BJP British Journal of Pharmacology

DOI:10.1111/bph.12414
www.brjpharmacol.org

Themed Section: The pharmacology of TRP channels

REVIEW

Transient receptor potential (TRP) channels: a clinical perspective

Yosuke Kaneko[1] and Arpad Szallasi[2]

[1]*Discovery Research Alliance, Ono Pharmaceutical Co. Ltd, Osaka, Japan, and* [2]*Department of Pathology and Laboratory Medicine, Monmouth Medical Center, Long Branch, NJ, USA*

Correspondence
Professor Arpad Szallasi, Department of Pathology and Laboratory Medicine, Monmouth Medical Center, 300 2nd Avenue, Long Branch, NJ 07757, USA.
E-mail: ASzallasi@SBHCS.com

Keywords
TRP channels; TRPV1; TRPV3; TRPV4; TRPA1; TRPM8; TRPCs; pain; respiratory disorders; bladder disorders; cancer

Received
9 July 2013
Revised
28 August 2013
Accepted
31 August 2013

Transient receptor potential (TRP) channels are important mediators of sensory signals with marked effects on cellular functions and signalling pathways. Indeed, mutations in genes encoding TRP channels are the cause of several inherited diseases in humans (the so-called 'TRP channelopathies') that affect the cardiovascular, renal, skeletal and nervous systems. TRP channels are also promising targets for drug discovery. The initial focus of research was on TRP channels that are expressed on nociceptive neurons. Indeed, a number of potent, small-molecule TRPV1, TRPV3 and TRPA1 antagonists have already entered clinical trials as novel analgesic agents. There has been a recent upsurge in the amount of work that expands TRP channel drug discovery efforts into new disease areas such as asthma, cancer, anxiety, cardiac hypertrophy, as well as obesity and metabolic disorders. A better understanding of TRP channel functions in health and disease should lead to the discovery of first-in-class drugs for these intractable diseases. With this review, we hope to capture the current state of this rapidly expanding and changing field.

LINKED ARTICLES
This article is part of a themed section on the pharmacology of TRP channels. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-10

Abbreviations
ADPKD, autosomal dominant polycystic kidney disease; ALS-G, Guam variant of amyotrophic lateral sclerosis; BDNF, brain-derived neurotrophic factor; CFA, complete Freund's adjuvant; COPD, chronic obstructive pulmonary disease; DNBS, dinitrobenzene sulphonic acid; FSGS, focal segmental glomerulosclerosis; GERD, gastroesophageal reflux disease; GLP-1, glucagon-like peptide-1; IBD, inflammatory bowel disease; WDR, wide dynamic range

Introduction

Regulated transport of ions *via* ion channels underpins a number of fundamental physiological functions (Bagal *et al.*, 2013). Conversely, inherited ('channelopathy') or acquired dysfunction of these channels disrupts physiological processes, leading to a broad array of disorders (Bagal *et al.*, 2013). Ion channels are important targets for many currently prescribed drugs, second only to GPCRs (Clare, 2010). Indeed, the worldwide sales of ion channel drugs are estimated to be in excess of $12 billion annually. Although ion channels have been successful drug targets, achieving subtype-selectivity has been a major challenge, particularly with voltage-gated sodium and calcium channels (Clare, 2010).

Recently, a number of novel, 'druggable' ion channels have been identified. Of these newly discovered channels, those of the transient receptor potential family [TRP; Figure 1 (Nilius and Owsianik, 2011); channel and receptor nomenclature follows Alexander *et al.*, 2013] are arguably the most appealing therapeutic targets (see Moran *et al.*, 2011; Fernandes *et al.*, 2012; Vay *et al.*, 2012; Kaneko and Szallasi, 2013). Generally speaking, TRP channels are cellular sensors involved in nociception (Patapoutian *et al.*, 2009), taste perception (Nilius and Appendino, 2013), thermosensation (Tominaga, 2007), mechano- and osmolarity sensing (Pedersen and Nilius, 2007; Guilak *et al.*, 2010). TRP channels also play a crucial role in normal physiological processes such as signal transmission (Minke, 2010; Wu *et al.*, 2010). Dysfunction of TRP channels has been implicated in various disease states (summarized in Figure 2) ranging from chronic pain and overactive bladder (TRPV1) through obesity (TRPV4 and TRPM5), diabetes (TRPV1, TRPM4), chronic cough (TRPA1, TRPV1), and chronic obstructive pulmonary disease (COPD; TRPV4) to cardiac hypertrophy (TRPC6), familial Alzheimer's disease (TRPM7), dermatological disorders (TRPV3 in Olmsted syndrome) and cancer (TRPC6, TRPV2 and

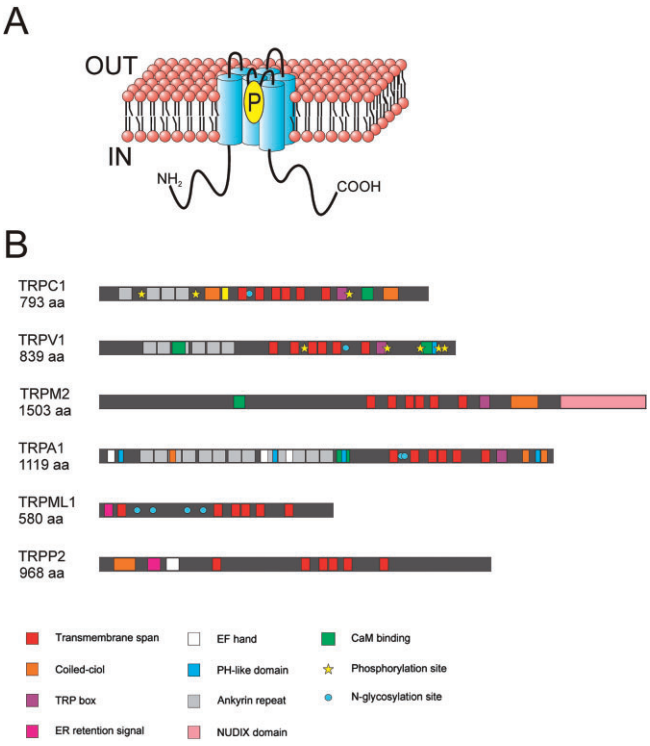


Figure 1

Simplified topographical structure of TRP channels (A). Please note the similarities and differences between TRP channel subfamilies (B). Reprinted, with permission, from Nilius and Owsianik (2011).

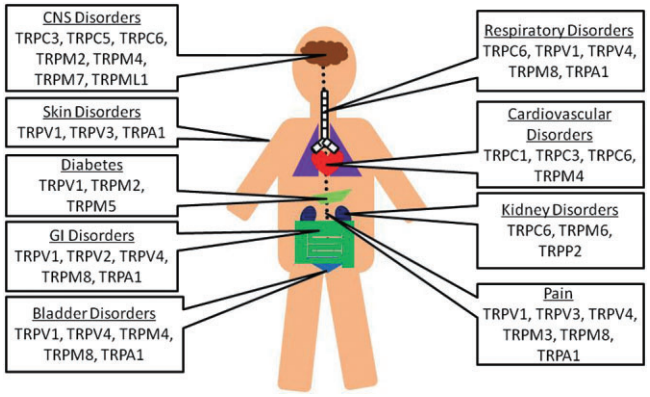
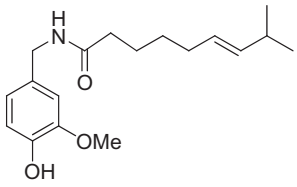


Figure 2

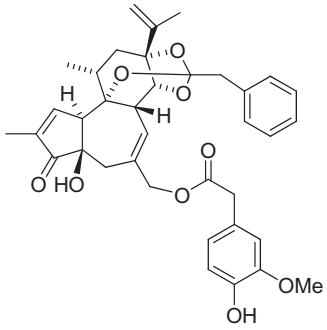
Schematic illustration of the tissue-distribution of TRP channels and their putative roles in the pathogenesis of human disease.

TRPM8). Gain-of-function mutations in genes encoding TRP channels have been linked to human diseases as exemplified by familial episodic pain syndrome (TRPA1; Kremeyer *et al.*, 2010). Taming these hyperactive TRP channels by antagonists may prove clinically beneficial. Loss-of-function mutations (e.g. loss of TRPML1 function in type-IV mucolipidosis) are also pathogenic, but their correction is more problematic (Dong *et al.*, 2008).

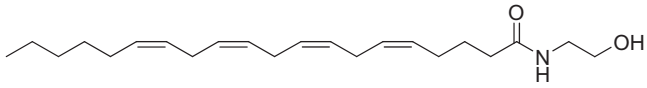
TRP channels are also primary targets for a number of natural products with therapeutic potential (summarized in



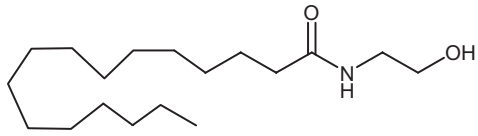
Capsaicin



RTX



Anandamide



Palmitoylethanolamide

Figure 3

Selected TRPV1 agonists: capsaicin (the pungent ingredient in hot chili peppers), resiniferatoxin (isolated from the cactus-like perennial *E. resinifera*), and the endocannabinoids anandamide and palmitoylethanolamide.

Table 1). For instance, TRPV1 is highly expressed in a distinct population of sensory neurons where it mediates excitation and subsequent desensitization to capsaicin (see Figure 3 for structure) and its ultrapotent analogue, resiniferatoxin (Szallasi and Blumberg, 1999). At present, resiniferatoxin (Figure 3) is undergoing clinical trials (NCT00804154) as a 'molecular scalpel' to achieve permanent analgesia in patients with intractable cancer pain (Iadarola and Mannes, 2011; Iadarola and Gonnella, 2013). TRPM8 is the 'menthol receptor' (Knowlton and McKemy, 2011) and TRPC6 is believed to mediate the mood-improving effect of hyperforin, the main ingredient in St. John's Wort (Leuner *et al.*, 2007).

Few generalizations can be made about TRP channels. Some show a highly restricted tissue expression pattern (TRPA1 and TRPV1 are predominantly expressed in sensory neurons; Patapoutian *et al.*, 2009) whereas others (TRPCs) are rather ubiquitously expressed (Singh *et al.*, 2012). Because

Table 1

Endogenous and exogenous ligands of TRP channels

TRP channels	Ligands	References
TRPV1	*Endogenous agonists:*	
	Anandamide*	Zygmunt *et al.* (1999)
	N-arachidonoyldopamine	Huang *et al.* (2002)
	N-oleoyldopamine	Chu *et al.* (2003)
	12- and 15-hydroperoxyeicosatetraenoic acid, 5- and 15-hydroxyeicosatetraenoic acid, Leukotriene B_4	Hwang *et al.* (2000)
	9- and 13-hydroxy-octadecadienoic acid(ODE), 9 and 13-oxoODE	Patwardhan *et al.* (2009)
	Oleoylethanolamide	Ahern (2003)
	Palmitoylethanolamide*	Ambrosino *et al.* (2013)
	Lysophosphatidic acid	Nieto-Posadas *et al.* (2011b)
	Endogenous antagonists:	
	Resolvin D2	Park *et al.* (2011a)
	Exogenous agonists	
	2-Aminoethoxydiphenyl borate (2-APB)	Hu *et al.* (2004)
	Ornithoctonus huwena toxin ['double-knot' toxin (DkTx)]	Bohlen *et al.* (2010)
	Capsaicin*	Caterina *et al.* (1997)
	Piperine	McNamara *et al.* (2005)
	Resiniferatoxin*	Szallasi and Blumberg (1989)
	Gingerol	Liu *et al.* (2000)
	Evodiamine	Pearce *et al.* (2004)
	Cannabidiol*	Bisogno *et al.* (2001)
	Cannabigerol	De Petrocellis *et al.* (2011)
	Polygodial	Andrè *et al.* (2006)
	Vanillotoxin	Siemens *et al.* (2006)
	Exogenous antagonists	
	Capsazepine	Dickenson and Dray (1991)
	Iodo-resiniferatoxin	Seabrook *et al.* (2002)
	BCTC	Valenzano *et al.* (2003)
	Thapsigargin	Toth *et al.* (2002)
	Yohimbine	Dessaint *et al.* (2004)
	AG489, AG505	Kitaguchi and Swartz (2005)
	ABT-102*, AMG-517*, AZD-1386*, DWP-05195, GRC-6211*, JTS-653*, MK-2295, PHE377, SB-705498*	Moran *et al.* (2011); Brederson *et al.* (2013)
TRPV2	*Endogenous agonists:*	
	Lysophosphatidylcholine, Lysophosphatidylinositol	Monet *et al.* (2009)
	Exogenous agonists	
	Cannabidiol*, Δ^9-tetrahydrocannabinol cannabinol*	Qin *et al.* (2008)
	2-APB	Hu *et al.* (2004)
	Probenecid	Bang *et al.* (2007)
	Exogenous antagonists	
	Tranilast	Hisanaga *et al.* (2009)

Table 1

Continued

TRP channels	Ligands	References
TRPV3	*Endogenous agonist:*	
	Farnesyl pyrophosphate	Bang *et al.* (2010a)
	Endogenous antagonists:	
	Isopentenyl pyrophosphate	Bang *et al.* (2011)
	Resolvin D1	Bang *et al.* (2010b)
	Exogenous agonists	
	Camphor	Moqrich *et al.* 2005)
	Menthol	Macpherson *et al.* 2006)
	Eugenol, thymol, carvacrol	Xu *et al.* (2006a)
	6-*t*-butyl-m-cresol, dihydrocarveol, (+)-borneol	Vogt-Eisele *et al.* (2007)
	2-APB	Hu *et al.* (2004)
	Incensole acetate	Moussaieff *et al.* (2008)
	Exogenous antagonist:	
	GRC15300	Khairatkar-Joshi *et al.* (2010)
TRPV4	*Endogenous agonists:*	
	Citric acid	Suzuki *et al.* (2003)
	5,6- and 8,9- epoxyeicosatrienoic acid	Watanabe *et al.* (2003)
	Dimethylallyl pyrophosphate	Bang *et al.* (2012)
	Endogenous antagonist:	
	Resolvin D1	Bang *et al.* (2010b)
	Exogenous agonists:	
	4α-Phorbol 12, 13-dedecanoate	Klausen *et al.* (2009)
	Bisandrographolide	Smith *et al.* (2006)
	Apigenin	Ma *et al.* (2012a)
	GSK1016790A*	Thorneloe *et al.* (2008)
	RN-1747	Vincent *et al.* (2009)
	Exogenous antagonists:	
	HC-067047*	Everaerts *et al.* (2010a)
	RN-1734	Vincent *et al.* (2009)
	GSK2193874	Huh *et al.* (2012; Thorneloe *et al.* (2012)
TRPV6	*Exogenous antagonist:*	
	2-APB	Kovacs *et al.* (2012)
TRPC3	*Exogenous antagonists:*	
	Pyr3*	Kiyonaka *et al.* (2009)
	Pyr10	Schleifer *et al.* (2012)
TRPC4	*Exogenous antagonist:*	
	ML204	Miller *et al.* (2011)
TRPC5	*Endogenous agonist:*	
	Lysophosphatidylcholine	Flemming *et al.* (2006)
	Sphingosine-1-phosphate	Xu *et al.* (2006b)
	Exogenous agonist:	
	Rosiglitazone	Majeed *et al.* (2011a)
	Progesterone and neurosteroids	Majeed *et al.* (2011b)

Table 1

Continued

TRP channels	Ligands	References
TRPC6	*Endogenous agonist:*	
	20-Hydroxyeicosatetraenoic acid	Basora *et al.* (2003)
	Exogenous agonists:	
	Hyperforin	Leuner *et al.* (2007)
	2,4-Diacylphloroglucinol	Leuner *et al.* (2010)
	Exogenous antagonist:	
	GsMTx-4	Spassova *et al.* (2006)
TRPM2	*Endogenous agonists:*	
	ADP-ribose	Perraud *et al.* (2005)
	Cyclic ADP-ribose	Kolisek *et al.* (2005)
	Exogenous antagonists:	
	N-(p-amylcinnamoyl)anthranilic acid	Kraft *et al.* (2006)
	Clotrimazole, econazole	Hill *et al.* (2004a)
	2-APB	Togashi *et al.* (2008)
	Flufenamic acid	Hill *et al.* (2004b; Naziroğlu *et al.* (2007)
TRPM3	*Endogenous agonists:*	
	Pregnenolone sulphate	Wagner *et al.* (2008)
	D-erythro-sphingosine	Grimm *et al.* (2005)
	Endogenous antagonist:	
	Progesterone	Majeed *et al.* (2012)
	Exogenous antagonist:	
	Rosiglitazone	Majeed *et al.* (2011a)
	Mefenamic acid	Klose *et al.* (2011)
	Naringenin, hesperetin, ononetin, eriodictyol	Straub *et al.* (2013)
	TM3E3 (polyclonal antibody)	Naylor *et al.* (2008)
TRPM4	*Exogenous agonist:*	
	BTP2	Takezawa *et al.* (2006)
	Exogenous antagonist:	
	9-Phenanthrol	Grand *et al.* (2008)
TRPM5	*Exogenous antagonist:*	
	Triphenylphosphine oxide	Palmer *et al.* (2010)
TRPM6	*Exogenous antagonist:*	
	2-APB	Li *et al.* (2006)
TRPM7	*Endogenous antagonist:*	
	Sphingosine	Qin *et al.* (2013)
	Exogenous antagonists:	
	2-APB*	Li *et al.* (2006)
	Carvacrol	Parnas *et al.* (2009)
	Nafamostat mesilate (dependent on extracellular divalent ions)	Chen *et al.* (2010)
	NDGA, AA861, MK886	Chen *et al.* (2010)
	Waixenicin A	Zierler *et al.* (2011)
	FTY720	Qin *et al.* (2013)
	Quinine, CyPPA, dequalinium, NS8593, SKA31, UCL 1684	Chubanov *et al.* (2012)

