British Journal of Pharmacology (2008) 155, 1145–1162

0007–1188/08 $32.00
www.brjpharmacol.org

REVIEW: NEW DRUG TARGETS

The pharmacological challenge to tame the transient receptor potential vanilloid-1 (TRPV1) nocisensor

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The transient receptor potential vanilloid-1 (TRPV1) cation channel is a receptor that is activated by heat ($>42\,^{\circ}C$), acidosis ($pH<6$) and a variety of chemicals among which capsaicin is the best known. With these properties, TRPV1 has emerged as a polymodal nocisensor of nociceptive afferent neurones, although some non-neuronal cells and neurones in the brain also express TRPV1. The activity of TRPV1 is controlled by a multitude of regulatory mechanisms that either cause sensitization or desensitization of the channel. As many proalgesic pathways converge on TRPV1 and this nocisensor is upregulated and sensitized by inflammation and injury, TRPV1 is thought to be a central transducer of hyperalgesia and a prime target for the pharmacological control of pain. As a consequence, TRPV1 agonists causing defunctionalization of sensory neurones and a large number of TRPV1 blockers have been developed, some of which are in clinical trials. A major drawback of many TRPV1 antagonists is their potential to cause hyperthermia, and their long-term use may carry further risks because TRPV1 has important physiological functions in the peripheral and central nervous system. The challenge, therefore, is to pharmacologically differentiate between the physiological and pathological implications of TRPV1. There are several possibilities to focus therapy specifically on those TRPV1 channels that contribute to disease processes. These approaches include (i) site-specific TRPV1 antagonists, (ii) modality-specific TRPV1 antagonists, (iii) uncompetitive TRPV1 (open channel) blockers, (iv) drugs interfering with TRPV1 sensitization, (v) drugs interfering with intracellular trafficking of TRPV1 and (vi) TRPV1 agonists for local administration.
British Journal of Pharmacology (2008) **155,** 1145–1162; doi:10.1038/bjp.2008.351; published online 22 September 2008

Keywords: transient receptor potential vanilloid-1 (TRPV1) cation channels; molecular nocisensors; primary afferent neurones; central nervous system; nociception; hyperalgesia; hyperthermia; thermoregulation; TRPV1 blockers; interference with TRPV1 trafficking

Abbreviations: CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; PIP2, phosphatidylinositol-4,5-bisphosphate; RNA, ribonucleic acid; TRP, transient receptor potential; TRPV1, transient receptor potential vanilloid-1

Pain, heat and spice

In the field of nociception there has been a long-standing debate as to whether pain arises from excitation of specific nociceptive afferent nerve fibres, as proposed by the specificity theory, or is simply the result of intense stimulation of afferent neurones as held by the intensity theory (Perl, 2007). The heat with which this debate was conducted could have been considerably lessened if it had been known that subpopulations of primary afferent neurones express specific nocisensors that transduce distinct noxious stimuli into propagated nerve activity as well as particular ion channels that control excitability and action potential propagation specifically in sensory neurones. Although pain arising from hollow viscera is in part encoded by the intensity of distension (Jänig, 2006), the specificity theory is now impressively backed by a large list of ion channels and G-protein-coupled receptors that enable afferent neurones to sense distinct modalities of pain. The pioneer that triggered this avalanche of discoveries was a family of closely related cation channels, denoted transient receptor potential (TRP), that act as molecular sensors for distinct pain, temperature, chemaesthesis and taste modalities (Table 1).

The implication of TRP channels in pain and sensation was first heralded when in 1997 the vanilloid receptor-1 was identified at the genetic and functional level (Caterina *et al.*, 1997). It was soon realized that this new ion channel was homologous to the TRP channel family and subsequently

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Received 29 April 2008; revised 18 June 2008; accepted 20 August 2008; published online 22 September 2008

Table 1 Overview of TRP channels, expressed by sensory neurones or cells associated with sensory neurones that are involved in nociception, thermosensation and chemaesthesis

TRP channel	*Pain modality*	*Thermosensation*	*Chemaesthesis*
TRPV1	Heat Acidosis Chemaesthetic (irritant) pain	>42 °C	Capsaicin (red pepper), resiniferatoxin (*Euphorbia*), gingerol and zingerone (ginger), piperine (black pepper), eugenol (clove), camphor, vanillatoxins 1-3 (Tarantula), ethanol, acid (pH<6)
TRPV2	Heat	>52 °C	Δ^9-tetrahydrocannabinol (Δ^9-THC)
TRPV3	Chemaesthetic (irritant) pain	>33 °C (warmth)	Carvacrol (oregano), eugenol, thymol (thyme), vanillin (vanilla), camphor, menthol (mint)
TRPV4	Acidosis	>25–34 °C (warmth)	Acid (pH<6)
TRPM8	Cold Chemaesthetic (irritant) pain	<25 °C	Menthol, icilin, geraniol, L-carvone, isopulegol, linalool
TRPA1	Chemaesthetic (irritant) pain	<17 °C	Allicin and diallyl disulphide (garlic), allyl isothiocyanate (mustard, horseradish, wasabi), cinnamaldehyde (cinnamon), carvacrol, gingerol, eugenol, icilin, acrolein, formaldehyde, methyl salicylate, Δ^9-THC

The thermo- and chemosensory properties referred to have been delineated by studying heterologously expressed TRP channels. The list of chemicals activating TRP channels is not complete. For references see Dhaka *et al.* (2006) and Bandell *et al.* (2007).

re-named transient receptor potential vanilloid-1 (TRPV1), which stands for transient receptor potential vanilloid-1 (Caterina and Julius, 2001; Clapham *et al.*, 2005). The story of TRPV1, however, had begun half a century ago, when the peculiar pharmacology of capsaicin was first revealed. Responsible for the pungency of red pepper (*Capsicum* spp.), the vanilloid capsaicin in its pure form is one of the most painful chemicals we know, conveying the sensation of 'hot' and 'burning'. It was the Hungarian pharmacologist Nicolas Jancsó who first recognized that capsaicin acts specifically on nociceptive afferent neurones (Jancsó, 1960). Further work by two eminent Hungarian research groups in Szeged and Pécs provided compelling evidence that the selectivity of capsaicin's action on afferent neurones can only be accounted for by an action on specific capsaicin receptors (Szolcsányi and Jancsó-Gábor, 1975; Jancsó *et al.*, 1977, 1987; Szolcsányi, 1982, 2004; Nagy *et al.*, 2004). The discovery of specific vanilloid-binding sites (Szallasi and Blumberg, 1999) and a selective capsaicin antagonist (Bevan *et al.*, 1992) were further important steps towards the identification of TRPV1 as the capsaicin receptor. Therapeutic opportunities were envisaged from the structure–activity relationship for the pain-producing effect of capsaicin (Szolcsányi and Jancsó-Gábor, 1975) and its axonal site of action following local administration to afferent neurones (Jancsó *et al.*, 1980).

TRPV1 was soon to be joined by other TRP channels with unique sensory modalities. The group of thermo-TRP channels is able to sense the whole spectrum of temperatures from painful cold to painful heat (Dhaka *et al.*, 2006). Moreover, they are able to detect specific chemical entities including unpleasant and/or painful toxins, whereby TRP channels subserve chemaesthesis, the chemical sense distinct from taste and smell (Bandell *et al.*, 2007). In this context it is perplexing to note that TRP channels are sensors for many spices (Table 1). Although most people perceive spices, at least some of them, as pleasant and heightening the taste of food, it seems that—in a biological sense—the chemicals responsible for the gustatory and olfactory pleasures of spices are elaborated by plants primarily for their defence (Max, 1992; Cromer and McIntyre, 2008). By some strange perversion, however, humans have learned to enjoy low doses of these deterrent chemicals, which is opposite to the strategy of plants to discourage predators by the unusual sensory quality of spices (Max, 1992). This argument is supported by the fact that capsaicin is a pungent chemical for mammals, but not birds which are supposed to help distributing the seeds of red pepper, given that the avian orthologue of TRPV1 lacks the binding site for capsaicin (Jordt and Julius, 2002).

Analysis of the molecular and functional properties of TRPV1 has shown that this ion channel is a polymodal nocisensor, which is subject to allosteric modulation by many proalgesic pathways. This aspect and the property to become sensitized by proinflammatory mediators have raised enormous interest in TRPV1 being a prime transducer of pathological pain. Indeed, the expression and/or activity of TRPV1 has been found upregulated under conditions of chronic pain and hyperalgesia. At the same time, however, it has emerged that TRPV1 has important functions in body homeostasis, for example, in thermoregulation. As a consequence, targeting TRPV1 in chronic pain carries great potential at a heavy risk. Besides briefly outlining the functional implications of TRPV1 in health and disease, the major objective of this article is to point out that TRPV1 may be a highly useful drug target if its pathological functions can pharmacologically be differentiated from its physiological implications.

