
Non-vanilloid SC0030	Suh et al., 2003
4-(2-Pyridyl)piperazine-1-carboxamides (Purdue)	Sun et al., 2003
Cinnamide SB-366791 (GlaxoSmithKline)	Gunthorpe et al., 2004
7-Hydroxynaphthalen-1-yl-urea and -amide compounds (Johnson & Johnson)	McDonnell et al., 2004

TRPV1 mRNA, in dorsal root ganglion neurons innervating the stomach (Schicho et al., 2004). The density of TRPV1-LI on nerve fibres of the human colon is enhanced in painful inflammatory bowel disease (Yiangou et al., 2001) and in the aganglionic bowel of patients with Hirschsprung's disease (Facer et al., 2001). Rectal hypersensitivity and faecal urgency are associated with a rise in the number of TRPV1-positive nerve fibres in the muscle, submucosa and mucosa of the rectum and of TRPV1-positive neurons in the myenteric and submucosal plexus (Chan et al., 2003).

5. Therapeutic options provided by TRPV1 channel blockers

The polymodal nociceptor properties of TRPV1 make this ion channel an intriguing target for novel therapies of abdominal pain and inflammation. It would appear, therefore, that TRPV1 channel blockers are of value in suppressing gastrointestinal hyperalgesia related to inflammation and other circumstances where there is activation (sensitization) or upregulation of TRPV1. This conjecture is supported by the beneficial effect of chronic capsaicin desensitization in functional dyspepsia and irritable bladder (Bortolotti et al., 2002; Cruz, 2004). Attempts to circumvent the initial pungency, which capsaicin and related TRPV1 agonists bring about, first led to the use and development of vanilloid-related compounds with reduced pungency but preserved ability to desensitize (Szallasi and Blumberg, 1999; Urban et al., 2000). The discovery of the first TRPV1 blocker, capsazepine (Bevan et al., 1992), and the elucidation of the function-relevant domains of TRPV1 have shifted the focus to the design of highly specific channel blockers (Table 4). The indication of these drugs is very likely to comprise visceral hyperalgesia, although the utility of TRPV1 blockers has not yet been ascertained in established paradigms of gastrointestinal nociception. In these tests, it will also be important to explore whether blockade of TRPV1 interferes with the physiological function of TRPV1-expressing neurons in gastrointestinal mucosal homeostasis within the foregut (Holzer, 1998).

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