Table 1

Continued

TRP channels	Ligands	References
TRPM8	*Exogenous agonists:*	
	Menthol	Peier *et al.* (2002a)
	Linalool, geraniol, hydroxycitronellal, WS-3, WS-23, FrescolatMGA, FrescolatML, PMD38, CoolactP, Cooling Agent 10	Behrendt *et al.* (2004)
	Cis- and trans-p-menthane3	Bandell *et al.* (2004)
	CPS-368	Sherkheli *et al.* (2010)
	Exogenous antagonists:	
	AMTB	Lashinger *et al.* (2008)
	BCTC	Behrendt *et al.* (2004)
	Benzimidazoles	Parks *et al.* (2011); Calvo *et al.* (2012)
	5-Benzyloxytryptamine	DeFalco *et al.* (2010)
	Compound 9l	Matthews *et al.* (2012)
	Tetrahydroisoquinoline 87	Tamayo *et al.* (2012)
	Arylglycine derivatives	Zhu *et al.* (2013)
TRPA1	*Endogenous agonists:*	
	15-Deoxy- $\Delta^{12,14}$-PGJ_2,	Materazzi *et al.* (2008;)
	8-Iso-PGA_2, PGA_2, Δ^{12}-PGJ_2	Taylor-Clark *et al.* (2008a)
	4-Hydroxynonenal	Trevisani *et al.* (2007)
	4-Oxononenal	Taylor-Clark *et al.* (2008b)
	Methylglyoxal	Ohkawara *et al.* (2012)
	Endogenous antagonists:	
	Resolvin D1 Resolvin D2	Bang *et al.* (2010b); Park *et al.* (2011a)
	Exogenous agonists:	
	Cinnamaldehyde, methyl salicylate, eugenol, gingerol	Bandell *et al.* (2004)
	Allicin, diallyl disulfide	Bautista *et al.* (2005)
	Δ^9-tetrahydrocannabinol, Isothiocyanates	Jordt *et al.* (2004)
	Acrolein	Bautista *et al.* (2006)
	Carvacrol	Xu *et al.* (2006a)
	Formalin	McNamara *et al.* (2007)
	α,β-Unsaturated aldehydes	Andrè *et al.* (2008)
	Auranofin	Hatano *et al.* (2013)
	Capsiate	Shintaku *et al.* (2012)
	Curcumin	Leamy *et al.* (2011)
	PF-4840154	Ryckmans *et al.* (2011)
	Apomorphine (agonist in low micromolar range and antagonist in higher concentration)	Schulze *et al.* (2013)
	Cannabichromene, cannabidiol, cannabinol*	De Petrocellis *et al.* (2008; 2011)
	Exogenous antagonists:	
	Camphor	Xu *et al.* (2005)
	Menthol	Macpherson *et al.* (2006)
	Thymol	Lee *et al.* (2008)
	HC-030031	McNamara *et al.* (2007)
	Chembridge-5861528	Wei *et al.* (2009)
	AP18	Petrus *et al.* (2007)
	A-967079	McGaraughty *et al.* (2010)
	AZ465	Nyman *et al.* (2013)
	GRC17536	Kaneko and Szallasi (2013)

Table 1

Continued

TRP channels	Ligands	References
TRPML1	*Exogenous agonists:*	
	SF-51, ML-SA1	Shen *et al.* (2012)
TRPML2	*Exogenous agonists:*	
	SID24801657, SID24787221	Saldanha *et al.* (2010–2009)
TRPML3	*Exogenous agonists:*	
	SID24801657, SID24787221	Saldanha *et al.* (2010–2009)

*Denotes structures shown in Figures 3–6.

members of the TRP family of channels (Figure 1) share much less homology with one another compared with other ion channel families (Wu *et al.*, 2010), the identification of highly subtype-selective compounds is likely to be more attainable.

Despite the striking progress in our understanding of TRP channel functions (see Owsianik *et al.*, 2006; Wu *et al.*, 2010; Li *et al.*, 2011a), some inherent problems persist. According to Bernd Nilius, TRP channels have a fair and an ugly face (Nilius, 2013). Activation or inhibition of a TRP channel may be beneficial in one organ and, at the same time, may induce unacceptable adverse effects in another. Indeed, the clinical development of first-generation TRPV1 antagonists was halted because they caused hyperthermia and put patients at risk for scalding injuries by elevating the heat pain threshold (see Moran *et al.*, 2011; Brederson *et al.*, 2013). Drug discovery companies that find a way for exploiting the 'fair face' of TRP channels without revealing the 'ugly face' will be able to create a new generation of targeted therapies.

TRP channels: a brief overview

TRP channels were initially discovered in a blind strain of *Drosophila* (Montell and Rubin, 1989). When exposed to prolonged intense light, these spontaneously mutant fruit flies showed transient calcium influx into their photoreceptor cells; this is why the mutant gene was termed *trp*, 'transient receptor potential'. This seminal finding paved the way to the discovery of the first mammalian TRP channels, called 'canonical' (TRPC) due to their homology to the *Drosophila* channel (Wes *et al.*, 1995; Zhu *et al.*, 1995).

Mammalian TRP channels comprise 28 members and are divided into six subfamilies: TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPP (Polycystin), TRPML (Mucolipin) and TRPA (Ankyrin) based on their homology of amino acid sequences (Figure 1; Clapham *et al.*, 2001; Wu *et al.*, 2010; Nelson *et al.*, 2011). The mucolipin and polycystin subfamilies were named after the diseases they are associated with, mucolipidosis and autosomal dominant polycystic kidney disease (ADPKD) respectively. The vanilloid subfamily was named after its founding member, the vanilloid (capsaicin) receptor TRPV1. The first melastatin channel (TRPM1) was discovered as a protein present in benign nevi and absent in malignant melanoma (Duncan *et al.*, 1998). As of today, the ankyrin subfamily has only one member, TRPA1, which (as the name implies) is rich in ankyrin repeats at its N-terminus.

As a general rule, TRP channels have six transmembrane spanning domains (S1–S6) with a pore-forming loop between S5 and S6 (Figure 1; Wu *et al.*, 2010). Both –NH2 and –COOH termini are located intracellularly. Many TRP channels are non-selective Ca^{2+}-permeable channels with permeability ratios $P_{Ca}/P_{Na} < 10$. TRPM4 and TRPM5, in particular, are only permeable to monovalent cations and they do not conduct Ca^{2+} and Mg^{2+}, while TRPV5 and TRPV6 are highly Ca^{2+} selective with $P_{Ca}/P_{Na} > 100$ (Owsianik *et al.*, 2006). Most TRPs form functional channels as homotetramers, but heteromultimerization is frequently observed (Cheng *et al.*, 2010). This creates a potential problem for drug discovery efforts as heteromultimers (that are not easily recreated in heterologous expression systems) may have distinct pharmacological properties.

TRP channels are 'cellular sensors' (Clapham, 2003) that respond to changes in the cellular environment, including temperature, stretch/pressure, chemicals, oxidation/reduction, osmolarity and pH, both acidic and alkaline (Moran *et al.*, 2011; Nieto-Posadas *et al.*, 2011a). Of note, a number of TRP channels are also activated by natural products, including herbs, spices, venoms and toxins (Vriens *et al.*, 2008). For example, TRPV1 is a shared target for capsaicin (Caterina *et al.*, 1997), jelly fish venoms and spider (tarantula) toxins (Cromer and McIntyre, 2008). A list of ligands for TRP channels is provided in Table 1. Representative chemical structures of TRP channel agonists (GSK101679A for TRPV4) and antagonists (GRC6211, AMG517, SB-705498, AZD1386, JTS-653 and ABT-102 for TRPV1; HC-067047 for TRPV4; Pyr3 for TRPC3; and AMTB for TRPM8) are shown in Figures 4 and 5. Despite decades of intensive search, only a few endogenous ligands of TRP channels have been identified, such as the endocannabinoids anandamide and palmitoylethanolamide, (structures shown in Figure 3) for TRPV1 (Zygmunt *et al.*, 1999; Ambrosino *et al.*, 2013)]. How TRP channels are modulated *in vivo* is still unknown.

Some TRPM channels like TRPM2 are unique in that they contain a functional nucleoside diphosphate linked to some other moiety/ADP ribose domain, as well as a kinase domain that bears some resemblance to PKA (see Eisfeld and Lückhoff, 2007). In other words, these TRPMs combine fea-

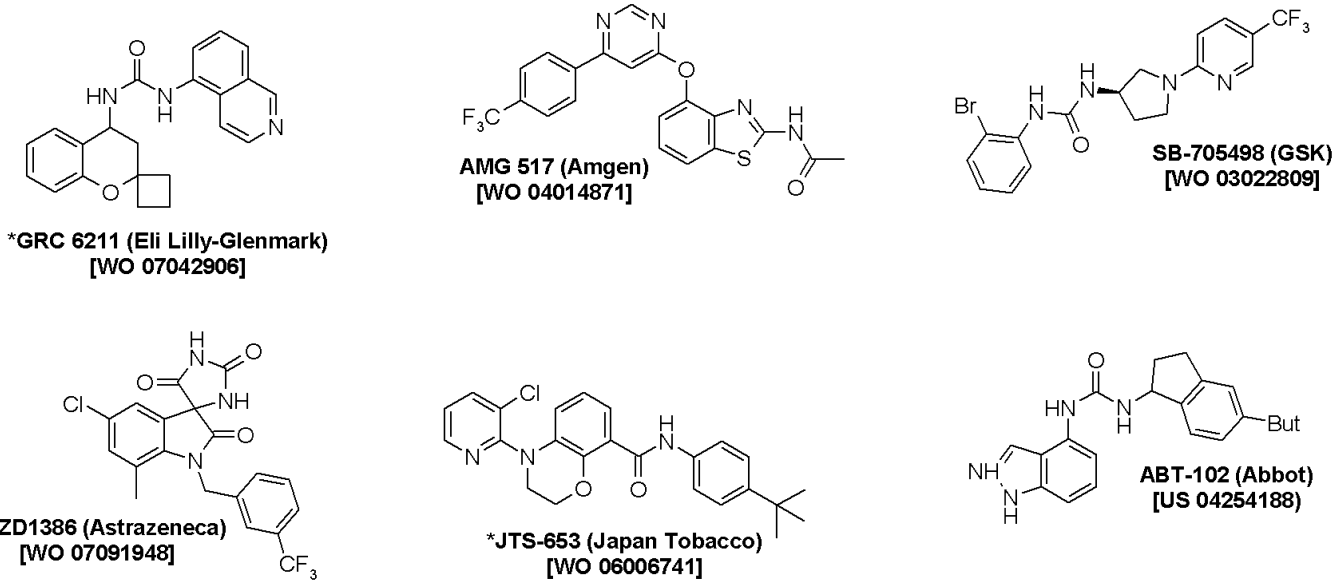


Figure 4

Small molecule TRPV1 antagonists: selected structures.

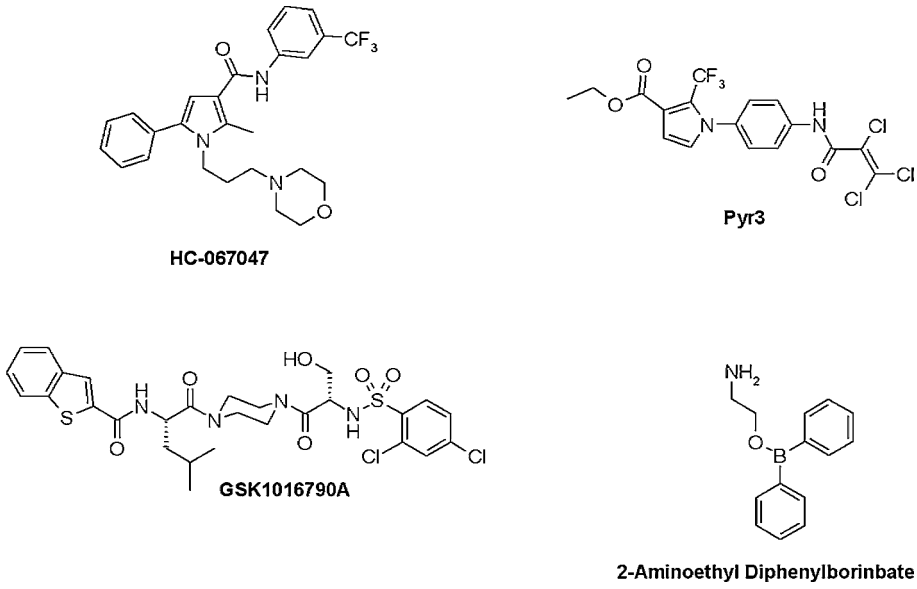


Figure 5

Representative examples of TRPV4 agonists (GSK1016790A), TRPV4 antagonists (HC-067047), TRPV3 agonists (2-ABT), and TRPC3 inhibitors (Pyr3).

tures of ion channels and enzymes and are thus referred to by some as 'chanzymes' (Montell, 2003). TRPM2 functions as a cellular redox (oxidative stress) sensor and has been implicated in the pathogenesis of bipolar disorder, diabetes, as well as cardiovascular and neurodegenerative disorders (Jiang *et al.*, 2010). Indeed, a mutant TRPM2 (Pro1018Leu) has been linked to the Guamanian amyotrophic lateral sclerosis (ALS-G)/Parkinsonism-dementia complex (Hermosura *et al.*, 2008).

Importantly, TRP channels are also stimulated by intracellular Ca^{2+} increase induced by the activation of GPCRs and mediate downstream signalling. Furthermore, the activity of TRP channels is modulated by various intracellular molecules including phosphatidylinositol 4,5-bisphosphate (PIP_2), DAG, ATP and calmodulin (see Wu *et al.*, 2010). Indeed, TRPCs are subdivided into two groups, TRPC1, C4 and C5 and TRPC3, C6, C7, depending on DAG-sensitivity (Wu *et al.*, 2010). For some TRP channels, like TRPV1, phosphorylation by PKs and dephosphorylation by phosphatases provide important contribution to setting the channel activity (reviewed in Szallasi *et al.*, 2007). Indeed, phosphorylation of TRPV1 by PKC is now

thought to represent a crucial biochemical mechanism by which TRPV1 is sensitized during inflammation to cause thermal hyperalgesia (Jeske *et al.*, 2009). Moreover, TRP channels were shown to interact with a growing number of intracellular proteins to form 'signalplexes' and 'channelosomes' (Planells-Cases and Ferrer-Montiel, 2007). Such interactions are now believed to be important for TRP channel trafficking, positioning and activity (Goswami, 2012). Recent research suggests that manipulation of the interaction between TRP channels and their regulatory proteins can be exploited for therapeutic purposes. A promising example of this approach, to prevent TRPV1 sensitization by blocking the interplay between TRPV1 and the scaffolding protein AKAP79 (Btesh *et al.*, 2013; Fischer *et al.*, 2013), will be discussed later under 'pain and TRP channels'.

Activation of TRP channels allows cations pass through the membrane and depolarize cells, leading to a wide range of cellular responses. Stimulated by a broad range of stimuli and expressed probably in all the cells in the body (Nilius, 2013), TRP channels are thought to play diverse physiological roles. Besides, extensive research in the field has demonstrated that TRP channels are involved in a number of diseases affecting the peripheral and CNS (Vennekens *et al.*, 2012; Morelli *et al.*, 2013), the respiratory (Preti *et al.*, 2012), genito-urinary (Skryma *et al.*, 2011), gastrointestinal (GI; Holzer, 2011), cardiovascular (Watanabe *et al.*, 2013) and immune systems (Schwartz *et al.*, 2007; Smith and Nilius, 2013), as well as in metabolic disorders including obesity and diabetes (Suri and Szallasi, 2008; Zhu *et al.*, 2011).

The direct link between TRP channels and human diseases have been revealed by human genetic studies demonstrating that mutations in TRP genes are causally associated with hereditary diseases, the so-called 'TRP channelopathies' (Nilius and Owsianik, 2010). Representative examples of these channelopathies include focal segmental glomerular sclerosis (FSGS), ADPKD and scapuloperoneal spinal muscular atrophy, which are linked to TRPC6 (Winn *et al.*, 2005), TRPP2 (Igarashi and Somlo, 2002) and TRPV4 (Auer-Grumbach *et al.*, 2010) respectively. Knockout and transgenic animal studies also revealed a pathogenic role for both the absence and hyperactivity of TRP channels. For example, TRPC3 (–/–) mice show defects in motor coordination and walking behaviour (Hartmann *et al.*, 2008) whereas transgenic mice overexpressing TRPC6 in their heart develop massive cardiac hypertrophy (Kuwahara *et al.*, 2006).

In summary, there is strong experimental and clinical evidence to substantiate TRP channels as appealing drug targets and a number of molecules targeting TRP channels have already advanced to clinical trials (Moran *et al.*, 2011; Brederson *et al.*, 2013; Table 2). Later, we provide an overview of TRP channels and diseases and discuss potential approaches for therapeutic intervention.

Pain and TRP channels

A number of TRP channels (including TRPV1, V3 and V4, TRPA1, TRPM3 and M8, TRPC1, C3 and C6) are expressed in nociceptive sensory neurons. Extensive research with genetically modified animals and pharmacological agents has confirmed that these TRP channels are involved in the generation and transduction of pain and thus represent promising targets for the development of novel analgesic agents (see Patapoutian *et al.*, 2009; Moran *et al.*, 2011; Brederson *et al.*, 2013).