Transient receptor potential cation channels

TRPV1 belongs to the large family of TRP ion channels, so named after the function these channels have in *Drosophila* phototransduction. By now at least 28 different TRP subunit genes have been identified in mammals, comprising six subfamilies: the classical or canonical TRPs, the vanilloid TRPs, the melastatin TRPs (TRPMs), the mucolipin TRPs, the polycystin TRPs and the ankyrin TRPs (TRPAs). Except for some polycystin TRPs, the primary structure of the TRP

channels consist of six transmembrane segments (Figure 1) with a pore domain between transmembrane segments 5 and 6 and with both the C- and N termini located intracellularly (Clapham *et al.*, 2005; Alexander *et al.*, 2008). This architecture is common to hundreds of ion channels but, despite the topographic similarities between the TRPs and the voltage-gated K^+ channels, the TRPs are only distantly related to these channels (Clapham *et al.*, 2005; Cromer and McIntyre, 2008). However, there is some functional relationship between these two classes of ion channels, given that peptide components of the tarantula venom, called 'vanilla-toxins', activate TRPV1 by interacting with a region that is homologous to the 'voltage sensor' in the $K_v1.2$ channel (Siemens *et al.*, 2006; Cromer and McIntyre, 2008).

Made up as tetramers of four subunits, TRP channels are opened or closed by conformational changes in the channel protein (Dhaka *et al.*, 2006; Bandell *et al.*, 2007). Unlike voltage-gated ion channels, TRP channels are in general only weakly sensitive to depolarization but open in response to changes in temperature, binding of ligands or other alterations of the channel protein (Clapham *et al.*, 2005; Matta and Ahern, 2007; Nilius *et al.*, 2007). As their activation is modulated by voltage changes, TRP channels are included in the large superfamily of voltage-gated-like ion channels (Bandell *et al.*, 2007; Nilius *et al.*, 2007). The ion selectivity differs markedly among the family of TRP channels, most of them being non-selective cation channels, which is also true for TRPV1 with its high permeability for Ca^{2+} (Caterina and Julius, 2001; Gunthorpe *et al.*, 2002; Patapoutian *et al.*, 2003; García-Sanz *et al.*, 2004). Interestingly, sustained exposure to agonists increases the Ca^{2+} permeability of TRPV1 and causes pore dilation (Chung *et al.*, 2008). TRPV1-bearing neurones are eventually overloaded by Ca^{2+}, which in conjunction with other factors can result in mitochondrial swelling, long-lasting defunctionalization or even degeneration of the neurones (Szolcsányi *et al.*, 1975; Jancsó *et al.*, 1977, 1984, 1985; Wood *et al.*, 1988; Szöke *et al.*, 2002). In addition, TRPV1 allows protons to enter the cell in an acidic environment, which results in intracellular acidification (Hellwig *et al.*, 2004; Vulcu *et al.*, 2004).

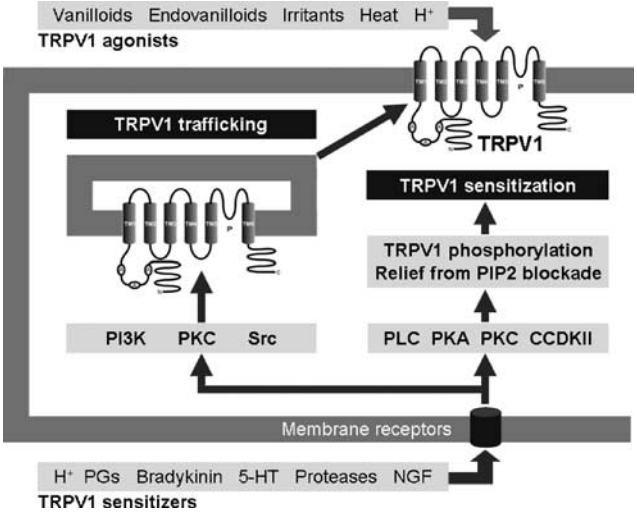

Figure 1 Two major pathways causing TRPV1 overactivity in sensory nerve endings: TRPV1 trafficking to the cell membrane and TRPV1 sensitization. A, ankyrin; C, C terminus; CCDKII, Ca^{2+}-calmodulin-dependent kinase II; 5-HT, 5-hydroxytryptamine; N, N terminus; NGF, nerve growth factor; P, pore; PGs, prostaglandins; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; Src, Src kinase, TM, transmembrane domain.

Distinct members of the TRPV, TRPM and TRPA subunit families have turned out to be particularly relevant to nociception, thermosensation and chemaesthesis (Table 1). There is emerging evidence that members of other TRP channel subfamilies also contribute to thermo- and chemosensation, much as TRP channels are involved in sweet, bitter, sour and umami taste sensation (Zhang *et al.*, 2003; Huang *et al.*, 2006; Bandell *et al.*, 2007; Montell and Caterina, 2007). Although less well studied, TRP channels may also contribute to transduction of mechanical stimuli as suggested by alterations of mechanosensation following knockout of specific TRP channels.

TRPV1, a molecular noci- and thermosensor

The existence of TRPV1 has long been envisaged from the specific action of capsaicin on nociceptive afferent neurones which, owing to this property, have become known as capsaicin-sensitive afferent neurones (Szolcsányi, 1982; Maggi and Meli, 1988; Holzer, 1991; Szallasi and Blumberg, 1999). TRPV1 is a polymodal nocisensor par excellence, being receptive to noxious heat ($>42\,^{\circ}C$), acidosis, endovanilloids and a variety of pungent compounds such as capsaicin, resiniferatoxin, piperine, gingerol, zingerone, camphor, eugenol, ethanol and the vanillatoxins 1–3 (Caterina and Julius, 2001; Trevisani *et al.*, 2002; Patapoutian *et al.*, 2003; Siemens *et al.*, 2006; Szallasi *et al.*, 2007; Cromer and McIntyre, 2008). Acid was initially thought to be the major endogenous agonist (Bevan and Geppetti, 1994), but later the cannabinoid receptor agonist anandamide and several other arachidonic acid-derived metabolites such as *N*-arachidonoyl-dopamine, *N*-oleoyldopamine, oleoylethanolamide, 12-(S)-hydroperoxyeicosatetraenoic acid, 15-(S)-hydroperoxyeicosatetraenoic acid and leukotriene B_4 were found to activate TRPV1 (Zygmunt *et al.*, 1999; Hwang *et al.*, 2000; Huang *et al.*, 2002; Szallasi *et al.*, 2007). As the potency of these endovanilloids at TRPV1 is in the $\mu mol\,L^{-1}$ range, the physiological and pathophysiological relevance of arachidonic acid-derived TRPV1 agonists *in vivo* is still debated.

The effect of acidosis on TRPV1 is two-fold. TRPV1 is gated open only if the extracellular pH is reduced below 6, in which case a sustained channel current is generated (Tominaga *et al.*, 1998; Jordt *et al.*, 2000). In contrast, mild acidosis in the range of pH 7–6 sensitizes TRPV1 to other stimuli such as capsaicin and heat (Tominaga *et al.*, 1998; McLatchie and Bevan, 2001; Ryu *et al.*, 2003; Neelands *et al.*, 2005). As a result, the temperature threshold for TRPV1 activation is lowered under acidotic circumstances so that this cation channel becomes active at normal body temperature (Tominaga *et al.*, 1998). Proton-induced sensitization involves both an increase in current activation and a decrease in current deactivation (Ryu *et al.*, 2003; Neelands

et al., 2005). Besides mild acidosis, many other signalling pathways (stimulated, for example, by inflammatory mediators such as prostaglandins, bradykinin, adenosine triphosphate, 5-hydroxytryptamine and nerve growth factor) cause allosteric modification of TRPV1 such that the probability of channel opening by heat, protons and capsaicin is enhanced (Caterina and Julius, 2001; Vellani *et al.*, 2001; Gunthorpe *et al.*, 2002; Trevisani *et al.*, 2002; Szallasi *et al.*, 2007). TRPV1 thus replicates the property of pain which, unlike any other sense, increases in intensity in the continued presence of a noxious stimulus (Zhang and McNaughton, 2006).

The property of TRPV1 to sensitize when exposed to painful stimuli has led to the hypothesis that TRPV1 is a prime factor in hyperalgesia (Reeh and Pethö, 2000). Sensitization of the ion channel depends on several mechanisms among which phosphorylation of TRPV1 by protein kinase A, protein kinase C and other kinases (Figure 1) is of particular importance (Premkumar and Ahern, 2000; Tominaga *et al.*, 2001; Vellani *et al.*, 2001; Kagaya *et al.*, 2002; Olah *et al.*, 2002; Bhave *et al.*, 2003; Varga *et al.*, 2006; Vetter *et al.*, 2006; Zhang and McNaughton, 2006; Nilius *et al.*, 2007). Whether pore dilation following sustained exposure to agonists (Chung *et al.*, 2008) contributes to sensitization remains to be investigated. Another mechanism whereby bradykinin, nerve growth factor and anandamide increase TRPV1 activity involves phospholipase C-mediated hydrolysis of phosphatidylinositol-4,5-bisphosphate which normally inhibits TRPV1 gating by agonists (Prescott and Julius, 2003). In addition, TRPV1 sensitization involves the rapid recruitment of an intracellular pool of TRPV1 to the cell membrane (Figure 1), a process in which phophoinositide 3-kinase and Src kinase has an important function (Zhang *et al.*, 2005; Stein *et al.*, 2006).