TRPV1

A subset of nociceptive neurons with somata in sensory (dorsal root and trigeminal) ganglia is distinguished by its unique sensitivity to capsaicin (Szallasi and Blumberg, 1999). The initial excitation by capsaicin of these neurons is followed by a lasting refractory state (traditionally referred to as desensitization) in which the cells are unresponsive not only to a repeated capsaicin challenge, but also to various unrelated stimuli like noxious heat and acids (see Szallasi and Blumberg, 1999). Thus, desensitization by capsaicin has a clear therapeutic potential. The receptor for capsaicin was identified as TRPV1 (Caterina *et al.*, 1997) and accumulating evidence suggests a crucial role for TRPV1 in pain sensation (see Szallasi *et al.*, 2007; Gomtsyan and Faltynek, 2010). First, TRPV1 is activated by multiple painful stimuli including noxious heat, pungent chemicals (capsaicin and jelly fish venom), and protons (Szallasi *et al.*, 2007). In addition, TRPV1 can be activated by voltage, lipids and phosphorylation (Pingle *et al.*, 2007). Second, TRPV1-deficient mice show reduced thermal hyperalgesia in response to inflammatory mediators such as bradykinin and/or NGF (Caterina *et al.*, 2000; Davis *et al.*, 2000; Chuang *et al.*, 2001). In addition, oleoylethanolamide, an endogenous TRPV1 agonist (Ahern, 2003), induces visceral pain-related behaviour in mice that is inhibited by the TRPV1 antagonist capsazepine and is absent in TRPV1-null animals (Wang *et al.*, 2005). Third, pharmacological blockade or knockdown of TRPV1 displays analgesic activity in various preclinical pain models, including arthritic (Szabó *et al.*, 2005; Joshi and Honore, 2010) and cancer pain (Jimenez-Andrade and Mantyh, 2010).

Somewhat unexpectedly, genotyping studies have so far failed to identify any TRPV1 polymorphism associated with neuropathic pain, although TRPV1 variants were correlated with altered somatosensory function in patients with neuropathic pain (Binder *et al.*, 2010). Parenthetically, the TRPV1 585 Ile-Ile genotype appears to lower the risk for developing painful knee osteoarthritis (Valdes *et al.*, 2011). But not all TRPV1 variants are harmless. For example, in a large European study, six TRPV1 gene SNPs appeared to confer higher risk for chronic cough [Smit *et al.*, 2012; although, in a different study, the loss-of-function TRPV1 variant I585V was associated with a lower risk for childhood asthma (Cantero-Recasens *et al.*, 2010).

Capsaicin-containing creams (e.g. Zostrix, 0.075%) have been used for decades for the treatment of chronic painful conditions such as diabetic neuropathy (Knotkova *et al.*, 2008). Despite their popularity, controlled clinical studies found no evidence that these creams had greater analgesic potency than placebo (see Szallasi and Sheta, 2012).

To increase the exposure of cutaneous nerve endings to capsaicin, occlusive patches (NGX-4010, Qutenza) and liquid formulations (NGX-1998, 20% capsaicin) were developed by Neuroges-X (San Mateo, CA, USA; Bley, 2012). Although in 2010, Qutenza was approved to treat post-herpetic neuralgia in the USA, the sales of this $700 pain patch never matched the company's expectations. In 2012, after the US Food and

Table 2

Drugs targeting TRP channels in clinical development

Action	Drug	Company	Therapy Area	Highest development status	ClinicalTrials.gov identifier
TRPV1 agonist	capsaicin	Not Assigned	Pain	Launched	
TRPV1 agonist	NGX-4010	Acorda Therapeutics Inc/Astellas Pharma Inc	Postherpetic neuralgia	Launched	
TRPV1 agonist	zucapsaicin	Sanofi-Aventis Canada Inc	Osteoarthritis	Registered	
TRPV1 agonist	zucapsaicin	Winston Pharmaceuticals Inc	Cluster headache	Phase 3	NCT00033839
TRPV1 agonist	MCP-101 (resiniferatoxin)	Mt Cook Pharma	Overactive bladder	Phase 2	N/A
TRPV1 antagonist	DWP-05195	Daewoong Pharmaceutical Co Ltd	Neuropathic pain	Phase 2	NCT01557010
TRPV1 antagonist	XEN-D0501	Provesica Ltd	Overactive bladder	Phase 2	N/A
TRPV1 siRNA	SYL-1001	Sylentis Sau	Ocular pain	Phase 2	NCT01776658
TRPV1 antagonist	Mavatrep	Johnson & Johnson Pharmaceutical Research & Development LLC	Osteoarthritis/Pain	Phase 1	NCT00933582 NCT01006304
TRPV1 antagonist	PHE-377	PharmEste SRL	Neuropathic pain	Phase 1	N/A
TRPV1 antagonist	MR-1817	Mochida Pharmaceutical Co Ltd	Pain	Phase 1	NCT00960180
TRPV1 antagonist	PAC-14028	Pacific Pharmaceuticals Co Ltd	Atopic dermatitis/IBD	Phase 1	NCT01638117
TRPV1 antagonist	SB-705498	GlaxoSmithKline plc	Pruritus	Phase 1	NCT01673529
TRPV3 antagonist	GRC-15300	Glenmark Pharmaceuticals Ltd/Sanofi	Neuropathic pain/Osteoarthritis	Phase 2	NCT01463397
TRPM8 agonist	Menthol	Not assigned	Carpal tunnel syndrome/Neck pain	N/A	NCT01716767 NCT01542827
TRPM8 agonist	D-3263	Dendreon Corp	Cancer	Phase 1	NCT00839631
TRPA1 antagonist	GRC-17536	Glenmark Pharmaceuticals Ltd	Diabetic peripheral neuropathy/ Respiratory disorders	Phase 2	NCT01726413
TRPA1 antagonist	CB-625	Cubist Pharmaceuticals/Hydra Biosciences	Inflammatory disease/ Pain	Phase 1	N/A

Drug Administration rejected Neuroges-X's request to extend the use of Qutenza to HIV-associated peripheral neuropathy, the company ceased operations and reached a tentative deal to sell Qutenza and the investigational liquid formulation NGX-1998 to Acorda (Ardsley, NY, USA; http://www.researchviews.com/healthcare/pharma/DealReports.aspx?sector=Pharma&DealID=191932).

Resiniferatoxin is currently undergoing clinical trials at the National Cancer Institute in patients with intractable cancer pain as a 'molecular scalpel' to achieve permanent analgesia (NCT00804154). In preclinical models of chronic pain, intrathecal resiniferatoxin induces a lasting analgesic effect by selectively ablating TRPV1-expressing sensory neurons in the dorsal root and trigeminal ganglia (Iadarola and Gonnella, 2013). In client-owned dogs with severe osteosarcoma pain, intrathecal resiniferatoxin was well-tolerated and effective: it provided significant pain relief and restored ambulation for several months after a single administration (Brown *et al.*, 2005; Iadarola and Gonnella, 2013). It is hoped that intrathecal resiniferatoxin will be a good alternative to narcotic analgesics in some cancer patients with localized pain, such as pain caused by bone metastasis.

After the cloning of TRPV1, there was a great deal of enthusiasm in the pharmaceutical industry to develop small-molecule TRPV1 antagonists as analgesic agents. Indeed, a number of TRPV1 antagonists including SB-705498 (GlaxoSmithKline), AMG517 (Amgen), AZD1386 (AstraZeneca), GRC-6211 (Lilly/Glenmark), MK-2295 (Merck/Neurogen), ABT-102 (Abbott) and PHE377 (PharmEste) have been advanced to Phase I and II clinical studies for indications related to pain (representative structures are shown in Figure 4; Moran *et al.*, 2011; Brederson *et al.*, 2013). The enthusiasm, however, was soon tempered by unforeseen adverse effects. Some TRPV1 antagonists (AMG517) caused marked hyperthermia, prompting their withdrawal from the clinical trials, whereas others (MK-2295) blunted noxious heat perception, putting patients at risk for scalding injuries (Moran *et al.*, 2011; Brederson *et al.*, 2013).

The magnitude of hyperthermia seems to vary depending on the chemical structure. While AZD1386 modestly increased body temperature (~0.4 °C on average) in patients with gastroesophageal reflux disease (GERD; Krarup *et al.*, 2011), AMG517 caused a lasting (1–4 days) and marked hyperthermia response (up to 40.2°C) in human volunteers (compare AZD1386 and AMG517 structures in Figure 4; Gavva *et al.*, 2008). In preclinical studies (in rodents and dogs), PHE377 (structure undisclosed) was devoid of any effect on body temperature at doses at which it inhibited both thermal and mechanical hyperalgesia (http://www.pharmeste.com/repository/contenuti/paragrafi/file/PharmEste_Leaflet_2012.PDF).

The site that mediates the hyperthermic action of TRPV1 antagonists is still hotly debated. In rodents, capsaicin evokes transient hypothermia (presumably by activating cooling mechanisms after tricking the animals into believing that they are hot), followed by a loss of the animals' ability to regulate their body temperature (rats desensitized to capsaicin develop hyperthermia when placed in a hot chamber; Szallasi and Blumberg, 1999). The effects of capsaicin on thermoregulation were linked to the CNS (Hajós *et al.*, 1985). However, TRPV1 antagonists that do or do not enter the CNS are comparable in their ability to elevate body temperature, making a CNS target extremely unlikely (Cui *et al.*, 2006). Consequently, it was postulated that TRPV1 in the periphery has an endogenous tone that is essential for maintaining normal body temperature (Gavva, 2008). However, rodents whose TRPV1 has been eliminated by genetic recombination (TRPV1 kncok out mice) or chemical ablation (neonatal capsaicin treatment) do not develop hyperthermia.

Similar to the hyperthermic response, the magnitude of blunted heat perception also seems to depend on the TRPV1 antagonist pharmacophore. The increase in heat pain threshold was first noted after the administration of 400 mg of SB-705498 to healthy human volunteers (Chizh *et al.*, 2007). Importantly, unlike the febrile reaction that disappeared upon repeated dosing, the impaired thermal sensitivity persisted during the whole course of the study (Chizh *et al.*, 2007). Impaired heat perception was also observed with MK-2295 (Eid, 2011), ABT-102 (Rowbotham *et al.*, 2011) and AZD1386 (Krarup *et al.*, 2011). Some volunteers receiving MK-2295 perceived potentially harmful temperature as innocuous (Eid, 2011). Indeed, minor (1st and 2nd degree) burns were reported in some clinical study subjects. Interestingly, another clinical study (XEN-D0501) found no evidence of scalding injuries in the study participants (Round *et al.*, 2011).

The heat sensor in TRPV1 is clearly distinct from the capsaicin and proton recognition sites (Szolcsányi and Sándor, 2012) and a new generation of modality-selective TRPV1 antagonists that cause neither hyperthermia nor impaired pain heat perception have been proposed (Szolcsányi and Sándor, 2012; Brederson *et al.*, 2013).

An attractive alternative approach to circumvent the side effects of TRPV1 antagonists is to target TRPV1 in diseased, but not in healthy, tissues (Szallasi and Blumberg, 2006). Phosphorylation of the TRPV1 protein by PKA and PKC is believed to play a crucial role in inflammatory sensitization (reviewed in Szallasi *et al.*, 2007). The interaction between both kinases and TRPV1 depends on the scaffolding protein AKAP79 (Zhang *et al.*, 2008). Recently, specific residues in TRPV1 and AKAP79 were discovered by site-directed mutagenesis experiments where these proteins interact (Btesh *et al.*, 2013; Fischer *et al.*, 2013). This information allowed the design and synthesis of peptides that can block the interaction between TRPV1 and AKAP79. In mice, these blocking peptides prevented the development of inflammatory thermal hyperalgesia but it remains to be seen if a similar strategy can be successful in chronic pain patients.

Neither AMG-9810 (a TRPV1 antagonist) nor HC-030031 (a TRPA1 blocker, see later) relieved ongoing pain in a mouse model of osteoarthritis, although both ameliorated thermal hyperalgesia (Okun *et al.*, 2012). Consisitent with these findings, in a randomized, double-blinded, prospective clinical trial with client-owned dogs suffering from severe hip osteoarthritic pain, the TRPV1 antagonist ABT-116 showed only marginal analgesic activity over placebo (Malek *et al.*, 2012). ABT-116 did not attenuate lameness in dogs with experimentally induced urate synovitis either at doses at which it caused seriously high rectal temperatures (Cathcart *et al.*, 2012). The striking difference in the analgesic activity of TRPV1 antagonists between rodent (where it potently reduces experimental osteoarthritic pain; Honore *et al.*, 2005; Puttfarcken *et al.*, 2010) and canine (without clinical benefits, see earlier)

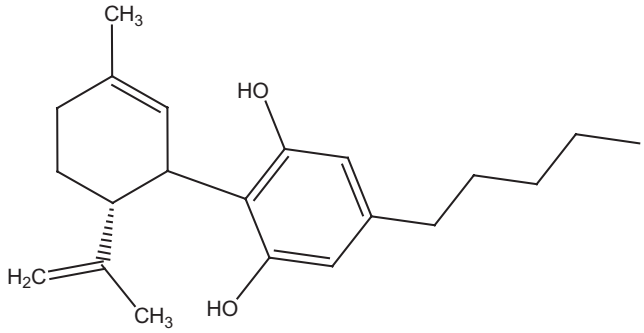
models of human osteoarthritic pain is puzzling and concerning. Indeed, osteoarthritic pain is a major clinical indication for TRPV1 antagonists and a number of TRPV1 antagonists have entered clinical trials for this indication (Table 2), but as yet, the results have not been disclosed.

TRPA1

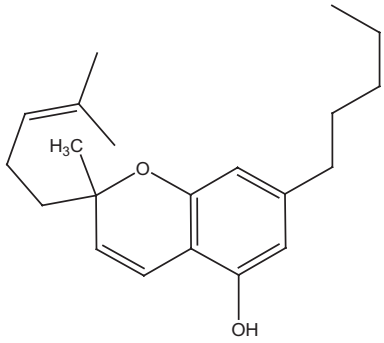
Unlike TRPV1 (which shows distinct structure-activity relations in its ligand-binding properties, hence the original name 'vanilloid receptor'), TRPA1 is activated by a wide range of irritant natural products, including allyl isothiocyanate (Jordt *et al.*, 2004; Capasso *et al.*, 2012), cinnamaldehyde (Bandell *et al.*, 2004) and allicin (Bautista *et al.*, 2005) found in mustard oil, cinnamon and garlic respectively. TRPA1 is also targeted by environmental irritants found in tear gas, exhaust fumes, household cleaning agents and cigarette smoke; examples include acrolein (Bautista *et al.*, 2006), formalin (McNamara *et al.*, 2007) and α,β-unsaturated aldehydes (Andrè *et al.*, 2008). Of note, TRPA1 binds umbellulone, an active ingredient in the Californian 'headache tree' *Umbellularia californica* (Nassini *et al.*, 2012a). Indeed, activation of TRPA1 expressed on meningeal afferents was implicated in the pathomechanism of migraine (Edelmayer *et al.*, 2012). Somewhat surprisingly for an 'irritant receptor,' TRPA1 is also activated by the non-pungent capsaicin analogue, capsiate (Shintaku *et al.*, 2012), as well as the non-psychotropic cannabinoid, cannabichromene (see Figure 6 for structure; De Petrocellis *et al.*, 2008; 2011). This is interesting because cannabichromene is thought to play a pivotal role in the anti-inflammatory and analgesic activity of medical marijuana and cannabichromene did ameliorate experimental murine colitis (Romano *et al.*, 2013). TRPA1 also acts as a receptor for reactive oxygen species (ROS; Bessac *et al.*, 2008), but it is debated if TRPA1 can be activated by noxious cold. In general, reactive chemicals activate TRPA1 by inducing covalent modification of cysteines in the N-terminus (Nilius *et al.*, 2011).

TRPA1 is well established as a pain sensor. A gain-of-function point mutation in TRPA1 (N855S) was identified as the cause of familial episodic pain syndrome, a rare human pain disorder characterized by severe upper body pain triggered by fasting and physical stress (Kremeyer *et al.*, 2010). TRPA1 is primarily expressed in sensory neurons (where it is highly coexpressed with TRPV1), but growing evidence suggests that functional TRPA1 is also present in non-neuronal tissues such as heart, small intestine, lung and pancreas (Stokes *et al.*, 2006). As discussed later under respiratory disorders, TRPA1 expressed by lung fibroblasts (Mukhopadhyay *et al.*, 2011) might play a role in the pathogenesis of asthma and COPD (Nassini *et al.*, 2012b).

TRPA1 expression in sensory neurons appears to be plastic and neuropathic injury increased neuronal expression of TRPA1 in humans (Anand *et al.*, 2008). Cyclopentenone PGs, metabolites of PGs enhancing pain sensation, cause a robust calcium response in dorsal root ganglion neurons and induce pain behaviour in wild-type mice, but not in TRPA1-deficient mice (Materazzi *et al.*, 2008). Interestingly, the pain phenotype of TRPA1 knockout and knock-down animals are different: inflammation-induced mechanical hyperalgesia is reduced in the knock-down mice, but not in the knockouts (see Garrison and Stucky, 2011; Nilius *et al.*, 2011). This



Cannabidiol



Cannabichromene

Figure 6

Selected plant cannabinoids that target TRP channels: cannabichromene (TRPA1 agonist) and cannabidiol (TRPM8 antagonist).

implies the existence of a compensatory mechanism that takes over the function of the missing TRPA1 in the knockout animals and restores mechanical hyperalgesia during inflammation.

Pharmacological inhibition of TRPA1 with HC-030031, a highly selective TRPA1 antagonist, attenuated formalin-induced pain (McNamara *et al.*, 2007) and reversed mechanical hypersensitivity following complete Freund's adjuvant (CFA) treatment. HC-030031 also displayed analgesic activity in the spinal nerve ligation model of neuropathic pain (Eid *et al.*, 2008). CHEM-5861528, a derivative of HC-030031, alleviated mechanical hyperalgesia in a rat model of diabetic neuropathic pain (Wei *et al.*, 2009; Koivisto *et al.*, 2012). Of note, methylglyoxal (an endogenous carbonyl compound that is produced in large amounts during hyperglycemic conditions) activates human TRPA1 (Ohkawara *et al.*, 2012). Furthermore, TRPA1 has been implicated in migraine (Edelmayer *et al.*, 2012), dental pain (Haas *et al.*, 2011), chemotherapy-induced neuropathic pain (Nassini *et al.*, 2013) and colicky pain of GI origin (Blackshaw *et al.*, 2013).

The Abbott TRPA1 antagonist A-967079 attenuated both evoked and spontaneous firing recorded from wide dynamic range (WDR) spinal cord neurons during CFA-induced inflammation (McGaraughty *et al.*, 2010) without having any

effect on body temperature (Chen *et al.*, 2011). However, in rats with osteoarthritic pain, A-967079 had no effect on spontaneous WDR firing (though it blocked evoked mechanical hyperalgesia), suggesting (somewhat disappointingly) that TRPA1 blockade may not alleviate the on-going, spontaneous 'nagging' pain in patients with osteoarthritis (McGaraughty *et al.*, 2010).

There is good evidence linking TRPA1 to the cold allodynia that develops during ciguatera (Vetter *et al.*, 2012) or following chemotherapy (Nassini *et al.*, 2013). In some studies, TRPA1 was directly activated by noxious cold (Story *et al.*, 2003). Paradoxically, TRPA1 expressed on polymodal C-fibres appears to be activated by hot temperatures (Hoffmann *et al.*, 2013). It is tempting to speculate that this mechanism is responsible for the development of inflammatory thermal hyperalgesia which is absent in the TRPA1 knockout mice (P. Reeh, pers. comm.).

To date, two TRPA1 antagonists have reached clinical stage of development, GRC1753 (Glenmark) for chronic pain and CB-625 for acute surgical pain (Cubist Pharmaceuticals Inc., Lexington, MA, USA; Hydra Biosciences, Inc., Cambridge, MA, USA).

TRPV3

TRPV3 is abundantly expressed in keratinocytes where it is thought to serve various functions (Nilius and Bíró, 2013). Keratinocytes release IL-1, a pro-inflammatory cytokine, in response to eugenol, a non-selective TRPV3 agonist (Xu *et al.*, 2006a). TRPV3 expression is significantly increased in keratinocytes in patients with breast pain (Gopinath *et al.*, 2005); by contrast, TRPV3 is decreased in keratinocytes in patients with diabetic neuropathy (Facer *et al.*, 2007). In addition, TRPV3 was significantly increased in brachial plexus nerves collected from patients with traumatic nerve injury (Facer *et al.*, 2007). Interestingly, Olmsted syndrome patients (a genetic disorder caused by a gain-of-function TRPV3 mutation; Lin *et al.*, 2012) suffer from intense itching but not pain.

TRPV3 is activated by warm temperatures in the range of 31–39°C and its activity is enhanced during repetitive heat stimulations (Xu *et al.*, 2002; Peier *et al.*, 2002b). TRPV3-null mice showed marked deficits in responses to innocuous and noxious heat (Moqrich *et al.*, 2005). GRC15300, a potent, selective, orally available TRPV3 antagonist demonstrated efficacy in inflammatory and neuropathic pain models, and this compound is being investigated in clinical trials (Khairatkar-Joshi *et al.*, 2010).

TRPM8, TRPV4, TRPM3 and TRPCs

TRPM8 is expressed in nociceptive Aδ and C fibres that are cold sensitive (McKemy *et al.*, 2002; Kobayashi *et al.*, 2005). TRPM8 is activated by cold temperatures in the range of 8–28°C, as well as by cooling compounds such as menthol and icilin (McKemy *et al.*, 2002; Peier *et al.*, 2002a). Topical menthol has been tried clinically as an analgesic in patients with carpal tunnel syndrome (NCT01716767) and neck pain (NCT01542827). Naturally occurring TRPM8 antagonists include the plant cannabinoids cannabidiol (see Figure 6 for structure), cannabinol and cannabiogerol (De Petrocellis *et al.*, 2008; 2011). Studies with TRPM8-null mice showed decreased sensitivity to cold temperature, as well as attenuated hypersensitivity to cold after nerve injury or inflammation (Bautista *et al.*, 2007; Colburn *et al.*, 2007). Synthetic TRPM8 antagonists were analgesic in a chronic constriction injury-induced model of neuropathic pain in rats (Parks *et al.*, 2011; Calvo *et al.*, 2012) but, as yet, no TRPM8 antagonist has advanced to clinical trials.

TRPV4 as a pain target is highly controversial. Intraplantar injection of the endogenous TRPV4 activator dimethylallyl pyrophosphate elicits nociceptive flinches (Bang *et al.*, 2012). Furthermore, TRPV4-deficient mice demonstrated decreased pain behaviour in inflammatory pain models (Todaka *et al.*, 2004; Alessandri-Haber *et al.*, 2006), as well as models of painful peripheral neuropathy (Alessandri-Haber *et al.*, 2008). Basal visceral nociception and TRPV4 agonist-induced visceral hypersensitivity were reduced by intervertebral injection of TRPV4-targeted siRNA (Cenac *et al.*, 2008). That said, none of the numerous gain-of-function TRPV4 channelopathies has a painful phenotype.

TRPM3-deficient mice showed impaired behavioural response to noxious heat and failed to develop inflammatory heat hyperalgesia (Vriens *et al.*, 2011). Naturally occurring TRPM3 blockers include the citrus fruit flavanones, naringenin and hesperetin (Straub *et al.*, 2013). Of TRPC channels expressed by sensory neurons, TRPC5 appears to be the most interesting given its postulated role in cold-sensation (Zimmermann *et al.*, 2011).

Respiratory disorders and TRP channels

The mammalian respiratory tract is densely innervated by sensory afferent fibres whose activation by irritant and/or inflammatory stimuli evokes a myriad of central and peripheral protective reflex responses, including cough, mucus secretion and bronchospasm (Canning, 2006). The pulmonary chemoreflex is a triad of bradycardia, bradypnea and hypotension. Of TRP channels expressed in these afferents, TRPA1 and TRPV1 have attracted the most attention as sensors of environmental irritants and reactive chemicals that threaten airway function and integrity.

TRPA1

Hypochlorite (the oxidizing mediator of chlorine) and hydrogen peroxide (a ROS) activate TRPA1 in chemosensory neurons in mice to cause respiratory depression, as well as pain behaviour, both of which were attenuated in TRPA1-deficient mice (Bessac *et al.*, 2008). Ozone, one of the major air pollutants, stimulated a subset of nociceptive sensory neurons isolated from vagal ganglia of wild-type mice, but not those from TRPA1 knockout mice (Taylor-Clark and Undem, 2010).

TRPA1 is also targeted by endogenously generated pro-inflammatory ligands as exemplified by nitro-oleic acid, a nitrated phospholipid produced during inflammation (Taylor-Clark *et al.*, 2009). Cigarette smoke is the major cause of COPD and is among the most prevalent triggers of asthma. Crotonaldehyde and acrolein, two main components of cigarette smoke, evoked Ca^{2+} influx in cultured guinea pig jugular ganglia neurons and promoted contraction of isolated guinea

pig bronchi (Andrè *et al.*, 2008). These responses were abolished by the selective TRPA1 antagonist HC-030031 (Andrè *et al.*, 2008). Moreover, inhalation of acrolein and other irritant TRPA1 agonists causes cough both in guinea pigs and human volunteers (Andrè *et al.*, 2009; Birrell *et al.*, 2009). Genetic deletion and/or pharmacological blockade of TRPA1 inhibited leukocyte infiltration in the airways, reduced cytokine and mucus production, and almost completely abolished airway hyperreactivity to contractile stimuli in a murine ovalbumin model of asthma (Caceres *et al.*, 2009).

In the lung, TRPA1 is also expressed by fibroblasts (Mukhopadhyay *et al.*, 2011). Most recently, this non-neuronal TRPA1 has been linked to non-neurogenic airway inflammation (Nassini *et al.*, 2012b). This is important because neurogenic inflammation, although predominant in preclinical models of asthma, plays lesser, if any, role in the human disease. Indeed, tachykinin receptor (NK1, 2 and 3) antagonists were without any clear benefit in clinical trials for asthma. Taken together, these findings suggest that selective TRPA1 antagonist may provide therapeutic benefits in respiratory diseases characterized by airway inflammation, such as asthma and COPD (Belvisi *et al.*, 2011; Preti *et al.*, 2012).

TRPV1

TRPV1 is another key player in the control of airway sensitivity. Indeed, inhaled capsaicin evokes multiple protective reflex responses in humans, including cough, sneezing and fluid secretion (Szallasi and Blumberg, 1999). In rodents, capsaicin also evokes the pulmonary chemoreflex, which is believed to represent the major dose-limiting factor for acute capsaicin administration (in desensitization studies, capsaicin needs to be given in increasing doses in consecutive days to avoid potentially fatal respiratory depression; Szallasi and Blumberg, 1999). The capsaicin inhalation test is broadly used to identify a subset of chronic cough patients with airway sensory hyperreactivity (Ternesten-Hasséus *et al.*, 2008). It is believed that these patients have overactive sensory nerves responsible for the airway symptoms and may benefit from inhaled TRPV1 (and/or TRPA1) antagonists (Millqvist, 2011). It is worth mentioning here that fatal asthma attacks were reported in asthma patients following incidental capsaicin inhalation (see Szallasi and Blumberg, 1999).

Hydrogen sulfide evokes neuropeptide release from isolated guinea pig airway tissue; it also contracts the guinea pig bronchus (Trevisani *et al.*, 2005). These effects are reduced by capsaicin desensitization or by the TRPV1 antagonist, capsazepine (Trevisani *et al.*, 2005). In anaesthetized guinea pigs, intratracheal instillation of hydrogen sulfide increases the total lung resistance and evokes neurogenic inflammation (airway plasma protein extravasation): these effects are reduced by capsazepine (Trevisani *et al.*, 2005). TRPV1 activators induce action potential discharge in murine vagal C-fibre terminals and this response was absent in TRPV1-deficient C-fibres (Kollarik and Undem, 2004). Pharmacological inhibition of TRPV1 significantly inhibited airway hyperresponsiveness to histamine in non-anaesthetized, ovalbumin-sensitized guinea pigs (Delescluse *et al.*, 2012). In addition, a recent study demonstrated that PGE_2 and bradykinin, two well-described endogenous inflammatory mediators, activated isolated guinea pig sensory ganglia and evoked cough in guinea pigs. Interestingly, effective blockade of this cough response required the simultaneous antagonism of both TRPV1 and TRPA1 receptors (Grace *et al.*, 2012).

Several lines of evidence implicate TRPV1 in the pathomechanism of chronic cough (see Spina and Page, 2013). The concentration at which inhaled capsaicin evokes coughing is markedly reduced in a subpopulation of chronic cough patients. These patients show increased TRPV1 expression in their airway nerves (Groneberg *et al.*, 2004). Furthermore, TRPV1 gene polymorphism was associated with cough sensitivity among subjects without asthma (Smit *et al.*, 2012). Nevertheless, TRPV1 as a target for anti-tussive drugs remains controversial because inhaled SB-705498, a selective TRPV1 antagonist, failed to ameliorate spontaneous coughing in chronic cough patients (C. Page, pers. comm.).

TRPM8

TRPM8, a cold-sensing TRP channel, is expressed in a subset of autonomic afferent nerves innervating the bronchopulmonary system and activation of these nerves may increase airway resistance (Xing *et al.*, 2008). If so, TRPM8 activation may be associated with cold-induced exacerbation of asthma and other pulmonary disorders (Xing *et al.*, 2008). On the other hand, respiratory irritant responses evoked by vapours containing cigarette smoke constituents (acrolein, acetic acid or cyclohexanone) were alleviated by menthol, and the effect of menthol was reversed by the TRPM8 antagonist AMTB (see Figure 5 for structure; Willis *et al.*, 2011). Indeed, menthol is added to some cigarette brands to minimize airway irritation. Furthermore, nasal application of TRPM8 agonists significantly increased the threshold of capsaicin-induced cough responses in human volunteers (Buday *et al.*, 2012). Clearly, TRPM8 activation can be both beneficial (for example, it may reduce airway irritancy) and harmful (it may exacerbate asthma), depending on the patient.

The role of TRPM8 in airways extends beyond the sensory nerves. In bronchial epithelium of patients with COPD, TRPM8 expression is markedly increased and stimulation with cold or menthol causes MUC5AC expression. MUC5AC expression is reduced by TRPM8 shRNA in normal human bronchial epithelial cells (Li *et al.*, 2011a). Considering that cold is one of the key triggers of COPD exacerbation and the enhanced mucus secretion contributes to morbidity of COPD by plugging airways and causing recurrent infection, TRPM8 may play an important role in the development of COPD and maybe also asthma.

TRPV4

The link between TRPV4 and human pulmonary disease was initially established by the discovery of TRPV4 gene polymorphism in COPD patients (Zhu *et al.*, 2009). Interestingly, one of these COPD-predisposing TRPV4 variants has a gain-of-function phenotype with enhanced Ca^{2+} influx and MMP-1 release evoked by diesel exhaust particles, indicating that altered activity of TRPV4 could drive the pathogenesis of COPD in some patients (Li *et al.*, 2011b). Normal TRPV4 activity may maintain ciliary movements and cilia on bronchial epithelial cells are essential for airway clearance. The Ca^{2+} overload secondary to this gain-of-function mutation is thought to impair ciliary function, leading to accumulation of harmful airborne particles in the lungs. Indeed,

impaired ciliary movement ('ciliopathy') is an early sign of COPD (http://weill.cornell.edu/news/releases/wcmc_2012/07_12_12b.shtml).

TRPV4 is also implicated in the pathogenesis of pulmonary oedema caused by high pulmonary venous pressure secondary to heart failure. TRPV4 activation evoked by elevated vascular pressure induces a marked increase in pulmonary endothelial cell permeability (Jian *et al.*, 2008). This observation is in line with the finding that systemic administration of a TRPV4 agonist elicited increased pulmonary vascular permeability, vascular haemorrhage, and circulatory collapse as a result of profound disruption of the endothelial permeability barrier (Willette *et al.*, 2008). Conversely, TRPV4 inhibition prevented the increased vascular permeability and resultant pulmonary oedema induced by elevated pulmonary venous pressure in isolated rodent and canine lungs (Thorneloe *et al.*, 2012). Of note, the expression of TRPV4 in the pulmonary vasculature is enhanced in lung sections obtained from heart failure patients (Thorneloe *et al.*, 2012). Collectively, these observations imply a therapeutic benefit for TRPV4 blockade in heart failure patients with pulmonary oedema.

TRPC6

Lung ischaemia–reperfusion is another cause of pulmonary oedema. The involvement of TRPC6 in this condition is implied by the finding that TRPC6-deficient mice fail to develop oedema following lung ischaemia–reperfusion (Weissmann *et al.*, 2012). It was suggested that TRPC6 is activated by DAG generated in a sequence of biochemical events starting from superoxide production by NADPH oxidase 2 (NOX2) and leading to elevated vascular permeability.

The role of TRPC6 in pulmonary system extends beyond oedema. For example, TRPC6 is implicated in the pathogenesis of idiopathic pulmonary hypertension. Three key studies showed that (i) TRPC6 expression was increased in pulmonary artery smooth muscle cells taken from idiopathic pulmonary hypertension patients (Yu *et al.*, 2004); (ii) TRPC6-deficient mice failed to develop pulmonary hypertension in response to chronic hypoxia (Weissmann *et al.*, 2006); and (iii) SNPs in the TRPC6 gene promoter region, which cause elevated expression of the channel, are associated with idiopathic pulmonary arterial hypertension (Yu *et al.*, 2009a).

Skin disorders and TRP channels

TRP channels are present in both neuronal and non-neuronal cells in the skin where they are thought to play a key role in itch, regulation of barrier function, keratinocyte differentiation, hair growth, inflammation and wound healing (see Moran *et al.*, 2011). TRPV1 is expressed in sensory nerves innervating the skin and genetic deletion or pharmacological inhibition of TRPV1 decreased histamine-induced scratching behaviour in mice (Shim *et al.*, 2007; Imamachi *et al.*, 2009). In keeping with this observation, scratching behaviour induced by LTB_4 was decreased by TRPV1 blockade through a mechanism involving attenuated migration of neutrophils to the skin (Fernandes *et al.*, 2013). Moreover, capsaicin injection into the mouse skin pretreated with CFA (but not into healthy skin) induced scratching behaviour, which was attenuated by capsazepine (Liang *et al.*, 2011). There is anecdotal evidence that desensitization to capsaicin creams may reduce itch associated with various aetiologies (Breneman *et al.*, 1992; Ellis *et al.*, 1993; Lysy *et al.*, 2003).

TRPA1 is highly co-expressed with TRPV1 in cutaneous sensory nerves. TRPA1 antagonism and/or genetic deletion, but not TRPV1 blockade, reduced scratching behaviour evoked by intradermal injection of hydrogen peroxide (Liu and Ji, 2012). Chloroquine and BAM8-22 induced itch through a TRPV1-independent mechanism by activating two other receptors, mas-related GPCR A3 (MrgprA3) and MrgprC11. Sensory neurons isolated from TRPA1-deficient mice exhibited markedly decreased responses to chloroquine and BAM8–22 and, accordingly, TRPA1-deficient mice exhibited reduced scratching in response to these pruritogens (Wilson *et al.*, 2011). Moreover, while LTB_4 induced scratching by activating both TRPV1 and TRPA1, the downstream mechanisms leading to itch differ between these channels, i.e. neutrophil migration and superoxide release respectively (Fernandes *et al.*, 2013). These findings suggest that (i) TRPA1 antagonists may be useful for the treatment of itch; and (ii) the spectrum of itch responsive to TRPA1 blockade may be different from that of TRPV1 antagonists.