Although phosphorylation causes sensitization, dephosphorylation of TRPV1 by protein phosphatases promotes desensitization which is a major mechanism of inhibitory regulation (Mohapatra and Nau, 2005). Desensitization of TRPV1 to capsaicin depends on extracellular Ca^{2+}, whereas that to heat is independent of Ca^{2+}, which attests to stimulus-dependent differences in the mechanism of desensitization (Bandell *et al.*, 2007). Desensitization of TRPV1 to capsaicin involves a number of intracellular components including protein kinase A, adenosine triphosphate and calmodulin (Bhave *et al.*, 2002; Mohapatra and Nau, 2003; Numazaki *et al.*, 2003; Rosenbaum *et al.*, 2004; Lishko *et al.*, 2007). 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; Mohapatra and Nau, 2005). In addition, desensitization appears to be related to a depletion of phosphatidylinositol-4,5-bisphosphate (Liu *et al.*, 2005; Stein *et al.*, 2006), which attests to a dual function of this phosphoinositide in sensitization and desensitization of TRPV1 (Lukacs *et al.*, 2007).

The ability of protons to sensitize TRPV1 to heat and other stimuli, on the one hand, and to activate TRPV1 *per se*, on the other hand, is mediated by different amino acid residues of the channel protein. Glu-600 on the extracellular side of transmembrane segment 5 is crucial for proton-induced sensitization of TRPV1, whereas Val-538 in the extracellular linker between transmembrane segments 3 and 4, Thr-633 in the pore helix and Glu-648 in the linker between the selectivity filter of the pore and transmembrane segment 6 are essential for proton-induced gating of TRPV1 (Jordt *et al.*, 2000; Ryu *et al.*, 2007). Mutation of the latter amino acid residues selectively abrogates proton-evoked currents but preserves the current responses to capsaicin and heat and their potentiation by mildly acidic pH (Jordt *et al.*, 2000; Ryu *et al.*, 2007). Thus, the sites in the TRPV1 protein targeted by protons differ from those targeted by heat and chemical ligands (Jordt *et al.*, 2000; Welch *et al.*, 2000; McLatchie and Bevan, 2001; Gavva *et al.*, 2004; Ryu *et al.*, 2007).

The vanilloid and fatty acid TRPV1 ligands bind to intracellular sites of the channel, and the amino acids critical for capsaicin/resiniferatoxin binding include Arg-491, Tyr-511, Ser-512, Ile-514, Val-518 and residue 547 (Met in rat, Leu in man), which are part of transmembrane segments 3 and 4 (Jordt and Julius, 2002; Jung *et al.*, 2002; Sutton *et al.*, 2005; Johnson *et al.*, 2006; Cromer and McIntyre, 2008). Apart from transient ligand binding, there is another mechanism of TRP channel activation which involves covalent binding of ligands and stable modification of the channel protein (Bandell *et al.*, 2007). This is also true for TRPV1 in which a single cystein residue in the N-terminal region of the protein enables pungent compounds from onion and garlic to activate the channel (Salazar *et al.*, 2008).

Activation of TRPV1 by heat is not fully understood, although it is known that the C terminus of thermo-TRP channels has an important function in this mode of channel opening (Brauchi *et al.*, 2006).

TRPV1 expression by the sensory system

The selectivity with which capsaicin has long been known to act on primary sensory neurones (Holzer, 1991; Szallasi and Blumberg, 1999) is due to the selective expression of TRPV1 by these nerve cells. The implications of capsaicin-sensitive afferent neurones have been extensively studied with two experimental paradigms: stimulation of afferent neurones by acute application of capsaicin and pretreatment of animals or tissues with high doses of capsaicin to 'desensitize' afferent neurones to the excitatory action of capsaicin and other stimulants. Importantly, 'capsaicin desensitization' is by no means equivalent to desensitization of the TRPV1 channel, but a method to defunctionalize afferent neurones by stimulation of TRPV1, which through excess influx of Ca^{2+} causes long-lasting functional and morphological alterations in afferent neurones. These nerve cells may even degenerate if, for example, a high dose of capsaicin is administered to newborn rats (Jancsó *et al.*, 1977) or micromolar concentrations of capsaicin are introduced in dorsal root ganglion (DRG) cultures (Wood *et al.*, 1988). Uptake of nerve growth factor is one of the elements that determines whether sensory neurones degenerate or undergo long-lasting defunctionalization following exposure to a high dose of capsaicin *in vivo* (Szöke *et al.*, 2002). As the whole sensory neurone is knocked down by 'capsaicin desensitization', referral to a 'capsaicin-sensitive' structure

or function in its historical connotation does not necessarily point to an implication of TRPV1. In addition, capsaicin at higher concentrations can act on ion channels unrelated to TRPV1 and cellular structures lacking TRPV1 (Holzer, 1991).

Numerous studies have confirmed that primary sensory neurones originating from the dorsal root, trigeminal and nodose ganglia are the major cellular systems expressing TRPV1 (Caterina *et al.*, 1997; Guo *et al.*, 1999; Michael and Priestley, 1999; Patterson *et al.*, 2003; Robinson *et al.*, 2004; Schicho *et al.*, 2004). In the dorsal root and trigeminal ganglia, TRPV1 is restricted to small and medium-sized somata that are known to give rise to unmyelinated (C-) and thinly myelinated (Aδ-) fibres (Caterina *et al.*, 1997; Guo *et al.*, 1999; Michael and Priestley, 1999). Following synthesis in the nerve cells, TRPV1-like immunoreactivity is transported into both the central and peripheral processes of primary afferent neurones (Guo *et al.*, 1999). The fibres of these neurones innervate virtually all tissues of the body including skin, muscle, bone, internal organs and vascular system. There are, however, regional differences in the relative proportion of sensory neurones that stain positive for TRPV1. Thus, TRPV1-immunoreactive fibres are considerably more prevalent in visceral than in somatic afferent nerves (Robinson *et al.*, 2004; Brierley *et al.*, 2005; Hwang *et al.*, 2005; Christianson *et al.*, 2006).

There are also regional and species differences in the chemical coding of primary afferent neurones expressing TRPV1. A large body of evidence indicates that calcitonin gene-related peptide (CGRP), substance P, somatostatin and other neuropeptides are messenger molecules characteristic of capsaicin-sensitive afferents (Green and Dockray, 1988; Holzer, 1991; Sternini, 1992; Szallasi and Blumberg, 1999). Immunocytochemistry has revealed that co-localization of TRPV1 with these neuropeptides varies with subpopulation of afferent neurones, region and species (Hwang *et al.*, 2005; Price and Flores, 2007). DRG neurones can be largely differentiated by their binding of isolectin B_4 and their responsiveness to different neurotrophins Guo *et al.*, 1999; Michael and Priestley, 1999; Liu *et al.*, 2004; Hwang *et al.*, 2005; Price and Flores, 2007). In adult rodents, the isolectin B_4-negative cell population responds to nerve growth factor, whereas isolectin B_4-positive cells respond to the glial cell line-derived family of neurotrophins. However, there is no clear distinction between these populations of DRG neurones in terms of their expression of TRPV1 and the neuropeptides substance P, CGRP and somatostatin (Price and Flores, 2007). In the rat, TRPV1 is found in both populations of DRG neurones but is more prevalent in isolectin B_4-positive cells (Guo *et al.*, 1999; Michael and Priestley, 1999; Liu *et al.*, 2004; Hwang *et al.*, 2005; Price and Flores, 2007), whereas in the mouse TRPV1 is largely absent from isolectin B_4-positive DRG cells (Zwick *et al.*, 2002; Woodbury *et al.*, 2004; Price and Flores, 2007). In both rat and mouse, however, TRPV1 abounds in visceral sensory neurones that bind little isolectin B_4 but are rich in CGRP and substance P (Ward *et al.*, 2003; Robinson *et al.*, 2004; Schicho *et al.*, 2004; Brierley *et al.*, 2005; Hwang *et al.*, 2005; Christianson *et al.*, 2006).

In addition to its prominent location in sensory neurones, TRPV1 has been encountered in afferent neurone-associated cells such as epithelial cells in the urinary bladder (Birder *et al.*, 2001, 2002), cells of the gastric mucosa (Nozawa *et al.*, 2001; Kato *et al.*, 2003; Kechagias *et al.*, 2005) and keratinocytes as well as mast cells in the skin (Ständer *et al.*, 2004; Bodó *et al.*, 2005; Facer *et al.*, 2007). The function of TRPV1 in these cellular systems has been less extensively studied than that in sensory neurones. It need be considered that some of the TRPV1-like immunoreactivity found in cells other than primary afferent neurones represents splice variants of TRPV1 whose function may differ from that of neuronal TRPV1 (Wang *et al.*, 2004; Szallasi *et al.*, 2007). Some authors have described expression of TRPV1 in neurones of the enteric nervous system whereas other authors failed to confirm this location (for a review see Holzer, 2004a), given that TRPV1 messenger ribonucleic acid (RNA) disappears from the rat stomach following extrinsic denervation (Schicho *et al.*, 2004).