TRPV3 is abundantly expressed in keratinocytes (Peier *et al.*, 2002b) and is thought to play a key role in barrier formation and hair morphogenesis. Activation of TRPV3 induces release of pro-inflammatory cytokines from murine keratinocytes (Xu *et al.*, 2006a). In human keratinocytes, TRPV3 activation decreased proliferation and induced apoptosis (Borbíró *et al.*, 2011). The same study demonstrated that TRPV3 activation resulted in hair shaft elongation, suppression of proliferation and induction of apoptosis in human organ-cultured hair follicles. Spontaneous mutant rodent strains (DS-Nh mice and WBN/Kob-Ht rats) that carry mutations for Gly573Ser and Gly573Cys in the TRPV3 gene, respectively, display a hairless or a pruritic dermatitis phenotype (Asakawa *et al.*, 2006; Yoshioka *et al.*, 2009). Interestingly, the same mutations together with another for Try692Gly in the TRPV3 gene were identified in patients with Olmsted syndrome, a rare disorder characterized by the combination of peri-orificial keratotic plaques, bilateral palmoplantar keratoderma, alopecia and intense itch. When expressed in heterologous systems, these TRPV3 mutants exhibited gain-of-function phenotypes (Lai-Cheong *et al.*, 2012; Lin *et al.*, 2012). Collectively, these observations suggest that TRPV3 plays a crucial role in skin keratinization, hair growth and itch. Therapeutic intervention by TRPV3 antagonists may reduce keratinization and itch in the skin, and potentially also alleviate alopecia. Of note, we already have a potential tool to test these predictions in GRC15300, a potent and selective TRPV3 antagonist, which is being evaluated in the clinics for pain (Khairatkar-Joshi *et al.*, 2010).

In human keratinocytes, TRPV1 agonist treatment suppressed proliferation and induced apoptosis (Tóth *et al.*, 2011). In human skin, TRPV1 expression was elevated in response to ultraviolet (UV) irradiation (Lee *et al.*, 2009). In the skin of hairless mice, UV irradiation up-regulated the expression of MMPs, pro-inflammatory cytokines, COX and p53; this was reduced by TRPV1 blockade (Lee *et al.*, 2011). Taken together, these findings suggest that TRPV1

antagonists may protect the skin from inflammation induced by UV light such as sunburn. In addition, topical TRPV1 antagonists may ameliorate thermal hyperalgesia after sunburn. TRPV1 has also been implicated in the pathogenesis of atopic dermatitis. Indeed, the TRPV1 antagonist PAC-14028 (AmorePacific Corp., Seoul, South Korea) is being investigated in patients with atopic dermatitis.

Bladder disorders and TRP channels

A number of TRP channels (including TRPV1, V2 and V4, TRPM4 and M8, TRPA1) are expressed in the bladder where they show distinct cellular distribution pattern and play different roles (see Skryma *et al.*, 2011; Avelino *et al.*, 2013).

TRPV1, the target for intravesical vanilloid therapy

TRPV1 is expressed in sensory neurons and urothelium. While TRPV1 in sensory C-fibre afferents is involved in the micturition reflex (Birder *et al.*, 2002) and thought to serve as sensor of painful bladder stimuli (Charrua *et al.*, 2007), the functional role (and the very existence) of TRPV1 in urothelium remains controversial (Everaerts *et al.*, 2010b).

TRPV1-deficient mice fail to develop bladder hyperreflexia during cystitis (Charrua *et al.*, 2007; Wang *et al.*, 2008) and the TRPV1 antagonist GRC6211 attenuates bladder overactivity in a rat model of bladder inflammation induced by LPS (Charrua *et al.*, 2009). GRC6211 also blocked the neurogenic detrusor overactivity ('neurogenic bladder') induced by chronic spinalization in the rat (Santos-Silva *et al.*, 2012).

The involvement of capsaicin-sensitive nerves in the human micturition reflex is well-established (Maggi *et al.*, 1989). When the descending neuronal control of the micturition reflex is lost (e.g. after spinal cord injury or due to multiple sclerosis, MS), the bladder becomes autonomic and the capsaicin-sensitive afferents take control of micturition ('neurogenic bladder'). This forms the foundation for the use of intravesical capsaicin administration in patients with neurogenic bladder: in these patients, capsaicin reduces the first desire to void by increasing bladder capacity and pressure threshold for micturition (Maggi *et al.*, 1989).

Although clinically effective in the long term, intravesical capsaicin is unacceptable for many patients because of the initial burning pain that it causes. Resiniferatoxin is a better-tolerated (much less painful) alternative for intravesical vanilloid therapy. Intravesical resiniferatoxin reduced the number of incontinent episodes (and even restored continence in some) in patients with neurogenic detrusor overactivity of spinal origin (Cruz *et al.*, 1997; Cruz and Dinis, 2007). The beneficial effects of intravesical resiniferatoxin were long-lasting (several months) and reversible. Repeat administration replicated the therapeutic value of the initial treatment. Importantly, biopsies taken from the bladder of patients undergoing intravesical vanilloid therapy did not show any significant histopathological and/or ultrastructural (electron microscopic) alterations.

TRPV4

In the bladder, TRPV4 is abundantly expressed in urothelial cells (Yu *et al.*, 2011). Stimulation of urothelial TRPV4 by stretch and/or hypo-osmolality induces ATP release which, in turn, activates purinergic P2X3 receptors in bladder afferents and evokes the micturition reflex (Birder *et al.*, 2007; Mochizuki *et al.*, 2009; Aizawa *et al.*, 2012). TRPV4 is also expressed in the detrusor muscle. Indeed, GSK1016790A, a potent and selective TRPV4 agonist (Figure 5), induces detrusor muscle contractions even in the absence of urothelium (Thorneloe *et al.*, 2008). Consistent with these findings, intravesical administration of GSK1016790A causes bladder overactivity in wild type, but not in TRPV4-deficient, mice (Thorneloe *et al.*, 2008). Moreover, TRPV4-null mice displayed reduced frequency of voiding, increased urine volume per episode, and spatially altered urine spot pattern (Gevaert *et al.*, 2007). TRPV4-null mice also showed reduced detrusor overactivity in a cyclophosphamide-induced cystitis model. HC-067047, a potent and selective TRPV4 antagonist, reduced micturition frequency in a rat model of cystitis (Everaerts *et al.*, 2010a). Of note, a subpopulation of patients with Charcot–Marie–Tooth disease type 2C, a genetic disease caused by gain-of-function mutation in TRPV4, display bladder urgency and incontinence (Landourè *et al.*, 2010). Collectively, these observations suggest that TRPV4 may represent a useful therapeutic target for the treatment of bladder dysfunction.

TRPM8

A subset of sensory bladder afferents expresses TRPM8 (Shibata *et al.*, 2011) and expression of this channel is elevated after bladder outlet obstruction in rats (Hayashi *et al.*, 2011). In patients with overactive and painful bladder syndromes, TRPM8 is similarly up-regulated in nerve fibres and its expression level significantly correlates with clinical scores (Mukerji *et al.*, 2006a). Intravesical cold saline instillation causes uninhibited detrusor contractions in patients with either idiopathic or neurogenic detrusor overactivity, but not in healthy volunteers (Mukerji *et al.*, 2006b). In rats, intravesical infusion of menthol evokes the micturition reflex (Nomoto *et al.*, 2008). Volume-induced bladder contraction and nociceptive reflex responses to noxious bladder distension are reduced by AMTB, a TRPM8 antagonist (Figure 5; Lashinger *et al.*, 2008). Additionally, in a cystometric study using rats, N-(4-*t*-butylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2H)-carboxamide (BCTC), another TRPM8 antagonist that also blocks TRPV1 and V4 channels, inhibited detrusor overactivity induced by menthol or cold stress (Lei *et al.*, 2013). Taken together, these observations imply that TRPM8 is involved in bladder pain and detrusor overactivity.

TRPA1

TRPA1 is highly expressed in sensory neurons innervating bladder where it is co-expressed with TRPV1 (Streng *et al.*, 2008). As with TRPM8, TRPA1 is up-regulated in bladder mucosa in patients with bladder outlet obstruction (Du *et al.*, 2008). Exposure of rat bladder strips to TRPA1 agonists induced contraction (Andrade *et al.*, 2006). *In vivo*, TRPA1 agonists increased the micturition frequency in rats, and desensitization of TRPV1-expressing C-fibres by capsaicin attenuated the effect of TRPA1 agonist (Du *et al.*, 2007; Streng *et al.*, 2008). Conversely, the TRPA1 antagonist

HC-030031 attenuated bladder overactivity in models of cyclophosphamide-induced cystitis and spinal cord injury (Andrade *et al.*, 2011; Meotti *et al.*, 2013). These findings identify TRPA1 as a potential drug target for bladder disorders.

TRPM4

TRPM4 is functionally expressed in the detrusor muscle of the rat and guinea pig. 9-Phenanthrol, a selective TRPM4 antagonist, reduced contraction of detrusor-isolated strips induced by various stimuli including electrical field stimulation (Smith *et al.*, 2013a,b). Further studies will be needed to elucidate the pathophysiological roles of TRPM4 in human bladder.

Inflammatory bowel disease (IBD) and TRP channels

TRP channels are widely expressed in the digestive tract, with important roles in taste, visceral sensation, GI motility, as well as absorptive and secretory functions (see Boesmans *et al.*, 2011; Holzer, 2011; Blackshaw *et al.*, 2013). Changes in TRP channel expression have been detected in a variety of GI ailments as exemplified by increased TRPV1 expression in both GERD (Matthews *et al.*, 2004; Bhat and Bielefeldt, 2006) and irritable bowel syndrome (Akbar *et al.*, 2008; Keszthelyi *et al.*, 2013). Indeed, TRPV1-null mice develop less oesophagitis after acid exposure compared with their wild-type littermates (Fujino *et al.*, 2006).

There is good evidence to suggest an important role for TRP channels (in particular, TRPV1 and TRPA1) in the development and maintenance of IBD. Increased TRPV1-like immunoreactivity was reported in colonic biopsies taken from patients with IBD, both Crohn's disease and ulcerative colitis (Yiangou *et al.*, 2001). In a rat model of IBD, desensitization to topical capsaicin of intestinal afferents was shown to reduce ulceration (Goso *et al.*, 1993). Furthermore, the TRPV1 antagonist JYL1421 suppressed colorectal distension and improved colitis in rats (Miranda *et al.*, 2007). TRPA1 expression is elevated in the inflamed mouse gut (Yang *et al.*, 2008; Izzo *et al.*, 2012). Experimental colitis induced by dinitrobenzene sulphonic acid (DNBS) was attenuated after both pharmacological blockade (by the TRPA1 antagonist HC-030031) and genetic inactivation of TRPA1 (Engel *et al.*, 2011). DNBS was shown to bind to cysteine residues in the intracytoplasmic N-terminus of the TRPA1 protein, identifying TRPA1 as a direct molecular target in DNBS-induced colitis (Engel *et al.*, 2011). The involvement of TRPA1 in IBD is, however, more complex as TRPA1 activation by cannabichromene (Figure 6) was reported to ameliorate murine colitis (Romano *et al.*, 2013).

In the GI tract, TRPV4 is expressed both in epithelial cells and sensory afferents (Brierley *et al.*, 2008). In IBD patients, increased TRPV4 mRNA levels were reported. In experimental animals, TRPV4 activation contributes to intestinal inflammation *via* chemokine release and TRPV4 blockade alleviates colitis symptoms (D'Aldebert *et al.*, 2011; Fichna *et al.*, 2012). Finally, TRPM8 is up-regulated both in mouse and human colon during colitis and TRPM8 activation by icilin attenuates inflammatory responses in a mouse model of IBD (Ramachandran *et al.*, 2013).

Diabetes and TRP channels

A growing number of TRP channels (TRPM2, M4 and M5, TRPA1) have been implicated in insulin release from pancreatic beta-cells (see Colsoul *et al.*, 2013). TRPM5 plays an important role in glucose-induced high-frequency oscillations. Indeed, membrane potential and cytosolic calcium level were reduced in islets derived from TRPM5-deficient mice, resulting in decreased glucose-induced insulin secretion (Colsoul *et al.*, 2010). Consequently, TRPM5-deficient mice showed impaired glucose tolerance (Brixel *et al.*, 2010; Colsoul *et al.*, 2010). In addition, TRPM5 mediates fructose-induced insulin release (downstream of sweet taste receptors) in murine islets (Kyriazis *et al.*, 2012). These observations indicate that TRPM5 may serve as a potential convergence point between sweet taste receptors and glucose-induced insulin secretion in pancreatic beta-cells (Kyriazis *et al.*, 2012). In accord with this hypothesis, SNPs in TRPM5 are associated with pre-diabetic phenotypes in subjects at increased risk for type 2 diabetes in a German population (Ketterer *et al.*, 2011). Collectively, these findings suggest that TRPM5 agonists may provide therapeutic benefits in patients with type 2 diabetes.

TRPM2 is another TRP channel implicated in insulin release from pancreatic beta-cells. Pharmacological inhibition or genetic deletion of TRPM2 reduced insulin secretion from islets induced by heat, glucose or glucagon-like peptide 1 (GLP-1) receptor agonists (Togashi *et al.*, 2008; Uchida *et al.*, 2011). TRPM2 is a non-selective Ca^{2+} permeable cation channel and TRPM2-mediated insulin secretion occurs partly by intracellular influx of Ca^{2+}. Interestingly, insulin secretion *via* TRPM2 can be induced by Ca^{2+} influx-independent mechanisms as glucose-induced insulin secretion was lost in islets from TRPM2-deficient mice in a condition that is supposed to completely inactivate the insulin release pathway mediated by K_{ATP} channel and voltage dependent Ca^{2+} channel (Uchida *et al.*, 2011). Importantly, TRPM2 knockout mice showed higher basal glucose levels and impaired glucose tolerance, indicating TRPM2 agonists may be useful as anti-diabetic agents (Uchida *et al.*, 2011). On the other hand, other studies indicate activation of TRPM2 by ROS leads to apoptosis in beta-cell lines (Hara *et al.*, 2002; Ishii *et al.*, 2006; Lange *et al.*, 2009). In addition, genotyping studies did not find any correlation between SNPs in the TRPM2 gene and type 2 diabetes (Romero *et al.*, 2010). Clearly, further investigation is required in order to establish the validity of TRPM2 as a therapeutic target in diabetes.

The roles of TRP channels in diabetes extend beyond insulin secretion from beta-cells. For example, there is good evidence that TRPV1 in sensory afferents (presumably following the release of sensory neuropeptides) plays a role in physiological glucose control (see Suri and Szallasi, 2008). Furthermore, dysregulated TRPV1 activity was implicated in the pathomechanisms of diabetes, both type 1 (Tsui *et al.*, 2007) and type 2 (Tsui *et al.*, 2011). Capsaicin evokes GLP-1 release from a murine entero-endocrine cell line *in vitro* and

when given intragastrically, capsaicin increases GLP-1 and insulin secretion in wild type, but not in TRPV1-deficient mice (Wang *et al.*, 2012). TRPV1-deficient mice also show improved glycemic control in a diet-induced obesity model (Marshall *et al.*, 2013). Desensitization to capsaicin was reported to increase glucose tolerance in Zucker diabetic fatty rats, a model of type-2 diabetes (Gram *et al.*, 2007). BCTC (a non-selective TRPV1 antagonist that also blocks TRPV4 and TRPM8 channels) improved glucose tolerance in rodent models of type-2 diabetes (Tanaka *et al.*, 2011). Finally, genetic deletion of TRPV1 protected mice from the development of autoimmune (type 1) experimental diabetes (Razavi *et al.*, 2006). Thus, the range of the experimental evidence implies a therapeutic potential for TRPV1 blockade in diabetic patients.

Obesity is an important cause of insulin resistance and type 2 diabetes. The exact role of TRPV1 in the control of appetite and body weight remains controversial. There is anecdotal evidence that dietary capsaicin suppresses appetite and keeps both experimental animals and human volunteers lean. Genetic deletion of TRPV1 appears to protect young mice from high-fat diet-induced obesity (Motter and Ahern, 2008) but when these mice grow older, they become 'lazy' (hypoactive) and fat (Garami *et al.*, 2011; Marshall *et al.*, 2013).

The involvement of TRPV4 in body weight control is likewise controversial. While two studies demonstrated that TRPV4-deficient mice were protected from diet-induced obesity (Kusudo *et al.*, 2012; Ye *et al.*, 2012), another study showed the opposite effect (O'Conor *et al.*, 2013). Even worse, in the latter study the TRPV4 (–/–) animals not only became obese but also showed severe, debilitating osteoarthritis.

The potential involvement of TRPM8 in obesity was recently suggested by the finding that chronic dietary menthol treatment prevented diet-induced obesity in wild-type, but not in TRPM8-deficient mice, through thermogenesis in brown adipose tissue, mediated by uncoupling protein 1 (UCP-1), (Ma *et al.*, 2012b).

For the sake of completeness, it should be mentioned here that TRP channels are also potential targets for managing the complications of diabetes, such as peripheral neuropathy, nephropathy, retinopathy, as well as cardiovascular disease. As mentioned earlier, TRPA1 and TRPV1 have been investigated as analgesic targets in diabetic neuropathic pain (Koivisto *et al.*, 2012). Of note, methylglyoxal, a metabolite of glucose, is capable of directly activating TRPA1, providing a potential link between elevated glucose levels and pain (Ohkawara *et al.*, 2012). With regard to diabetic nephropathy, podocyte foot processes and slit diaphragms contribute to the formation of the glomerular filter in the kidney and dysfunction of podocytes leads to proteinuria (Faul *et al.*, 2007). TRPC6 expression is elevated in podocytes by high glucose levels. Moreover, TRPC6 mediates high glucose-induced podocyte apoptosis where TRPC6 is activated by ROS generated from glucose (Liu *et al.*, 2013; Yang *et al.*, 2013). These observations suggest a role for TRPC6 in the development of diabetic nephropathy. Last, TRPV4 in ocular endothelial cells has been implicated in the pathogenesis of diabetic retinopathy (and other ocular neovascularization disorders).

Cancer and TRP channels

The link between TRP channels and cancer is a speculative, potentially rewarding, but highly controversial area of research. Clearly, the expression of several TRP channels (including TRPV1, V2, V6, TRPC3, C5, C6, TRPM1, M2, M3, M4, M7 and TRPM8, TRPA1) is altered in various cancers (see Santoni and Farfariello, 2011; Liberati *et al.*, 2013). Some authors argue that TRP channels are involved in the proliferation and migration of cancer cells, as well as in their resistance to chemotherapeutic agents (see Liberati *et al.*, 2013; Lehen'kyi and Prevarskaya, 2011). Sceptics point out that altered TRP channel expression may be simply an epiphenomenon to cancer progression and not a contributor to disease.

Of note, prostatic adenocarcinoma shows increased TRPM8 expression that appears to correlate with the aggressiveness of the disease. Recently, D-3263, a TRPM8 agonist, has entered Phase 1 clinical trials (NCT00839631) with the hope that it will kill TRM8-expressing cancer cells by calcium and sodium overload through TRPM8 activation (see Santoni and Farfariello, 2011). If this trial is successfully completed, a similar approach may be tried for other cancers that overexpress TRP channels such as TRPC6 in glioblastoma and TRPV2 in ovarian carcinoma.

Kidney disorders and TRP channels

TRPP2, TRPC6 and TRPM6 are causative genes of some genetic kidney disorders (Nilius and Owsianik, 2010). Mutations in PKD2, a gene coding TRPP2, are responsible for ADPKD, the most common inherited renal disease characterized by the growth of numerous cysts in both kidneys, and in many cases, hypertension, leading to renal failure (Peters *et al.*, 1993; Mochizuki *et al.*, 1996). TRPP2 forms a complex with polycystin-1 (Yu *et al.*, 2009b), a gene product of another causative gene of ADPKD, in primary cilia of renal epithelial cells and vascular endothelial cells and this complex is proposed to transduce extracellular shear stress induced by blood flow or urine flow into intracellular Ca^{2+} signals (Nauli *et al.*, 2003; AbouAlaiwi *et al.*, 2009). Cystic renal epithelial cells have lowered intracellular Ca^{2+} level (Yamaguchi *et al.*, 2006) and triptolide, a compound derived from traditional Chinese medicine, suppressed cyst formation by restoring Ca^{2+} signalling in a TRPP2-dependent mechanism in a murine model of ADPKD (Leuenroth *et al.*, 2007).

Interestingly, TRPV4 is reported to form a complex with TRPP2 to serve as a mechano- and thermosensitive molecular sensor in the cilium (Köttgen *et al.*, 2008). Chronic treatment with a low-dose TRPV4 agonist attenuated the renal cyst enlargement in an animal disease model of autosomal recessive polycystic kidney disease, which was also associated with reduced intracellular Ca^{2+} level (Siroky *et al.*, 2006).

Mutations in TRPC6 are responsible for FSGS, a disease characterized by glomerular scarring, resulting in proteinuria, oedema and kidney failure. Some of the TRPC6 mutants cloned from FSGS patients show a gain-of-function phenotype (Reiser *et al.*, 2005; Winn *et al.*, 2005). TRPC6-deficient

mice fail to develop angiotensin II (Ang-II)-induced albuminuria (Eckel *et al.*, 2011) while podocyte-specific overexpression of TRPC6 induces kidney dysfunction analogous to human FSGS (Krall *et al.*, 2010). In addition, expression of TRPC6 is elevated both in patients with acquired forms of proteinuric kidney disease and in a model of podocyte injury in rats (Möller *et al.*, 2007). Although the mechanism of TRPC6-mediated podocyte dysfunction has not been clarified, NFAT-dependent gene transcription may be involved in the pathway (Wang *et al.*, 2010). On the other hand, down-regulation of TRPC6 leads to loss of stress fibres upon Ang-II treatment in podocytes (Tian *et al.*, 2010). TRPC6-deficient mice were originally reported to be hypertensive, although compensatory up-regulation of TRPC3 and TRPC7 may have contributed to the observed phenotype (Dietrich *et al.*, 2005).

TRPM6 is permeable to Mg^{2+} and Ca^{2+}. TRPM6 is unique among TRP channels in that it has a large carboxyl terminal PK domain, analogous to TRPM7. TRPM6 is primarily expressed in the kidney and intestine and is considered to be responsible for absorption of Mg^{2+}. Loss-of-function mutation in TRPM6 is responsible for a rare hereditary disease characterized by profound hypomagnesaemia associated with hypocalcaemia (see Nilius and Owsianik, 2010). Accordingly, TRPM6 agonists may be useful in the management of disorders characterized by hypomagnesaemia.

CNS disorders and TRP channels

A number of TRP channels are expressed in the brain where they are believed to play key roles in the development of neurological and psychiatric disorders (see Vennekens *et al.*, 2012). TRPC3 is a non-selective cation channel that is activated through PLC and activation of inositol trisphosphate receptors. TRPC3 is abundantly expressed in cerebellum, cortex and hippocampus where it plays a pivotal role in brain-derived neurotrophic factor (BDNF)-mediated survival and growth-cone guidance in cerebellar granule neurons (Li *et al.*, 2005; Jia *et al.*, 2007). In addition, TRPC3 can be activated downstream of $mGlu_1$ receptors and induces slow excitatory postsynaptic potentials in cerebellar Purkinje cells (Hartmann *et al.*, 2008). Interestingly, both TRPC3 knockout mice and 'moonwalker mice' (that possess a gain-of-function mutation in TRPC3) exhibit similarly impaired walking behaviours (Hartmann *et al.*, 2008; Becker *et al.*, 2009). Considering this obvious discrepancy, further investigation will be needed to assess whether or not TRPC3 provides a drug discovery opportunity for ataxia.

TRPC6 is a close homologue of TRPC3, and similarly to TRPC3, TRPC6 promotes BDNF-mediated survival and growth-cone turning in cerebellar granular cells (Li *et al.*, 2005; Jia *et al.*, 2007). Overexpression of TRPC6 in cultured hippocampal neurons increases the density of dendritic spine, while down-regulation of TRPC6 with siRNA reduces the spine density (Tai *et al.*, 2008; Zhou *et al.*, 2008). TRPC6 transgenic mice exhibited improved spatial learning and memory in the Morris water maze test, suggesting a crucial role of TRPC6 in learning and memory formation through regulation of synaptic plasticity (Zhou *et al.*, 2008).

TRPC5 is highly expressed in hippocampus and amygdala (Riccio *et al.*, 2009). TRPC5-deficient mice displayed anxiolytic-like phenotype in elevated plus-maze, open field and social interaction tests, but not in novelty-suppressed feeding tests, suggesting that TRPC5 is involved in innate fear (Riccio *et al.*, 2009). In addition, synaptic responses mediated by activation of mGlu receptors and cholecystokinin CCK_2 receptors, both of which are implicated in anxiety, are diminished in lateral nucleus of the amygdala derived from TRPC5-null mice (Riccio *et al.*, 2009). Collectively, these data suggest that TRPC5 may serve as a therapeutic target for anxiety. Parenthetically, TRPV1 (–/–) mice were also reported to show reduced fear and anxiety behaviour (Marsch *et al.*, 2007). This finding, however, has recently been questioned by another study in which only minimal brain TRPV1 expression was found using a sensitive reporter mouse model (Cavanaugh *et al.*, 2011).

Growth cone collapse induced by semaphorin 3A is reduced in hippocampal neurons from TRPC5-deficient mice (Kaczmarek *et al.*, 2012). If this observation is replicated by pharmacological inhibition of TRPC5, it may imply a beneficial effect for TRPC5 antagonists in neurodegenerative disorders.

TRPM2 and TRPM7 are potential therapeutic targets for stroke. TRPM2 is expressed in microglia and neurons in the brain and may serve as a redox sensor. Activation of TRPM2 by oxidative stress could lead to cell death. Indeed, TRPM2-deficient mice showed resistance against neuronal death in a focal ischaemia model of stroke (Miller and Zhang, 2011). Likewise, TRPM7-induced Ca^{2+} overload leads to cell death. In a murine model of brain ischaemia, down-regulation of TRPM7 by shRNA protected rats from ischaemia-induced deficits (Sun *et al.*, 2009). Interestingly, FTY720, an immunosuppressive drug approved for the treatment of MS, inhibits TRPM7 (Qin *et al.*, 2013). It is tempting to speculate that FTY720 suppressed axonal and neuronal loss, one of the main characteristics of MS, partly through its inhibitory effect on TRPM7.

Genetic studies found that SNPs in TRPM2 and TRPM7 genes were associated with two related neurodegenerative disorders, ALS-G and Parkinsonism dementia respectively (Plato *et al.*, 2002). Of note, a different study in a Japanese population did not find significant correlation between SNP in TRPM7 and the ALS-Parkinsonism dementia complex (Hara *et al.*, 2010).

TRPM4 may be involved in axonal and neuronal degeneration in MS. In experimental autoimmune encephalomyelitis, a murine model of MS, TRPM4-deficient mice were protected from axonal and neuronal injury (Schattling *et al.*, 2012). The same study demonstrated that TRPM4-deficient neurons were resistant to excitotoxic stress and energy deficiency *in vitro*.

TRPML1 is a Ca^{2+}- and Fe^{2+}-permeable non-selective cation channel expressed predominantly in late endosomes and lysosomes (Nilius and Owsianik, 2010). Loss-of-function mutations in TRPML1 (Dong *et al.*, 2008) are responsible for mucolipidosis type IV, a hereditary lysosomal storage disorder characterized by severe psychomotor retardation, ophthalmologic abnormalities, blood iron deficiency and achlorhydria (Sun *et al.*, 2000; Raychowdhury *et al.*, 2004). The pathological mechanisms arising from mutations in TRPML1 have not been clarified.

Blockade of TRPML1-mediated Ca^{2+} release from late endosome/lysosome vesicles may reduce fusion and trafficking of these organelles (LaPlante *et al.*, 2004). The observed deficiency in lysosome functions could allow accumulation of lipids, followed by impaired autophagosome degradation that normally clears toxic proteins and damaged cell organelles (Vergarajauregui and Puertollano, 2008). Indeed, lysosomal lipid accumulation, defects in membrane trafficking and altered Ca^{2+} homeostasis are common characteristics observed in various lysosomal storage disorders including Nieman-Pick (NP) syndrome. A recent study demonstrated that increasing TRPML1 expression or using ML-SA1, a small-molecule TRPML1 agonist, restored trafficking defects and reduced lysosome storage and cholesterol accumulation in NP type C macrophages, suggesting that TRPML1 agonist may be useful for the treatment of the NP syndrome and potentially, other lysosomal storage disorders (Shen *et al.*, 2012).

Cardiovascular disorders and TRP channels

Cardiac hypertrophy is associated with arrythmias, decompensation and sudden death. Signal transduction pathways that link pathogenic signals to cardiomyocyte hypertrophy may be exploited for therapeutic intervention. There is emerging evidence that the calcineurin/NFAT complex (probably in concert with the MAPK pathway) is one of the key mechanisms that switch on the genes that cause cardiac hypertrophy (see Eder and Molkentin, 2011). Calcineurin is a serine/threonine phosphatase controlled by intracellular Ca^{2+} levels and increases in intracellular Ca^{2+} through TRPC channels (in particular TRPC1, C3 and C6) may activate the calcineurin/NFAT pathway (see Watanabe *et al.*, 2013). Indeed, TRPC1 knock-down by siRNA diminished the hypertrophy phenotype of cultured cardiac myocytes in response to endothelin-1 (ET-1), Ang-II and phenylephrine (Ohba *et al.*, 2007). Consistently, siRNA targeting TRPC1 reduced NFAT activation and hypertrophic response mediated by 5-HT2A receptors in cardiomyoblasts (Vindis *et al.*, 2010). Importantly, TRPC1-deficient mice failed to develop maladaptive cardiac hypertrophy induced by hemodynamic stress and neuro-hormonal excess (Seth *et al.*, 2009). Taken together, these findings imply an important role for TRPC1 channels in the pathogenesis of cardiac hypertrophy.

TRPC3 is another promising target for cardiac hypertrophy. TRPC3 transgenic mice exhibit increased activation of the calcineurin/NFAT pathway, leading to cardiomyopathy and cardiac hypertrophy when challenged by neuroendocrine agonists and/or pressure overload (Nakayama *et al.*, 2006). In keeping with this finding, Pyr3, a selective TRPC3 antagonist (Figure 5), protected mice from pressure overload-induced cardiac hypertrophy (Kiyonaka *et al.*, 2009).

TRPC6 may be also involved in cardiac hypertrophy as knock-down of this gene by siRNAs diminished Ang–II-induced NFAT activation and hypertrophic responses in rat cardiomyocytes (Onohara *et al.*, 2006). Conversely, cardiac-specific overexpression of TRPC6 in transgenic mice led to massive cardiac hypertrophy (Kuwahara *et al.*, 2006).

There is good evidence that TRP channels also contribute to the pathogenesis of hypertension. Expression of TRPC3 is elevated in patients with malignant hypertension in the vascular endothelium of pre-glomerular arterioles (Thilo *et al.*, 2009). ET-1 induces activation of the inositol trisphosphate receptor IP_3R1 in arterial myocytes and causes physical coupling of the IP_3R1 N-terminus to the TRPC3 channel C-terminus, leading to TRPC3 activation and vasoconstriction (Adebiyi *et al.*, 2010). In addition, the kinase WNK4, which is a causative gene of hereditary hypertension, controls blood pressure by restricting TRPC3-mediated Ca^{2+} influx in the vasculature (Park *et al.*, 2011b). Collectively, these observations suggest that TRPC3 blockade may be a novel approach to mitigate hypertension. TRPM4 may be also involved in the control of blood pressure as TRPM4-deficient mice showed a hypertensive phenotype, because of elevated catecholamine secretion from adrenal chromaffin cells (Mathar *et al.*, 2010).

Mutations in TRPM4 are reported to be associated with multiple cardiac conduction disorders, including progressive familial heart block type I (Kruse *et al.*, 2009), isolated cardiac conduction diseases (Liu *et al.*, 2010) and atrioventricular block and right bundle branch block (Stallmeyer *et al.*, 2012). The first two reports demonstrated that mutant TRPM4 underwent reduced deSUMOylation, resulting in constitutive SUMOylation and impaired endocytosis, leading to elevated levsl of TRPM4 channels on the cell surface. Such enhanced surface expression of mutant TRPM4 channel may disturb cardiac conduction by prolonging membrane depolarization and increasing inactivation of Na^+ channels. On the other hand, heart rates were not altered in TRPM4-null mice while these animals showed hypertension due to enhanced release of catecholamines (Mathar *et al.*, 2010). Lastly, TRPA1 (highly expressed in endothelial cells) has been implicated in the regulation of heart rate and blood pressure (see Earley, 2012).

Conclusions and perspectives

The TRP channel story began in 1969 with the description of a spontaneous *Drosophila* mutant in which, during prolonged illumination, photoreceptors showed an abnormal, transient response (Cosens and Manning, 1969). Exactly 20 years later, the mutant gene responsible for this abnormal light response was identified and termed '*trp*' (for transient receptor potential; Montell and Rubin, 1989). 1995 witnessed the discovery of the first mammalian TRP channel, TRPC1 (Wes *et al.*, 1995; Zhu *et al.*, 1995). Within a few years after this seminal discovery, the family of TRP channels exploded to include such long sought-after drug targets as the vanilloid (capsaicin) receptor TRPV1 (Caterina *et al.*, 1997), the camphor receptor TRPV3 (Peier *et al.*, 2002b) and the menthol receptor TRPM8 (McKemy *et al.*, 2002). The initial emphasis of drug discovery efforts was on TRP channels expressed on nociceptive neurons (Patapoutian *et al.*, 2009). Indeed, it took less than a decade to develop the first TRPV1 antagonists to be tried in the clinics as novel analgesic drugs (Szallasi *et al.*, 2007). Antagonists targeting TRPA1 and TRPV3 were quick to follow (Brederson *et al*, 2013). At the same time, exciting new discoveries have expanded the therapeutic potential of drugs targeting TRP channels into new disease areas, ranging from

respiratory diseases (cough, COPD and asthma) through cardiovascular, bladder, metabolic (including obesity and diabetes) and neurological disorders to stroke and cancer.

The rapid progress in TRP channel research has brought the understanding of the roles these channels play in health and disease within reach. However, of the 28 mammalian TRP channels, only 4 (TRPV1 and V3, TRPA1, and TRPM8) have been exploited so far to reach clinical stage of drug development despite accumulating evidence to implicate other TRP channels in diseases. Clearly, several key questions remain to be answered in order to facilitate the translation of the findings in basic research to clinical applications.