Implications of TRPV1 in inflammation, pain and hyperalgesia

In most tissues, stimulation of sensory neurones by noxious stimuli has two different effects: local release of neuropeptides from the peripheral nerve fibres in the tissue and induction of autonomic reflexes, sensation and pain (Holzer, 1988; Maggi and Meli, 1988). By releasing peptide transmitters in the periphery, sensory nerve fibres can modify vascular, immune and visceral smooth muscle functions. Following tissue irritation or injury, some of these reactions (for example, vasodilatation and plasma protein extravasation) contribute to the process of neurogenic inflammation. This efferent-like mode of operation may take place independently of nociception, and it has been hypothesized that some DRG neurones are specialized in controlling peripheral effector mechanisms only, whereas other DRG neurones may be specialized in the afferent mode of action or both (Holzer and Maggi, 1998). The neuropeptides involved in the efferent-like mode of operation include CGRP, somatostatin and the tachykinins substance P and neurokinin A (Maggi, 1995; Pintér *et al.*, 2006). Calcitonin gene-related peptide and the tachykinins facilitate inflammation, whereas the effects of somatostatin are of an anti-inflammatory nature (Pintér *et al.*, 2006; Helyes *et al.*, 2007). There is an increasing body of experimental and clinical findings that TRPV1 has a function in inflammatory processes and in the pain and hyperalgesia associated with inflammation, injury, acidosis and malignancies. The evidence for this concept is severalfold as summarized in Table 2.

Table 3 presents a select overview of results that attest to an implication of TRPV1 in inflammation and in the hyperalgesia associated with inflammation, nerve injury, cancer and other disorders in a variety of tissues including skin, skeletal muscle, bone, joints and visceral organs such as the heart, respiratory system, digestive tract and urogenital system. As these implications of TRPV1 have been repeatedly reviewed elsewhere (Holzer, 2004a; Immke and Gavva, 2006; Szallasi *et al.*, 2007; Gunthorpe and Szallasi, 2008), only some functions are exemplified here. Experimental inflammation in the skin leads to upregulation of TRPV1

Table 2 Summary of experimental and clinical findings attesting to a role of TRPV1 in inflammation and in hyperalgesia associated with inflammation, injury, acidosis and malignancies

Activation, inhibition or deletion of TRPV1 modifies inflammatory processes in a tissue- and condition-specific manner
Activation of TRPV1 stimulates afferent neurones and elicits pain in humans and pain-related behaviour in animals
The expression of TRPV1 by sensory neurones and associated cells is upregulated under conditions of inflammation and hyperalgesia in both rodents and humans
Many noxious stimuli converge on TRPV1 to reduce its threshold for activation by heat, capsaicin, protons and other agonists
Thermal hyperalgesia in response to experimental inflammation is attenuated by TRPV1 knockout
Hypersensitivity to mechanical noxious stimuli following nerve injury or visceral inflammation is reduced by TRPV1 knockout
TRPV1 antagonists block behavioural pain responses to thermal, chemical and mechanical stimuli in experimental models of inflammatory, neuropathic, ischaemic, acidotic and cancer pain

expression and function in DRG neurones, particularly in the population of isolectin B_4-positive somata (Carlton and Coggeshall, 2001; Ji *et al.*, 2002; Breese *et al.*, 2005). This sequel of inflammation depends on nerve growth factor which, by a post-transcriptional mechanism involving mitogen-activated protein kinase p38, increases the protein but not messenger RNA levels of TRPV1 in DRG neurones (Ji *et al.*, 2002). The TRPV1 blocker SB-705498 has been found to elevate the heat pain threshold in the normal human skin and to increase the heat pain tolerance in human skin exposed to ultraviolet B irradiation (Chizh *et al.*, 2007).

TRPV1 in the digestive tract has been attributed diverse functions in tissue homeostasis and abdominal pain (Holzer, 2004a). Administration of capsaicin to the gastric and duodenal mucosa increases mucosal blood flow, a response which is mimicked by exposure to excess acid (Holzer, 1998). The acid-evoked hyperaemia in the duodenal mucosa is inhibited by the TRPV1 antagonist capsazepine, which indicates that acid activates TRPV1 on sensory nerve fibres that releases the vasodilator peptide CGRP (Akiba *et al.*, 2006b). Through activation of a similar mechanism capsaicin is able to protect the oesophageal, gastric and intestinal mucosa from a variety of injurious chemical insults (Holzer, 1998). Paradoxically, knockout of TRPV1 has been reported to ameliorate acid-induced injury in the oesophagus and stomach (Fujino *et al.*, 2006; Akiba *et al.*, 2006a). Analysis of this observation in the stomach revealed that disruption of the TRPV1 gene causes a compensatory upregulation of other protective mechanisms in the gastric mucosa (Akiba *et al.*, 2006a). Apart from protecting the gastrointestinal mucosa (Holzer, 1998; Massa *et al.*, 2006), TRPV1 has also been found to exacerbate inflammation in certain models of pancreatitis, ileitis and colitis (Table 3). Emerging evidence indicates that TRPV1 contributes to pancreatic islet inflammation associated with type I diabetes and has a function in insulin-dependent glucose regulation, type II diabetes, adipogenesis and obesity (Razavi *et al.*, 2006; Gram *et al.*, 2007; Zhang *et al.*, 2007; Suri and Szallasi, 2008). It awaits to be explored how these implications are reflected in the pharmacological profile of TRPV1 blockers.

Activation of TRPV1 on afferent neurones innervating the gut elicits pain in humans and pain-related behaviour in rodents, and there is emerging evidence that TRPV1 contributes to the chemical and mechanical hyperalgesia associated with gastrointestinal inflammation (Table 3). TRPV1 in afferent neurones has been found upregulated not only in inflammation but also in the absence of overt inflammation as is typical of functional gastrointestinal disorders (Holzer, 2008). This is true for patients with irritable bowel syndrome in which the increased density of TRPV1 in the rectosigmoid colon correlates with pain severity (Akbar *et al.*, 2008). Non-erosive reflux disease (Bhat and Bielefeldt, 2006), idiopathic rectal hypersensitivity and faecal urgency (Chan *et al.*, 2003) are other instances of TRPV1 upregulation in the absence of inflammation. Moreover, hypersensitivity to capsaicin characterizes a proportion of patients with functional dyspepsia (Hammer *et al.*, 2008). A function of TRPV1 in this disorder is also suggested by the beneficial effect of repeated capsaicin intake (Bortolotti *et al.*, 2002). Experimental findings have likewise shown that TRPV1 has a bearing on post-inflammatory colonic hyperalgesia in rodents, given that upregulation of TRPV1 expression and function persists long after the initial inflammatory insult has subsided (Eijkelkamp *et al.*, 2007; Jones *et al.*, 2007; Winston *et al.*, 2007; Holzer, 2008). A possible function of TRPV1 in emesis (Andrews *et al.*, 2000) requires further study.

Several experimental studies indicate that TRPV1 not only contributes to thermal and chemical nociception but also to inflammatory or neuropathic mechanical hyperalgesia in skin, bone, joint, gastrointestinal tract and urinary bladder (Table 3). This implication of TRPV1 is surprising in as much as TRPV1 channels have not yet been characterized as mechanosensitive. It may be, however, that TRPV1 has an impact on the excitability and sensory gain of TRPV1-bearing mechanosensitive nerve fibres, especially when its expression or function is upregulated.

Implications of TRPV1 in thermosensation and thermoregulation

It does not come as a surprise that the sensation caused by capsaicin is described as 'hot' and 'burning', given that TRPV1 is a heat sensor (Caterina *et al.*, 1997; Tominaga *et al.*, 1998). Surprising, however, is that TRPV1 knockout mice have a normal body temperature and do not seem to have a deficit in heat sensing (Szelényi *et al.*, 2004; Woodbury *et al.*, 2004; Iida *et al.*, 2005), except that heat hyperalgesia in response to inflammation (Caterina *et al.*, 2000; Davis *et al.*, 2000) or heat injury (Bölcskei *et al.*, 2005) and fever in response to the bacterial pyrogen lipopolysaccharide (Iida *et al.*, 2005) are attenuated. The maintenance of basal thermoregulation in TRPV1 knockout mice was explained by a redundancy of heat sensors, whereas developmental compensations in heat sensing were little considered. The latter possibility, though, is a very likely explanation, given that many TRPV1 blockers cause substantial hyperthermia (Steiner *et al.*, 2007; Gavva *et al.*, 2007a).