First, TRP channels have polymodal gating mechanisms and most also show a broad range of tissue distribution. Even TRPV1 (traditionally considered as a 'signature of polymodal sensory neurons') seems to be expressed at unexpected locations such as the skin, urothelium and mast cells (see Szallasi and Blumberg, 1999; Szallasi *et al.*, 2007). Consequently, pharmacological modulation of TRP channels may cause unacceptable, on-target, adverse effects. It was a sobering experience when many TRPV1 antagonists had to be withdrawn from the clinical trials due to either hyperthermia and/or impaired noxious heat sensation (see Moran *et al.*, 2011; Brederson *et al.*, 2013). Of note, TRPV1 antagonists vary significantly in the magnitude of these side effects, raising the possibility that such second-generation antagonists may be synthesized that show an improved clinical benefit to adverse effect ratio.

For other TRP channels, on-target side effects may represent an even bigger problem. For example, blockade of TRPM4 may be beneficial for the treatment of MS (Schattling *et al.*, 2012) and anaphylaxis (Smith and Nilius, 2013), but it may cause dangerous cardiac arrhythmias and hypertension (Abriel *et al.*, 2012). Although both gain- and loss-of-function TRPV4 mutations have been linked to human disease, this channel is another problematic drug target especially when activated by agonists (Nilius and Voets, 2013). Indeed, systemic activation of TRPV4 by GSK1016790A led to endothelial failure and cardiovascular collapse (Willette *et al.*, 2008). To a certain degree, this issue may be circumvented by organ-specific drug delivery: for example, when applied topically to the skin, GSK1016790A promoted intercellular junction development and thus augmented barrier function with no apparent adverse effects (Kida *et al.*, 2012). Selective modulation of TRP channels in diseased, but not in healthy, tissues (e.g. targeting TRPV1-AKAP79 interaction during inflammation) is another attractive approach to circumvent side effects.

Second, most of our understanding regarding the contribution of TRP channels to diseases is derived from studies with *in vitro* systems or preclinical rodent models, which do not always mirror human diseases. In this context, hereditary diseases caused by mutations in TRP channels (so-called 'TRP channelopathies') provide less uncertainty. Unfortunately, gain- and loss-of-function mutations often produce similar phenotypes. In terms of drug discovery, diseases caused by gain-of-function mutations in TRP channels could be more approachable as over-activation of channels could be inhibited by small molecules, while those caused by loss-of-function mutations, particularly truncation types, are difficult to target with small molecules and a less-validated approach such as gene therapy may be required to restore the normal TRP channel function. Besides the direct reversal of dysfunctional TRP channels, modulating the function of the intact TRP channels by therapeutic intervention might provide benefit when diseases related to those channelopathies are caused by mutations in other genes or environmental factors. One such example, although largely speculative, may be the use of a TRPP2 agonist for ADPKD, caused by mutations in PKD1.

Third, for many diseases we already have symptomatic therapeutic modalities and what we really need is a disease-modifying drug. For example, β-agonists improve lung functions in COPD patients, but they do not reverse (or at least halt) disease progression. Likewise, many drugs improve insulin-sensitivity in patients with type 2 diabetes, but these drugs do not fully prevent diabetic complications and neither do they prevent the exhaustion of islet cells.

The advantages and disadvantages of TRP channel agonists and antagonists over currently available therapeutic options need to be carefully weighed. For example, what would be the advantage of TRPA1 and/or TRPM8 antagonists over inhaled glucocorticoids and bronchodilators in patients with asthma? Or how about inhaled TRPV4 antagonists in patients with COPD? One may speculate, but the answers to these questions must come from clinical trials.

These obstacles are real, but probably not insurmountable, and the potential benefits are considerable. Drug discovery companies that can find creative ways to capitalize on targeting TRP channels in disease (and to spare those mediating important physiological functions) may develop novel, first-in-class drugs.

Conflict of interest

Yosuke Kaneko is employed by Ono Pharmaceuticals Ltd. The company does not sell any drugs mentioned in this paper.

References

AbouAlaiwi WA, Takahashi M, Mell BR, Jones TJ, Ratnam S, Kolb RJ *et al.* (2009). Ciliary polycystin-2 is a mechanosensitive calcium channel involved in nitric oxide signaling cascades. Circ Res 104: 860–869.

Abriel H, Syam N, Sottas V, Amarouch MY, Rougier JS (2012). TRPM4 channels in the cardiovascular system: physiology, pathophysiology, and pharmacology. Biochem Pharmacol 84: 873–881.

Adebiyi A, Zhao G, Narayanan D, Thomas-Gatewood CM, Bannister JP *et al.* (2010). Isoform-selective physical coupling of TRPC3 channels to IP3 receptors in smooth muscle cells regulates arterial contractility. Circ Res 106: 1603–1612.

Ahern GP (2003). Activation of TRPV1 by the satiety factor oleoylethanolamide. J Biol Chem 278: 30429–30434.

Aizawa N, Wyndaele JJ, Homma Y, Igawa Y (2012). Effects of TRPV4 cation channel activation on the primary bladder afferent activities of the rat. Neurourol Urodyn 31: 148–155.

Akbar A, Yiangou F, Facer P, Walters JR, Anand P, Ghosh S (2008). Increased capsaicin receptor TRPV1-expressing sensory nerve fibers in irritable bowel syndrome and their correlation with abdominal pain. Gut 57: 923–929.

Alessandri-Haber N, Dina OA, Joseph EK, Reichling D, Levine JD (2006). A transient receptor potential vanilloid 4-dependent mechanism of hyperalgesia is engaged by concerted action of inflammatory mediators. J Neurosci 26: 3864–3874.

Alessandri-Haber N, Dina OA, Joseph EK, Reichling DB, Levine JD (2008). Interaction of transient receptor potential vanilloid 4: integrin, and SRC tyrosine kinase in mechanical hyperalgesia. J Neurosci 28: 1046–1057.

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Catterall WA, Spedding M, Peters JA, Harmar AJ and CGTP Collaborators (2013). The Concise Guide to PHARMACOLOGY 2013/14: Overview. Br J Pharmacol 170: 1449–1867.

Ambrosino P, Soldovieri MV, Russo C, Taglialatela M (2013). Activation and desensitization of TRPV1 channels in sensory neurons by the PPARα agonist palmitoylethanolamide. Br J Pharmacol 168: 1430–1444.

Anand U, Otto WR, Facer P, Zebda N, Selmer I, Gunthorpe MJ *et al.* (2008). TRPA1 receptor localization in the human peripheral nervous system and functional studies in cultured human and rat sensory neurons. Neurosci Lett 438: 221–227.

Andrade EL, Ferreira J, André E, Calixto JB (2006). Contractile mechanisms coupled to TRPA1 receptor activation in rat urinary bladder. Biochem Pharmacol 72: 104–114.

Andrade EL, Forner S, Bento AF, Leite DF, Dias MA, Leal PC *et al.* (2011). TRPA1 receptor modulation attenuates bladder overactivity induced by spinal cord injury. Am J Physiol Renal Physiol 300: F1223–F1234.

Andrè E, Campi B, Trevisani M, Ferreira J, Malheiros A, Yunes RA *et al.* (2006). Pharmacological characterisation of the plant sesquiterpenes polygodial and drimanial as vanilloid receptor agonists. Biochem Pharmacol 71: 1248–1254.

Andrè E, Campi B, Materazzi S, Trevisani M, Amadesi S, Massi D *et al.* (2008). Cigarette smoke-induced neurogenic inflammation is mediated by alpha,beta-unsaturated aldehydes and the TRPA1 receptor in rodents. J Clin Invest 118: 2574–2582.

Andrè E, Gatti R, Trevisani M, Preti D, Baraldi PG, Patacchini R *et al.* (2009). Transient receptor potential ankyrin receptor 1 is a novel target for pro-tussive agents. Br J Pharmacol 158: 1621–1628.

Asakawa M, Yoshioka T, Matsutani T, Hikita I, Suzuki M, Oshima I *et al.* (2006). Association of a mutation in TRPV3 with defective hair growth in rodents. J Invest Dermatol 126: 2664–2672.

Auer-Grumbach M, Olschewski A, Papić L, Kremer H, McEntagart ME, Uhrig S *et al.* (2010). Alterations in the ankyrin domain of TRPV4 cause congenital distal SMA, scapuloperoneal SMA and HMSN2C. Nat Genet 42: 160–164.

Avelino A, Charrua A, Frias B, Cruz C, Boudes M, de Ridder D *et al.* (2013). Transient receptor potential channels in bladder function. Acta Physiol (Oxf) 207: 110–122.

Bagal SK, Brown AD, Cox PJ, Omoto K, Owen RM, Pryde DC *et al.* (2013). Ion channels as therapeutic targets: a drug discovery perspective. J Med Chem 56: 593–624.

Bandell M, Story GM, Hwang SW, Viswanath V, Eid SR, Petrus MJ *et al.* (2004). Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin. Neuron 41: 849–857.

Bang S, Kim KY, Yoo S, Lee SH, Hwang SW (2007). Transient receptor potential V2 expressed in sensory neurons is activated by probenecid. Neurosci Lett 425: 120–125.

Bang S, Yoo S, Yang TJ, Cho H, Hwang SW (2010a). Farnesyl pyrophosphate is a novel pain-producing molecule via specific activation of TRPV3. J Biol Chem 285: 19362–19371.

Bang S, Yoo S, Yang TJ, Cho H, Kim YG, Hwang SW (2010b). Resolvin D1 attenuates activation of sensory transient receptor potential channels leading to multiple anti-nociception. Br J Pharmacol 161: 707–720.

Bang S, Yoo S, Yang TJ, Cho H, Hwang SW (2011). Isopentenyl pyrophosphate is a novel antinociceptive substance that inhibits TRPV3 and TRPA1 ion channels. Pain 152: 1156–1164.

Bang S, Yoo S, Yang TJ, Cho H, Hwang SW (2012). Nociceptive and pro-inflammatory effects of dimethylallyl pyrophosphate via TRPV4 activation. Br J Pharmacol 166: 1433–1443.

Basora N, Boulay G, Bilodeau L, Rousseau E, Payet MD (2003). 20-hydroxyeicosatetraenoic acid (20-HETE) activates mouse TRPC6 channels expressed in HEK293 cells. J Biol Chem 278: 31709–31716.

Bautista DM, Movahed P, Hinman A, Axelsson HE, Sterner O, Högestätt ED *et al.* (2005). Pungent products from garlic activate the sensory ion channel TRPA1. Proc Natl Acad Sci U S A 102: 12248–12252.

Bautista DM, Jordt SE, Nikai T, Tsuruda PR, Read AJ, Poblete J *et al.* (2006). TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. Cell 124: 1269–1282.

Bautista DM, Siemens J, Glazer JM, Tsuruda PR, Basbaum AI, Stucky CL *et al.* (2007). The menthol receptor TRPM8 is the principal detector of environmental cold. Nature 448: 204–208.

Becker EB, Oliver PL, Glitsch MD, Banks GT, Achilli F, Hardy A *et al.* (2009). A point mutation in TRPC3 causes abnormal Purkinje cell development and cerebellar ataxia in moonwalker mice. Proc Natl Acad Sci U S A 106: 6706–6711.

Behrendt HJ, Germann T, Gillen C, Hatt H, Jostock R (2004). Characterization of the mouse cold-menthol receptor TRPM8 and vanilloid receptor type-1 VR1 using a fluorometric imaging plate reader (FLIPR) assay. Br J Pharmacol 141: 737–745.

Belvisi MG, Dubuis E, Birrell MA (2011). Transient receptor potential A1 channels: insights into cough and airway inflammatory disease. Chest 140: 1040–1047.

Bessac BF, Sivula M, von Hehn CA, Escalera J, Cohn L, Jordt SE (2008). TRPA1 is a major oxidant sensor in murine airway sensory neurons. J Clin Invest 118: 1899–1910.

Bhat JM, Bielefeldt K (2006). Capsaicin receptor (TRPV1) and non-erosive reflux disease. Eur J Gastroenterol Hepatol 18: 263–270.

Binder A, May D, Baron R, Maier C, Tölle TR, Treede RD *et al.* (2010). Transient receptor potential channel polymorphisms are associated with the somatosensory function in neuropathic pain patients. PLoS One 6: e17387.

Birder LA, Nakamura Y, Kiss S, Nealen ML, Barrick S, Kanai AJ *et al.* (2002). Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci 5: 856–860.

Birder LA, Kullmann FA, Lee H, Barrick S, de Groat W, Kanai A *et al.* (2007). Activation of urothelial transient receptor potential vanilloid 4 by 4alpha-phorbol 12,13-didecanoate contributes to altered bladder reflexes in the rat. J Pharmacol Exp Ther 323: 227–235.

Birrell MA, Belvisi MG, Grace M, Sadofsky L, Faruqi S, Hele DJ *et al.* (2009). TRPA1 agonists evoke coughing in guinea pig and human volunteers. Am J Respir Crit Care Med 180: 1042–1047.

Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I *et al.* (2001). Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 134: 845–852.

Blackshaw LA, Brierley SM, Harrington AM, Hughes PA (2013). TRP channels in visceral pain. Open Pain J 6: 23–30.

Bley K (2012). Effects of topical capsaicin on cutaneous innervation: implications for pain management. Open Pain J 5: 23–28.

Boesmans W, Owsianik G, Tack J, Voets T, Vanden Berghe P (2011). TRP channels in neurogastroenterology: opportunities for therapeutic intervention. Br J Pharmacol 162: 18–37.

Bohlen CJ, Priel A, Zhou S, King D, Siemens J, Julius D (2010). A bivalent tarantula toxin activates the capsaicin receptor, TRPV1, by targeting the outer pore domain. Cell 141: 834–845.

Borbíró I, Lisztes E, Tóth BI, Czifra G, Oláh A, Szöllösi AG *et al.* (2011). Activation of transient receptor potential vanilloid-3 inhibits human hair growth. J Invest Dermatol 131: 1605–1614.

Brederson JD, Kym PR, Szallasi A (2013). Targeting TRP channels for pain relief. Eur J Pharmacol 716: 61–76.

Breneman DL, Cardone JS, Blumsack RF, Lather RM, Searle EA, Pollack VE (1992). Topical capsaicin for treatment of hemodialysis-related pruritus. J Am Acad Dermatol 26: 91–94.

Brierley SM, Page AJ, Hughes PA, Adam B, Liebregts T, Cooper NJ *et al.* (2008). Selective role for TRPV4 ion channels in visceral sensory pathways. Gastroenterol 134: 2059–2069.

Brixel LR, Monteilh-Zoller MK, Ingenbrandt CS, Fleig A, Penner R, Enklaar T *et al.* (2010). TRPM5 regulates glucose-stimulated insulin secretion. Pflugers Arch 460: 69–76.

Brown DC, Iadarola MJ, Perkowski SZ, Erin H, Shofer F, Laszlo KJ *et al.* (2005). Physiologic and antinociceptive effects of intrathecal resiniferatoxin in a canine bone cancer model. Anesthesiology 103: 1052–1059.

Btesh J, Fischer MJ, Stott K, McNaughton PA (2013). Mapping the binding site of TRPV1 on AKAP79: implications for inflammatory hyperalgesia. J Neurosci 33: 9184–9193.

Buday T, Brozmanova M, Biringerova Z, Gavliakova S, Poliacek I, Calkovsky V *et al.* (2012). Modulation of cough response by sensory inputs from the nose – role of trigeminal TRPA1 versus TRPM8 channels. Cough 8: 11.

Caceres AI, Brackmann M, Elia MD, Bessac BF, del Camino D, D'Amours M *et al.* (2009). A sensory neuronal ion channel essential for airway inflammation and hyperreactivity in asthma. Proc Natl Acad Sci USA 106: 9099–9104.

Calvo RR, Meegalla SK, Parks DJ, Parsons WH, Ballentine SK, Lubin ML *et al.* (2012). Discovery of vinylcycloalkyl-substituted benzimidazole TRPM8 antagonists effective in the treatment of cold allodynia. Bioorg Med Chem Lett 22: 1903–1907.

Canning BJ (2006). Anatomy and neurophysiology of the cough reflex: ACCP evidence-based clinical practice guidelines. Chest 129: 33–47.

Cantero-Recasens G, Gonzalez JR, Fandos C, Duran-Tauleria E, Smit LA, Kauffmann F *et al.* (2010). Loss of function of transient receptor potential vanilloid 1 (TRPV1) genetic variant is associated with lower risk of active childhood asthma. J Biol Chem 285: 27532–27535.

Capasso R, Aviello G, Romano B, Borrelli F, De Petrocellis L, Di Marzo V *et al.* (2012). Modulation of mouse gastrointestinal motility by allyl isothiocyanate, a constituent of cruciferous vegetables (Brassicaceae): evidence for TRPA1-independent effects. Br J Pharmacol 165: 1966–1977.

Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D (1997). The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 389: 816–824.

Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR *et al.* (2000). Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 288: 306–313.

Cathcart CJ, Johnson SA, Reynolds LR, Al-Nadaf S, Budsberg SC (2012). Efficacy of ABT-116, an antagonist of the transient receptor potential vanilloid type 1, in providing analgesia for dogs with chemically induced synovitis. Am J Vet Res 73: 19–26.

Cavanaugh DJ, Chesler AT, Jackson AC, Sigal YM, Yamanaka H, Grant R *et al.* (2011). Trpv1 reporter mice reveal highly restricted brain distribution and functional expression in arteriolar smooth muscle cells. J Neurosci 31: 5067–5077.

Cenac N, Altier C, Chapman K, Liedtke W, Zamponi G, Vergnolle N (2008). Transient receptor potential vanilloid-4 has a major role in visceral hypersensitivity symptoms. Gastroenterology 135: 937–946.

Charrua A, Cruz CD, Cruz F, Avelino A (2007). Transient receptor potential vanilloid subfamily 1 is essential for the generation of noxious bladder input and bladder overactivity in cystitis. J Urol 177: 1537–1541.