Table 3 Select implications of TRPV1 in inflammation, pain and hyperalgesia

Tissue	*Pathophysiological process*	*Type of evidence*	*References*
Skin	Experimental inflammation in rodents	Upregulation of expression and function of TRPV1 in DRG neurones	Carlton and Coggeshall (2001); Ji *et al.* (2002); Breese *et al.* (2005)
Skin	Inflammation-induced thermal hyperalgesia in rodents	Attenuation by TRPV1 knockout and antagonism	Caterina *et al.* (2000); Davis *et al.* (2000); Lehto *et al.* (2008)
Skin	Thermal and mechanical hyperalgesia because of thermal injury in mice	Attenuation by TRPV1 knockout	Bölcskei *et al.* (2005)
Skin	Thermal hyperalgesia of human skin because of ultraviolet B irradiation	Increase in heat pain tolerance by TRPV1 antagonism	Chizh *et al.* (2007)
Skin	Nocifensive response to intraplantar phorbol 12-myristate 13-acetate in mice	Abolition by TRPV1 knockout	Bölcskei *et al.* (2005)
Skin	Acid-induced pain in rodents	Attenuation by TRPV1 knockout and antagonism	Caterina *et al.* (2000); Davis *et al.* (2000); Pomonis *et al.* (2003)
Skin/leg	Experimental nerve injury in rodents (neuropathic pain)	Downregulation of TRPV1 in the damaged nerve fibres, but upregulation and ectopic expression of TRPV1 in non-damaged fibres, particularly those of the Aδ type	Hudson *et al.* (2001); Rashid *et al.* (2003)
Skin/leg	Mechanical hyperalgesia because of inflammation or nerve injury in rodents (inflammatory or neuropathic pain)	Attenuation by TRPV1 antagonism	Pomonis *et al.* (2003); Honore *et al.* (2005); Culshaw *et al.* (2006)
Skeletal muscle	Hypertensive response to muscle exercise in rodents (acid-induced pain)	Attenuation by TRPV1 antagonism	Gao *et al.* (2007)
Bone	Hyperalgesia associated with an *in vivo* bone cancer model in mice	Attenuation by TRPV1 knockout and antagonism	Ghilardi *et al.* (2005)
Joints	Experimental joint inflammation and mechanical hyperalgesia in rodents	Attenuation of inflammation and hyperalgesia by TRPV1 knockout	Keeble *et al.* (2005); Szabó *et al.* (2005); Barton *et al.* (2006)
Respiratory system	Bronchoconstriction, microvascular leakage, hypersecretion and cough	Induction by TRPV1 agonism	Geppetti *et al.* (2006); Kollarik *et al.* (2007); Szallasi *et al.* (2007); McLeod *et al.* (2008)
Respiratory system	Patients with chronic cough	Upregulation of TRPV1 in bronchi	Geppetti *et al.* (2006); Kollarik *et al.* (2007); Szallasi *et al.* (2007)
Respiratory system	Cough induced by citric acid in normal guinea-pigs or by antigen in allergic guinea-pigs	Attenuation by TRPV1 antagonism	Geppetti *et al.* (2006); Kollarik *et al.* (2007); Szallasi *et al.* (2007); McLeod *et al.* (2008)
Respiratory system	Patients with asthma and chronic obstructive pulmonary disease	Increased sensitivity to the protussive effect of TRPV1	Geppetti *et al.* (2006); Kollarik *et al.* (2007); Szallasi *et al.* (2007)
Heart	Acidosis-evoked release of CGRP from sensory nerve fibres in the mouse heart	Abolition by TRPV1 knockout	Strecker *et al.* (2005)
Heart	Recovery of cardiac function after exposure to ischaemia/reperfusion (protection from and adaptation to ischaemic stress)	Attenuation by TRPV1 knockout and antagonism	Wang and Wang (2005); Zvara *et al.* (2006); Zhong and Wang (2007)
Oesophageal and gastrointestinal mucosa	Hyperaemia, secretion of bicarbonate secretion and protection from chemical injury in rats and humans	Induction by TRPV1 agonism	Holzer (1998, 2004b); Massa *et al.* (2006)
Ileal mucosa	Ileitis induced by *Clostridium difficile* toxin A in rodents	Attenuation by TRPV1 antagonism	McVey and Vigna (2001)
Colonic mucosa	Colitis induced by dextrane sulfate or trinitrobenzene sulphonic acid	Attenuation by TRPV1 antagonism	Kihara *et al.* (2003); Kimball *et al.* (2004); Miranda *et al.* (2007)
Digestive tract	Abdominal pain in rodents and humans	Induction by intraluminal capsaicin	Drewes *et al.* (2003); Schmidt *et al.* (2004); Holzer (2004a); Hammer *et al.* (2008)
Digestive tract	Acid-induced stimulation of vagal and spinal afferent nerve fibres in mice	Prevention by TRPV1 knockout and antagonism	Rong *et al.* (2004); Sugiura *et al.* (2007); Bielefeldt and Davis (2008)
Digestive tract	Acid-induced oesophagitis, gastric acid-evoked injury of the stomach, trinitrobenzene sulphonic acid-induced pancreatitis and colitis in rodents	Upregulation of TRPV1 in vagal and spinal afferent neurones	Schicho *et al.* (2004); Banerjee *et al.* (2007); Miranda *et al.* (2007); Xu *et al.* (2007)
Digestive tract	Patients with erosive gastro-oesophageal reflux disease, non-erosive reflux disease, irritable bowel syndrome, inflammatory bowel disease, idiopathic rectal hypersensitivity and faecal urgency	Upregulation of TRPV1 in the mucosa	Yiangou *et al.* (2001); Chan *et al.* (2003); Matthews *et al.* (2004); Bhat and Bielefeldt (2006); Akbar *et al.* (2008)

Table 3 *Continued*

Tissue	*Pathophysiological process*	*Type of evidence*	*References*
Upper gastrointestinal tract	Functional dyspepsia	Hypersensitivity to the algesic effect of capsaicin	Hammer *et al.* (2008)
Upper gastrointestinal tract	Functional dyspepsia	Beneficial effect of TRPV1 ablation	Bortolotti *et al.* (2002)
Colon	Hyperalgesia to intraluminal acid and colorectal distension in mice with acute experimental colitis	Attenuation by TRPV1 knockout and antagonism	Jones *et al.* (2005, 2007); Miranda *et al.* (2007)
Colon	Post-inflammatory chemical and mechanical hyperalgesia in rodents	Attenuation by TRPV1 knockout and antagonism	Eijkelkamp *et al.* (2007); Jones *et al.* (2007); Winston *et al.* (2007)
Peritoneal cavity	Behavioural pain response to intraperitoneal injection of acetic acid in rodents	Attenuation by TRPV1 antagonism	Ikeda *et al.* (2001); Rigoni *et al.* (2003); Tang *et al.* (2007)
Pancreas	Pancreatitis induced by caerulein	Attenuation by TRPV1 antagonism	Nathan *et al.* (2001)
Pancreas	Islet inflammation in non-obese diabetic mice (genetic model of type I diabetes)	Prevention by TRPV1 ablation	Razavi *et al.* (2006); Suri and Szallasi (2008)
Pancreas	Pain behaviour associated with L-arginine-induced necrotizing pancreatitis in rodents	Attenuation by TRPV1 antagonism	Wick *et al.* (2006)
Urinary bladder	Responsiveness of afferent neurones to bladder distension and intravesical acid in rodents	Attenuation by TRPV1 knockout and antagonism	Birder *et al.* (2002); Daly *et al.* (2007)
Urinary bladder	Increase in distension-induced afferent signalling and hyper-reflexia associated with experimental inflammation of the rodent urinary bladder	Attenuation by TRPV1 ablation and knockout	Jaggar *et al.* (2001); Charrua *et al.* (2007)
Urinary bladder	Patients with neurogenic bladder overactivity and sensory urgency	Upregulation of TRPV1 in the urinary bladder	Brady *et al.* (2004); Liu *et al.* (2007)
Urinary bladder	Patients with urinary bladder pain and hyperreflexia	Beneficial effect of TRPV1 ablation	Bley (2004); Brady *et al.* (2004); Avelino and Cruz (2006); Cruz and Dinis (2007)

TRPV1 ablation refers to pretreatment with capsaicin or resiniferatoxin to defunctionalize afferent neurones.

An implication of TRPV1 in heat sensing has long been envisaged from the effects of capsaicin and resiniferatoxin to cause hypothermia (Szolcsányi, 1982; Szallasi and Blumberg, 1999). In addition, pretreatment of rodents with a high dose of capsaicin to defunctionalize sensory and hypothalamic neurones leads to prolonged hyperthermia and impairs the animals' ability to recognize high ambient temperatures and to mount appropriate heat dissipation responses (Jancsó-Gábor *et al.*, 1970a; Szolcsányi, 1982). As the thermoregulatory behaviour of rats treated with capsaicin as neonates or adults is differentially altered, it has been suggested that peripheral capsaicin-sensitive mechanisms are more relevant to body temperature regulation than central capsaicin-sensitive mechanisms (Dib, 1983; Hajós *et al.*, 1983). It needs to be taken into account, however, that capsaicin-induced ablation of sensory neurones reduces the DRG expression of several thermo-TRP channels including TRPV1, TRPM8 and TRPA1 (Yamashita *et al.*, 2008). TRPV1 is expressed by somatic and visceral sensory neurones that monitor the external environmental and internal body temperature, respectively, and by neurones in the preoptic/anterior hypothalamus which functions both as a sensor of local temperature and an integrator of sensory input from the periphery (Figure 2). It is now emerging that an important function of TRPV1 is to monitor and control core body temperature (Montell and Caterina, 2007). This

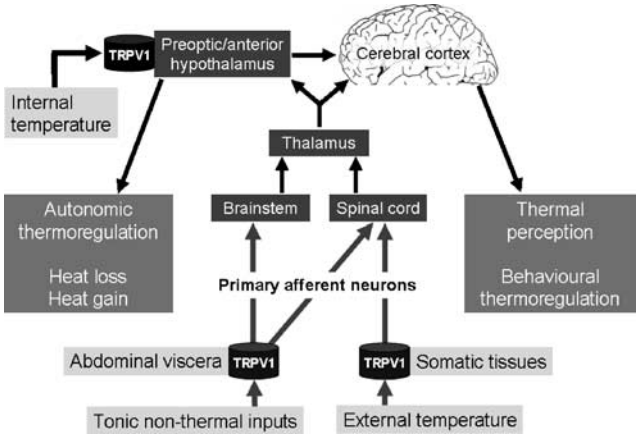

Figure 2 Involvement of peripheral and central TRPV1 in thermoregulation.

implication is based on the ability of several TRPV1 blockers to prevent the hypothermic effect of capsaicin and to raise body temperature in rats, mice, dogs, monkeys and humans by a peripheral site of action (Steiner *et al.*, 2007; Gavva *et al.*, 2007a, b, 2008).

The hyperthermic action of TRPV1 blockers involves cutaneous vasoconstriction and shivering-related thermogenesis,

but not warmth-seeking behaviour and is inhibited by the antipyretic drug acetaminophen (Steiner *et al*., 2007; Gavva *et al*., 2007b, 2008). As the hyperthermic effect of the TRPV1 antagonist AMG0347 is absent in TRPV1 knockout mice, it is entirely the result of TRPV1 blockade. Because the magnitude of the hyperthermic effect is independent of the baseline temperature, it has been concluded that the rise of body temperature results from blockade of tonic TRPV1 activation by non-thermal factors (Steiner *et al*., 2007). These non-thermal factors do not seem to include protons (Gavva *et al*., 2007a) but otherwise have not yet been identified. It is very likely that the site of the hyperthermic action of TRPV1 blockers is outside the blood–brain barrier (Figure 2), because i.c.v. or i.t. AMG0347 is no more effective in causing hyperthermia than intravenous administration (Steiner *et al*., 2007). Both brain-penetrant and peripherally restricted TRPV1 antagonists are in fact fully active in raising body temperature (Gavva *et al*., 2007a). The site where TRPV1 blockers act to raise body temperature is by all means on sensory nerve fibres within the abdominal cavity (Figure 2), because localized intra-abdominal 'desensitization of TRPV1' by intraperitoneal resiniferatoxin blocks the hyperthermic action of AMG0347 (Steiner *et al*., 2007). Identification of the non-thermal factors that act on visceral afferent neurones to moderate body temperature may open up opportunities to differentiate between the unwanted hyperthermic and wanted analgesic effects of TRPV1 antagonists.

Phase I trials have established that the TRPV1 antagonist AMG517 (1–25 mg taken orally as a single dose) raises body temperature in humans for an approximate duration of 1 day, the magnitude of hyperthermia being related to the plasma concentration of the drug (Gavva *et al*., 2008). As in rats, dogs and monkeys, the hyperthermic effect of AMG517 in human volunteers was transient and attenuated following repeated dosing (2–10 mg taken orally as a single daily dose for 7 days) although, relative to placebo-treated control subjects, the mean maximal body temperatures of all subjects stayed significantly higher over the 7-day treatment period (Gavva *et al*., 2007b, 2008). In a phase Ib trial involving patients undergoing molar extraction in whom AMG517 (2–15 mg taken orally as a single dose) was evaluated for the control of postoperative pain, body temperatures of 39–40.2 °C were found to persist for 1–4 days in 33% of the nine subjects studied (Gavva *et al*., 2008). Thus, marked interindividual differences in the susceptibility to the hyperthermic effect of the TRPV1 blocker were observed. The long duration of action is likely to be related to the long plasma half life (13–23 days) of AMG517 in humans (Gavva *et al*., 2008). In the only other phase I trial of a TRPV1 blocker reported to date, no information on the effect of SB-705498 on body temperature was provided (Chizh *et al*., 2007).

TRPV1 expression and function in the central nervous system

Although sensitivity to capsaicin is a prominent feature of many primary afferent neurones, it has long been known that capsaicin can act on central neurones, notably on warm-sensitive neurones in the preoptic/anterior hypothalamus (Jancsó-Gábor *et al*., 1970b; Szolcsányi *et al*., 1971). Later it was found that a number of neurones 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, 1992; Kim *et al*., 2005). It thus did not come as a total surprise that TRPV1 messenger RNA and protein as well as TRPV1-like binding sites are widely distributed in the rodent brain (Mezey *et al*., 2000; Szabo *et al*., 2002; Roberts *et al*., 2004; Tóth *et al*., 2005; Cristino *et al*., 2006). A quantitative comparison, however, has shown that the levels of TRPV1 messenger RNA in the brain are substantially lower than those in the DRG ganglia (Sanchez *et al*., 2001). Notable levels of TRPV1 are found in the cortex, several areas of the limbic system (hippocampus, amygdala, habenula), striatum, substantia nigra, thalamus, preoptic area, hypothalamus, periaqueductal grey, reticular formation, locus coeruleus and cerebellum (Mezey *et al*., 2000; Sanchez *et al*., 2001; Szabo *et al*., 2002; Roberts *et al*., 2004; Tóth *et al*., 2005; Cristino *et al*., 2006).

The wide distribution of TRPV1 in the central nervous system raises the possibility that this ion channel could be involved in many brain functions (Steenland *et al*., 2006). In the preoptic/anterior hypothalamus, capsaicin stimulates and subsequently desensitizes thermosensitive neurones, which results in hypothermia and impaired thermoregulation against overheating, respectively (Jancsó-Gábor *et al*., 1970b; Szolcsányi *et al*., 1971; Szolcsányi, 1982; Hori, 1984). These actions of capsaicin are mediated by TRPV1, activation of which in the medial preoptic nucleus causes hypothermia by modification of neurotransmission through glutamate and γ-aminobutyric acid (Karlsson *et al*., 2005). Stimulation of glutamate release is a mechanism whereby TRPV1 activation in the paraventricular nucleus of the hypothalamus excites pre-autonomic neurones (Li *et al*., 2004) and in the ventral tegmental area stimulates mesolimbic dopaminergic neurones (Marinelli *et al*., 2005). Long-term depression in hippocampal interneurones depends on TRPV1, which points to a possible function of this ion channel in the control of learning, epileptic activity and synaptic plasticity (Gibson *et al*., 2008). Besides cognition, emotional processes may also involve TRPV1, given that anxiety, conditioned fear and hippocampal long-term potentiation are reduced in TRPV1 knockout mice (Marsch *et al*., 2007).

Increasing evidence suggests that TRPV1 participates in the processing of pain signals within the brain (Marinelli *et al*., 2005; Cui *et al*., 2006; Steenland *et al*., 2006; Palazzo *et al*., 2008). Thus, TRPV1 stimulation in the periaqueductal grey by capsaicin or anandamide causes analgesia, an effect that depends on the release of glutamate and stimulation of descending antinociceptive pathways (Palazzo *et al*., 2008). Other sites in the brain where TRPV1 might modify nociception include the locus coeruleus (Hajós *et al*., 1986), the ventral tegmental area (Marinelli *et al*., 2005) and the anterior cingulate cortex (Steenland *et al*., 2006).

The potentials and risks of TRPV1 as a drug target

Recognition of TRPV1 as a multimodal nocisensor, its sensitization by a number of proalgesic pathways and its

upregulation under conditions of hyperalgesia have made this ion channel an attractive target for novel antinociceptive drugs. Pain and hyperalgesia may be attenuated at the very site of their generation, given that TRPV1 is preferentially expressed by afferent neurones and sensory neuron-associated cells. This concept is particularly attractive because it offers the opportunity to develop antinociceptive drugs with a peripherally restricted site of action, avoiding unwanted effects on the central nervous system, although there is information that brain-penetrant TRPV1 blockers are more powerful than peripherally restricted compounds (Cui *et al*., 2006). As any nocisensor, however, TRPV1 has an important function in the maintenance of homeostasis in the face of pending tissue injury. Interference with molecular probes that are physiologically so important is liable to have adverse effects, unless selective inhibition of 'excess' nocisensors can be achieved whereas their physiological function is preserved. In view of these issues and the bewildering array of its functional implications, TRPV1 need be considered a pharmacological drug target of high potential and high risk.

TRPV1 function can be pharmacologically manipulated by two principal approaches: stimulant/defunctionalizing TRPV1 agonists and TRPV1 antagonists (Roberts and Connor, 2006; Gharat and Szallasi, 2008; Gunthorpe and Szallasi, 2008). The current patent literature discloses more than 1000 natural and synthetic compounds as TRPV1 activators or blockers (Gharat and Szallasi, 2008). It is important to realize that the pharmacological mechanism and biological result of the two approaches are profoundly different. Although TRPV1 antagonists specifically modify the function of the ion channel, stimulant/defunctionalizing TRPV1 agonists target the cellular function of capsaicin-sensitive afferent neurones (Holzer, 1991; Szallasi *et al*., 2007). The 'desensitization' that is brought about by capsaicin, resiniferatoxin or synthetic analogues such as *N*-[4-(2-aminoethoxy)-3-methoxy-phenyl]-methyl-*N*′-[4-(1-1-dimethylethyl)phenyl]-methyl-urea (SDZ 249–665) (Urban *et al*., 2000) reflects 'defunctionalization' of the whole afferent neurone expressing TRPV1 for a prolonged period of time. In the case of capsaicin, the defunctionalizing action is preceded by the compound's powerful effect to cause pain and irritation, whereas resiniferatoxin and SDZ 249–665 are examples of TRPV1 agonists whose action manifests itself primarily in a defunctionalization of nociceptive neurones.

Given that sensory neurones express many nocisensors, it has been argued that local 'desensitization' of afferent neurones by topical TRPV1 agonists is more efficacious in silencing pain and safer than just targeting one nocicensor with a systemic TRPV1 antagonist. In practice, though, the initial painful effect of TRPV1 agonists requires analgesic/anaesthetic co-medication, and a therapeutic effect is achieved only after repeated administration of the compounds for several weeks because of the low doses used and the limited absorption of the drug. Intravesical resiniferatoxin has been shown to be beneficial in patients with neurogenic bladder disorders in which activation of afferent neurones by mechanical and chemical stimuli is likely to have a function, but the results of various clinical studies have been inconsistent (Avelino and Cruz, 2006; Cruz and Dinis, 2007). Several phase II and III trials have been launched to evaluate the efficacy and safety of defunctionalizing TRPV1 agonists such as transacin and civamide for indications as diverse as post-herpetic neuropathy, human immunodeficiency virus-associated neuropathy, cluster headache, migraine and osteoarthritic, musculoskeletal as well as postoperative pain (Szallasi *et al*., 2007; Knotkova *et al*., 2008). It remains to be seen how these site-specific therapeutic regimens involving high-dose patches, intranasal formulations and injectable preparations fare in terms of onset, duration, magnitude and selectivity of action.

Most efforts have been directed at developing compounds that block TRPV1 activation in a competitive or noncompetitive manner. The first of this kind, capsazepine, has been extensively used in the exploration of the pathophysiological implications of TRPV1. However, the results obtained with this compound need to be judged with caution because the selectivity of capsazepine as a TRPV1 blocker is limited by its inhibitory action on nicotinic acetylcholine receptors, voltage-activated Ca^{2+} channels and other TRP channels such as TRPM8 (Docherty *et al*., 1997; Liu and Simon, 1997; Behrendt *et al*., 2004). The TRPV1 blockers that have been designed following the molecular identification of TRPV1 can be categorized into vanilloid-derived and non-vanilloid compounds (Gharat and Szallasi, 2008). The latter class of TRPV1 blockers comprises several different chemical entities (Tables 4 and 5) reviewed in detail elsewhere (Gharat and Szallasi, 2008).

As TRPV1 is activated by multiple stimuli that interact with different domains of the channel protein, some TRPV1 blockers are stimulus-specific (Gavva *et al*., 2005a; Lehto *et al*., 2008). For instance, AMG0610 and SB-366791 inhibit the activation of rat TRPV1 by capsaicin but not acid, whereas iodo-resiniferatoxin, BCTC, AMG6880, AMG7472, AMG9810 and A-425619 are TRPV1 antagonists that do not

Table 4 Select classes of non-vanilloid TRPV1 blockers found in the patent literature

Pyridyl piperazine carboxamides such BCTC
Tetrahydropyridine amides
4-Fluopyridine amides
Spiroisoxazolopyridine amides
Piperazinyl benzimidazoles
Benzimidazole derivatives
Benzamides
Pyridoindazolones
Piperazinyl pyrimidines
Bicyclic pyrimidin-4-(3H)-ones
Phenylchromones
Biaryl carboxamides
Aminoquinazolines
1,3-Disubstituted urea derivatives such as A-425619 and SB-705498
Aryl cinnamides such as AMG9810

A-425619: 1-isoquinolin-5-yl-3-(4-trifluoromethyl-benzyl)-urea; AMG9810: (E)-3-(4-t-butylphenyl)-N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acrylamide; BCTC: N-(4-tertiarybutylphenyl)-4(3-cholorphyridin-2-yl)-tetrahydropyrazine-1(2H)-carboxamide; SB-705498: N-(2-bromophenyl)-N′-[((R)-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)]urea. Detailed information on the compounds listed in the table is given by Gharat and Szallasi (2008).

Table 5 Four classes of rat TRPV1 antagonists with distinct pharmacological action profiles

Profile	*Examples*	*Response to capsaicin ($0.5\ \mu mol\ L^{-1}$)*	*Response to pH 5*	*Response to heat (45 °C)*	*Effect on body temperature in rodents*
A	A-425619, AMG0347, AMG517, AMG6880, AMG7472, AMG8163, AMG9810, BCTC, iodo-resiniferatoxin, SB-705498	Block	Block	Block	Hyperthermia
B	AMG0610, AMG8563, capsazepine; SB-366791	Block	Partial block	Block	Hyperthermia
C	AMG8562	Block	Potentiation	Block	No change
D	AMG7905	Block	Potentiation	Potentiation	Hypothermia

A-425619: 1-isoquinolin-5-yl-3-(4-trifluoromethyl-benzyl)-urea; AMG0347: (E)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-3-(2-(piperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)acrylamide; AMG517: N-(4-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yloxy]-benzothiazol-2-yl)-acetamide I; AMG0610: (2E)-3-(6-tert-butyl-2-methylpyridin-3-yl)-N-(1H-indol-6-yl)acrylamide; AMG6880: (2E)-3-[2-piperidin-1-yl-6-(trifluoromethyl)pyridin-3-yl]-N-quinolin-7-ylacrylamide; AMG7472: 5-chloro-6-{(3R)-3-methyl-4-[6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1H-benzimidazol-2-yl]piperazin-1-yl}pyridin-3-yl)methanol; AMG7905: N-(6-(2-(cyclohexylmethylamino)-4-(trifluoromethyl)phenyl)pyrimidin-4-yl)benzo[d]thiazol-6-amine; AMG8163: tert-butyl-2-(6-([2-(acetylamino)-1,3-benzothiazol-4-yl]oxy)-pyrimidin-4-yl)-5-(trifluoromethyl)phenylcarbamate; AMG8562: (R,E)-N-(2-hydroxy-2,3-dihydro-1H-inden-4-yl)-3-(2-(piperidin-1-yl)-4-(trifluoromethyl)phenyl) acrylamide; AMG8563: (S,E)-N-(2-hydroxy-2,3-dihydro-1H-inden-4-yl)-3-(2-(piperidin-1-yl)-4-(trifluoromethyl)phenyl)acrylamide; AMG9810: (E)-3-(4-t-butylphenyl)-N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acrylamide; BCTC: N-(4-tertiarybutylphenyl)-4(3-cholorphyridin-2-yl)-tetrahydropyrazine-1(2H)-carboxamide; SB-366791: (2E)-3-(4-chlorophenyl)-N-(3-methoxyphenyl)acrylamide; SB-705498: N-(2-bromophenyl)-N′-[((R)-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)] urea. Adapted from Lehto *et al.* (2008).

differentiate between capsaicin and protons (Seabrook *et al.*, 2002; Gavva *et al.*, 2004, 2005a, b; Neelands *et al.*, 2005). On the other hand, AMG8562 does not block heat-evoked activation of rat TRPV1 (Lehto *et al.*, 2008). Importantly, there are also species differences in the stimulus selectivity of TRPV1 blockers. For instance, capsazepine and SB-366791 are more effective in blocking proton-induced gating of human TRPV1 than of rat TRPV1 (Gunthorpe *et al.*, 2004; Gavva *et al.*, 2005a), and AMG8562 antagonizes heat activation of human but not rat TRPV1 (Lehto *et al.*, 2008).

Although the vast list of emerging TRPV1 blockers (Gharat and Szallasi, 2008) attests to the antinociceptive potential that is attributed to this class of pharmacological agent, it is important to be aware of the likely drawbacks these compounds may have. It has repeatedly been argued that TRPV1 subserves important homeostatic functions, and that the challenge for an effective and safe therapy with TRPV1 blockers will be to suppress the pathological contribution of 'excess' TRPV1 while preserving its physiological function (Holzer, 2004b; Hicks, 2006; Storr, 2007; Szallasi *et al.*, 2007). This concept is impressively portrayed by the emerging function of TRPV1 in thermoregulation as revealed by the hyperthermic action of TRPV1 blockers (Gavva *et al.*, 2007a, b, 2008). Hyperthermia is an adverse effect of TRPV1 blockade that went unnoticed after disruption of the TRPV1 gene (Szelényi *et al.*, 2004; Woodbury *et al.*, 2004), most probably because of developmental compensations in heat sensing.

Apart from the thermoregulatory perils of TRPV1 antagonism (Caterina, 2008), blockade of TRPV1 will also interfere with the physiological function of this nocicensor to survey the physical and chemical environment and, if necessary, to initiate protective responses. Such a function is obvious in the gastrointestinal tract in which capsaicin-sensitive afferent neurones constitute a neural alarm system which helps maintaining mucosal homeostasis in the face of pending injury. As TRPV1 is involved in this task (Holzer, 2004a; Akiba *et al.*, 2006b), TRPV1 antagonism may result in enhanced vulnerability of the gastrointestinal mucosa. Similarly, endotoxin-induced pulmonary inflammation, lung injury and bronchial hyper-reactivity are exacerbated in TRPV1 knockout mice, most probably because the anti-inflammatory and antinociceptive action of somatostatin released from TRPV1-bearing sensory neurones is lacking (Helyes *et al.*, 2007). A deficiency in this protective somatostatin mechanism may also explain why the mechanical hyperalgesia associated with experimental polyneuropathy models is enhanced after TRPV1 gene deletion (Bölcskei *et al.*, 2005). Another caveat derives from the widespread distribution of TRPV1 in the peripheral and central nervous system. Although adverse effects on the brain may be avoided by the development of peripherally restricted TRPV1 antagonists, it has been reported that a significant penetration into the brain is necessary for a TRPV1 antagonist to produce broad-spectrum analgesia (Cui *et al.*, 2006). Recent work suggests, however, that deletion or blockade of TRPV1 in the brain affects cognitive as well as emotional-affective processes (Marsch *et al.*, 2007; Gibson *et al.*, 2008).

Table 6 Approaches to focus therapy specifically on TRPV1 channels upregulated in disease while sparing their physiological function

Site-specific TRPV1 antagonists
Modality-specific TRPV1 antagonists
Uncompetitive TRPV1 (open channel) blockers
Drugs interfering with the sensitization of TRPV1
Drugs interfering with the intracellular trafficking of TRPV1
Defunctionalizing TRPV1 agonists for local administration

Novel approaches to TRPV1 pharmacology

The pharmacological profile of many TRPV1 antagonists to cause hyperthermia represents a hurdle to their use as first-line therapeutics (Caterina, 2008; Gavva *et al.*, 2008). This does not discount the further development of drugs targeting TRPV1, because there are several approaches on the horizon to focus therapy specifically on those TRPV1 channels that are involved in the disease process (Table 6).

Much as the use of defunctionalizing TRPV1 agonists needs to be restricted to the region affected by inflammation

and hyperalgesia, TRPV1 antagonists could be formulated such that they can be administered in an anatomically confined manner that prevents access of the drug to visceral TRPV1 channels that are most relevant to thermoregulation (Caterina, 2008). Another approach of site-specific TRPV1 blockade that has been tested experimentally is to interfere with the synthesis of new TRPV1 channels by small RNA interference (TRPV1 knockdown) or antisense oligonucleotides. Thus, i.t. administration of small interfering RNA or a TRPV1 antisense oligonucleotide attenuates visceral and neuropathic pain in rats (Christoph *et al*., 2006, 2007). The expression of TRPV1 by sensory neurones outside the brain offers a further pharmacological opportunity for a site-specific pharmacological intervention with sensory neuron functions. Thus, the TRPV1 channel can be used as a vehicle for the cellular influx of membrane-impermeant local anaesthetics such as the lidocaine derivative QX-314 (Binshtok *et al*., 2007). When TRPV1 is activated by capsaicin, QX-314 gains access to the intracellular space and, subsequently, blocks voltage-gated sodium channels and action potential conduction only in sensory neurones expressing TRPV1. In this way, local anaesthetics can be made selective for nociceptive afferent neurones, avoiding their unwanted action on non-nociceptive sensory, autonomic and motor neurones (Binshtok *et al*., 2007).

The property of TRPV1 to function as a multimodal nocisensor offers the opportunity to design modality-specific TRPV1 blockers, compounds that prevent activation of TRPV1 by distinct stimuli while sparing the channel's sensitivity to other stimuli. The feasibility of this approach has already been proved (Table 5), given that there are antagonists that inhibit TRPV1 activation by capsaicin and heat but not acid (Gavva *et al*., 2005a), whereas other compounds antagonize capsaicin but not heat (Lehto *et al*., 2008). On the basis of these properties, the available TRPV1 blockers have been divided into four categories with distinct pharmacological action profiles Lehto *et al*. (2008) as summarized in Table 5. Thus, TRPV1 antagonists that do not cause hyperthermia are in sight (Lehto *et al*., 2008). The existence of stimulus-dependent differences in the mechanism of channel desensitization (Bandell *et al*., 2007) is a further aspect relevant to the modality-specific manipulation of TRPV1.

Whereas competitive and non-competitive TRPV1 antagonists will block TRPV1 channels that are both physiologically expressed and pathologically overexpressed, uncompetitive TRPV1 antagonists may be used to differentiate between normal and exaggerated activity of TRPV1. Unlike competitive and non-competitive antagonists that prevent activation of a receptor by an agonist, uncompetitive agonists require receptor activation by an agonist before they can bind to a separate allosteric binding site. By preferentially binding to the active, open state of the channel, uncompetitive TRPV1 (open channel) blockers may preferentially silence overactive TRPV1. This type of antagonism entails that the same antagonist concentration can antagonize higher agonist concentrations better than lower agonist concentrations (Lipton, 2007). The principle of uncompetitive channel blockade is part of the general concept that drugs should be activated by the pathological state that they are intended to inhibit (Lipton, 2007). It is easily conceivable that the complex post-translational regulation of TRPV1 function may be amenable to such a disease-specific type of blockade. For instance, in an experimental model of feline interstitial cystitis, TRPV1 currents in DRG neurones are enhanced in amplitude and desensitize very slowly, because TRPV1 appears to be maximally phosphorylated by protein kinase C (Sculptoreanu *et al*., 2005). As the structure–activity relationship of TRPV1 agonists and antagonists is differentially modulated by phosphatase inhibition, Pearce *et al*. (2008) have envisaged the possibility to tailor agonists and antagonists such that they act best on TRPV1 in a specific regulatory environment.

A rational therapeutic approach would be to prevent or reverse the increase in sensitivity and activity of TRPV1 associated with the disease. Overactivity of the ion channel seems to be brought about by two principal mechanisms, TRPV1 sensitization and TRPV1 trafficking to the cell membrane (Figure 1). It is through these mechanisms that a number of pro-inflammatory mediators reduce the activation threshold of TRPV1 by heat, protons and vanilloids. Although phosphorylation and relief from phosphatidylinositol-4,5-bisphosphate blockade sensitizes TRPV1 (Premkumar and Ahern, 2000; Vellani *et al*., 2001; Olah *et al*., 2002; Prescott and Julius, 2003), dephosphorylation by protein phosphatases leads to desensitization of TRPV1. As a balance between phosphorylation and dephosphorylation appears to determine the activity of the channel (Jung *et al*., 2004; Mohapatra and Nau, 2005; Zhang and McNaughton, 2006; Lukacs *et al*., 2007), both interference with sensitization mechanisms and promotion of TRPV1 desensitization would be pharmacological opportunities to reduce the sensory gain of TRPV1.

An intriguing approach that appears increasingly feasible is interference with the rapid trafficking of TRPV1 between cytosolic membrane compartments (endosomes, vesicles) and the cell membrane (Figure 1), which will result in a reduction of the availability of TRPV1 channels on the cell surface (Morenilla-Palao *et al*., 2004; Planells-Cases *et al*., 2005; Zhang *et al*., 2005). Most membrane receptors reside in macromolecular complexes that include regulatory, signalling and scaffolding proteins. For instance, A-kinase-anchoring protein-150 mediates phosphorylation of TRPV1 by protein kinase A and in this way contributes to thermal hyperalgesia (Jeske *et al*., 2008). Phosphoinositide 3-kinase is relevant to sensitization of TRPV1 by nerve growth factor and insulin-like growth factor because—together with TRPV1 and growth factor receptors—it is part of a signal transduction complex that facilitates the translocation of TRPV1 to the plasma membrane (Van Buren *et al*., 2005; Zhang *et al*., 2005; Stein *et al*., 2006). Protein kinase C, Src kinase, snapin, synaptotagmin IX and soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor also form part of the signal transduction complexes relevant to TRPV1 exocytosis (Morenilla-Palao *et al*., 2004; Planells-Cases *et al*., 2005; Van Buren *et al*., 2005; Zhang *et al*., 2005).

Thus, sensitization of TRPV1 is due not only to an enhancement of channel currents but also to a rapid translocation of TRPV1 from a cytosolic pool to the plasma membrane (Morenilla-Palao *et al*., 2004; Planells-Cases *et al*.,

2005; Van Buren *et al*., 2005; Zhang *et al*., 2005; Stein *et al*., 2006). The trafficking of TRPV1 (and other channels) to the cell surface is blocked by botulinum neurotoxin A (Morenilla-Palao *et al*., 2004), which may explain why intradetrusor injection of botulinum neurotoxin A in patients with urinary bladder overactivity reduces TRPV1- and purinoceptor $P2X_3$-like immunoreactivity in the detrusor muscle and causes improvement of clinical and urodynamic parameters (Apostolidis *et al*., 2005). Intravesical administration of botulinum toxin likewise counteracts acetic acid-evoked bladder overactivity in rats (Chuang *et al*., 2004).

Acknowledgements

Work performed in the laboratory was supported by the Zukunftsfonds Steiermark (Grant 262), the Austrian Scientific Research Funds (FWF Grant L25-B05), the Jubilee Foundation of the Austrian National Bank (Grant 9858) and the Austrian Federal Ministry of Science and Research. I thank Ulrike Holzer-Petsche for critically reading the paper and Evelin Painsipp for graphical assistance.

Conflict of interest

The author states no conflict of interest.

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