Charrua A, Cruz CD, Narayanan S, Gharat L, Gullapalli S, Cruz F *et al.* (2009). GRC-6211, a new oral specific TRPV1 antagonist, decreases bladder overactivity and noxious bladder input in cystitis animal models. J Urol 181: 379–386.

Chen HC, Xie J, Zhang Z, Su LT, Yue L, Runnels LW (2010). Blockade of TRPM7 channel activity and cell death by inhibitors of 5-lipoxygenase. PLoS One 5: e11161.

Chen J, Joshi SK, DiDomenico S, Perner RJ, Mikusa JP, Gauvin DM *et al.* (2011). Selective blockade of TRPA1 channel attenuates pathological pain without altering noxious cold sensation or body temperature regulation. Pain 152: 1165–1172.

Cheng W, Sun C, Zheng J (2010). Heteromerization of TRP channel subunits: extending functional diversity. Protein Cell 1: 802–810.

Chizh BA, O'Donnell MB, Napolitano A, Wang J, Brooke AC, Aylott MC *et al.* (2007). The effects of the TRPV1 antagonist SB-705498 on TRPV1 receptor-mediated activity and inflammatory hyperalgesia in humans. Pain 132: 132–141.

Chu CJ, Huang SM, De Petrocellis L, Bisogno T, Ewing SA, Miller JD *et al.* (2003). N-oleoyldopamine, a novel endogenous capsaicin-like lipid that produces hyperalgesia. J Biol Chem 278: 13633–13639.

Chuang HH, Prescott ED, Kong H, Shields S, Jordt SE, Basbaum AI *et al.* (2001). Bradykinin and nerve growth factor release the capsaicin receptor from PtdIns(4,5)P2-mediated inhibition. Nature 411: 957–962.

Chubanov V, Mederos y Schnitzler M, Meißner M, Schäfer S, Abstiens K, Hofmann T *et al.* (2012). Natural and synthetic modulators of SK (K(ca)2) potassium channels inhibit magnesium-dependent activity of the kinase-coupled cation channel TRPM7. Br J Pharmacol 166: 1357–1376.

Clapham DE (2003). TRP channels as cellular sensors. Nature 426: 517–524.

Clapham DE, Runnels LW, Strübing C (2001). The TRP ion channel family. Nat Rev Neurosci 2: 387–396.

Clare JJ (2010). Targeting ion channels for drug discovery. Discov Med 9: 253–260.

Colburn RW, Lubin ML, Stone DJ Jr, Wang Y, Lawrence D, D'Andrea MR *et al*. (2007). Attenuated cold sensitivity in TRPM8 null mice. Neuron 54: 379–386.

Colsoul B, Schraenen A, Lemaire K, Quintens R, Van Lommel L, Segal A *et al*. (2010). Loss of high-frequency glucose-induced Ca2+ oscillations in pancreatic islets correlates with impaired glucose tolerance in Trpm5–/– mice. Proc Natl Acad Sci U S A 107: 5208–5213.

Colsoul B, Nilius B, Vennekens R (2013). Transient receptor potential (TRP) cation channels in diabetes. Curr Top Med Chem 13: 258–269.

Cosens DJ, Manning A (1969). Abnormal electroretinogram from a *Drosophila* mutant. Nature 224: 285–287.

Cromer BA, McIntyre P (2008). Painful toxins acting on TRPV1. Toxicon 51: 163–173.

Cruz F, Dinis P (2007). Resiniferatoxin and botulinum toxin type A for treatment of lower urinary tract symptoms. Neurourol Urodyn 26: 920–927.

Cruz F, Guimaräes M, Silva C, Reis M (1997). Suppression of bladder hyperreflexia by intravesical resiniferatoxin. Lancet 350: 640–641.

Cui M, Honore P, Zhong C, Gauvin G, Mikusa J, Hernandez G *et al*. (2006). TRPV1 receptors in the CNS play a key role in broad-spectrum analgesia of TRPV1 antagonists. J Neurosci 26: 9385–9393.

D'Aldebert E, Cenac N, Rousset P, Martin L, Rolland C, Chapman K *et al*. (2011). Transient receptor potential vanilloid 4 activated inflammatory signals by intestinal epithelial cells and colitis in mice. Gastroenterology 140: 175–285.

Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P *et al*. (2000). Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. Nature 405: 183–187.

De Petrocellis L, Vellani V, Schiano-Morinello A, Marini P, Magherini PC, Orlando P *et al*. (2008). Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyryn type-1 and melastatin-8. Br J Pharmacol 325: 1007–1015.

De Petrocellis L, Ligresti A, Morinello AS, Allara M, Bisogno T, Petrosino S *et al*. (2011). Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol 163: 1479–1494.

DeFalco J, Steiger D, Dourado M, Emerling D, Duncton MA (2010). 5-benzyloxytryptamine as an antagonist of TRPM8. Bioorg Med Chem Lett 20: 7076–7079.

Delescluse I, Mace H, Adcock JJ (2012). Inhibition of airway hyper-responsiveness by TRPV1 antagonists (SB-705498 and PF-04065463) in the unanaesthetized, ovalbumin-sensitized guinea pig. Br J Pharmacol 166: 1822–1832.

Dessaint J, Yu W, Krause JE, Yue L (2004). Yohimbine inhibits firing activities of rat dorsal root ganglion neurons by blocking Na+ channels and vanilloid VR1 receptors. Eur J Pharmacol 485: 11–20.

Dickenson AH, Dray A (1991). Selective antagonism of capsaicin by capsazepine: evidence for a spinal receptor site in capsaicin-induced antinociception. Br J Pharmacol 104: 1045–1049.

Dietrich A, Mederos Y Schnitzler M, Gollasch M, Gross V, Storch U, Dubrovska G *et al*. (2005). Increased vascular smooth muscle contractility in TRPC6–/– mice. Mol Cell Biol 25: 6980–6989.

Dong XP, Cheng X, Mills E, Delling M, Wang F, Kurtz T *et al*. (2008). The type IV mucolipidosis-associated protein TRPML1 is an endolysosomal iron release channel. Nature 455: 992–996.

Du S, Araki I, Yoshiyama M, Nomura T, Takeda M (2007). Transient receptor potential channel A1 involved in sensory transduction of rat urinary bladder through C-fiber pathway. Urology 70: 826–831.

Du S, Araki I, Kobayashi H, Zakoji H, Sawada N, Takeda M (2008). Differential expression profile of cold (TRPA1) and cool (TRPM8) receptors in human urogenital organs. Urology 72: 450–455.

Duncan LM, Deeds J, Hunter J, Shao J, Holmgren LM, Woolf EA *et al*. (1998). Down-regulation of the novel gene *melastatin* correlates with potential for melanoma metastasis. Cancer Res 58: 1515–1520.

Earley S (2012). TRPA1 channels in the vasculature. Br J Pharmacol 167: 13–22.

Eckel J, Lavin PJ, Finch EA, Mukerji N, Burch J, Gbadegesin R *et al*. (2011). TRPC6 enhances angiotensin II-induced albuminuria. J Am Soc Nephrol 22: 526–535.

Edelmayer RM, Le LN, Yan J, Wei X, Nassini R, Materazzi S *et al*. (2012). Activation of TRPA1 on dural afferents: a potential mechanism of headache pain. Pain 153: 1949–1958.

Eder P, Molkentin JD (2011). TRPC channels as effectors of cardiac hypertrophy. Circ Res 108: 265–272.

Eid SR (2011). The effects of the TRPV1 antagonist SB-705498 on TRPV1 receptor-mediated activity and inflammatory hyperalgesia in humans. Pain 132: 132–141.

Eid SR, Crown ED, Moore EL, Liang HA, Choong KC, Dima S *et al*. (2008). HC-030031, a TRPA1 selective antagonist, attenuates inflammatory- and neuropathy-induced mechanical hypersensitivity. Mol Pain 4: 48.

Eisfeld J, Lückhoff A (2007). TRPM2. Hand Exp Pharmacol 179: 237–252.

Ellis CN, Berberian B, Sulica VI, Dodd WA, Jarratt MT, Katz HI *et al*. (1993). A double-blind evaluation of topical capsaicin in pruritic psoriasis. J Am Acad Dermatol 29: 438–442.

Engel MA, Becker C, Reeh PW, Neurath MF (2011). Role of sensory neurons in colitis: increasing evidence for a neuroimmune link in the gut. Inflamm Bowel Dis 17: 1030–1033.

Everaerts W, Zhen X, Ghosh D, Vriens J, Gevaert T, Gilbert JP *et al*. (2010a). Inhibition of the cation channel TRPV4 improves bladder function in mice and rats with cyclophosphamide-induced cystitis. Proc Natl Acad Sci U S A 107: 19084–19089.

Everaerts W, Vriens J, Owsianik G, Appendino G, Voets T, De Ridder D *et al*. (2010b). Functional characterization of transient receptor potential channels in mouse urothelial cells. Am J Physiol Renal Physiol 298: F692–F701.

Facer P, Casula MA, Smith GD, Benham CD, Chessell IP, Bountra C *et al*. (2007). Differential expression of the capsaicin receptor TRPV1 and related novel receptors TRPV3, TRPV4 and TRPM8 in normal human tissues and changes in traumatic and diabetic neuropathy. BMC Neurol 7: 11.

Faul C, Asanuma K, Yanagida-Asanuma E, Kim K, Mundel P (2007). Actin up: regulation of podocyte structure and function by components of the actin cytoskeleton. Trends Cell Biol 17: 428–437.

Fernandes ES, Fernandes MA, Keeble JE (2012). The functions of TRPA1 and TRPV1: movign away from sensory nerves. Br J Pharmacol 166: 510–521.

Fernandes ES, Vong CT, Quek S, Cheong J, Awal S, Gentry C *et al.* (2013). Superoxide generation and leukocyte accumulation: key elements in the mediation of leukotriene B4-induced itch by transient receptor potential ankyrin 1 and transient receptor potential vanilloid 1. FASEB J 27: 1664–1673.

Fichna J, Mokrowieczka A, Cygankiewicz AI, Zakrzewski PA, Malecka-Panas E, Janecka A *et al.* (2012). Transient receptor potential vanilloid 4 blockade protects against experimental colitis in mice: a new strategy for inflammatory bowel disease treatment? Neurogastroenterol Motil 24: e557–e560.

Fischer MJ, Betsh J, McNaughton PA (2013). Disrupting sensitization of transient receptor potential vanilloid subtype 1 inhibits inflammatory hyperalgesia. J Neurosci 33: 7407–7414.

Flemming PK, Dedman AM, Xu SZ, Li J, Zeng F, Naylor J *et al.* (2006). Sensing of lysophospholipids by TRPC5 calcium channel. J Biol Chem 281: 4977–4982.

Fujino K, de la Fuente SG, Takami Y, Takahashi G, Mantyh CR (2006). Attenuation of acid-induced esophagitis in VR-1 deficient mice. Gut 55: 34–40.

Garami A, Pakai E, Oliveira DL, Steiner AA, Wanner SP, Almeida MC *et al.* (2011). Thermoregulatory phenotype of the Trpv1 knockout mouse: thermoeffector dysbalance with hyperkinesis. Neurosci 31: 1721–1733.

Garrison SR, Stucky CL (2011). The dynamic TRPA1 channel: a suitable pharmacological target? Curr Pharm Biotechnol 12: 1689–1697.

Gavva NR (2008). Body-temperature maintenance as the predominant function of the vanilloid receptor TRPV1. Trends Pharmacol Sci 29: 550–557.

Gavva NR, Treanor JJ, Garami A, Fang L, Surapaneni S, Akrami A *et al.* (2008). Pharmacological blockade of the vanilloid receptor TRPV1 elicits marked hyperthermia in humans. Pain 136: 202–210.

Gevaert T, Vriens J, Segal A, Everaerts W, Roskams T, Talavera K *et al.* (2007). Deletion of the transient receptor potential cation channel TRPV4 impairs murine bladder voiding. J Clin Invest 117: 3453–3462.

Gomtsyan A, Faltynek C (eds) (2010). Vanilloid Receptor TRPV1 in Drug Discovery: Targeting Pain and Other Pathological Disorders. John Wiley & Sons: Hoboken, NJ.

Gopinath P, Wan E, Holdcroft A, Facer P, Davis JB, Smith GD *et al.* (2005). Increased capsaicin receptor TRPV1 in skin nerve fibres and related vanilloid receptors TRPV3 and TRPV4 in keratinocytes in human breast pain. BMC Womens Health 5: 2.

Goso C, Evengelista S, Tramontana M, Manzini S, Blumberg PM, Szallasi A (1993). Topical capsaicin administration protects against trinitrobenzene sulfonic acid-induced colitis in the rat. Eur J Pharmacol 249: 185–190.

Goswami C (2012). TRP-mediated cytoskeletal reorganization: implications for disease and drug development. In: Szallasi A, Bíró T (eds). TRP Channels in Drug Discovery. Methods in Pharmacology and Toxicology, Springer Protocols. Humana Press/Springer: New York, Heidelberg, Dordrecht, London, pp. 13–39.

Grace M, Birrell MA, Dubuis E, Maher SA, Belvisi MG (2012). Transient receptor potential channels mediate the tussive response to prostaglandin E2 and bradykinin. Thorax 67: 891–900.

Gram DX, Ahren B, Nagy I, Olsen UB, Brand CL, Sundler F *et al.* (2007). Capsaicin-sensitive sensory fibers in the islets of Langerhans contribute to defective insulin secretion in Zucker diabetic rat, an animal model for some aspects of human type 2 diabetes. Eur J Neurosci 25: 213–223.

Grand T, Demion M, Norez C, Mettey Y, Launay P, Becq F *et al.* (2008). 9-phenanthrol inhibits human TRPM4 but not TRPM5 cationic channels. Br J Pharmacol 153: 1697–1705.

Grimm C, Kraft R, Schultz G, Harteneck C (2005). Activation of the melastatin-related cation channel TRPM3 by D-erythro-sphingosine [corrected]. Mol Pharmacol 67: 798–805.

Groneberg DA, Niimi A, Dinh QT, Cosio B, Hew M, Fischer A *et al.* (2004). Increased expression of transient receptor potential vanilloid-1 in airway nerves of chronic cough. Am J Respir Crit Care Med 170: 1276–1280.

Guilak F, Leddy HA, Liedtke W (2010). Transient receptor potential vanilloid 4: the sixth sense of the musculoskeletal system? Ann NY Acad Sci 1192: 404–409.

Haas ET, Rowland K, Gautam M (2011). Tooth injury increases expression of the cold sensitive TRP channel TRPA1 in trigeminal neurons. Arch Oral Biol 56: 1604–1609.

Hajós M, Obál F Jr, Jancsó G, Obál F (1985). Capsaicin impairs preoptic serotonin-sensitive structures mediating hypothermia in rats. Neurosci Lett 54: 97–102.

Hara K, Kokubo Y, Ishiura H, Fukuda Y, Miyashita A, Kuwano R *et al.* (2010). TRPM7 is not associated with amyotrophic lateral sclerosis-parkinsonism dementia complex in the Kii peninsula of Japan. Am J Med Genet B Neuropsychiatr Genet 153B: 310–313.

Hara Y, Wakamori M, Ishii M, Maeno E, Nishida M, Yoshida T *et al.* (2002). LTRPC2 Ca2+-permeable channel activated by changes in redox status confers susceptibility to cell death. Mol Cell 9: 163–173.

Hartmann J, Dragicevic E, Adelsberger H, Henning HA, Sumser M, Abramowitz J *et al.* (2008). TRPC3 channels are required for synaptic transmission and motor coordination. Neuron 59: 392–398.

Hatano N, Suzuki H, Muraki Y, Muraki K (2013). Stimulation of human TRPA1 channels by clinical concentrations of the antirheumatic drug auranofin. Am J Physiol Cell Physiol 304: C354–C361.

Hayashi T, Kondo T, Ishimatsu M, Takeya M, Igata S, Nakamura K *et al.* (2011). Function and expression pattern of TRPM8 in bladder afferent neurons associated with bladder outlet obstruction in rats. Auton Neurosci 164: 27–33.

Hermosura MC, Cui AM, Go RC, Davenport B, Shetler CM, Heizer JW *et al.* (2008). Altered functional properties of a TRPM2 variant in Guamanian ALS and PD. Proc Natl Acad Sci USA 105: 18029–18034.

Hill K, McNulty S, Randall AD (2004a). Inhibition of TRPM2 channels by the antifungal agents clotrimazole and econazole. Naunyn Schmiedebergs Arch Pharmacol 370: 227–237.

Hill K, Benham CD, McNulty S, Randall AD (2004b). Flufenamic acid is a pH-dependent antagonist of TRPM2 channels. Neuropharmacology 47: 450–460.

Hisanaga E, Nagasawa M, Ueki K, Kulkarni RN, Mori M, Kojima I (2009). Regulation of calcium-permeable TRPV2 channel by insulin in pancreatic beta-cells. J Biol Chem 279: 35741–35748.

Hoffmann T, Kistner K, Miermeister F, Winkelmann R, Wittmann J, Fischer MJ *et al.* (2013). TRPA1 and TRPV1 are differentially involved in heat nociception of mice. Eur J Pain 17: 1472–1482.

Holzer P (2011). Transient receptor potential (TRP) channels as drug targets for diseases of the digestive system. Pharmacol Ther 131: 142–170.

Honore P, Wismer CT, Mikusa J, Zhu CZ, Zhong C, Gauvin DM *et al.* (2005). A-425619 [1-isoquinolin-5-yl-3-(4-trifluoromethyl-benzyl)-urea], a novel transient receptor potential type V1 receptor antagonist, relieves pathophysiological pain associated with inflammation and tissue injury in rats. J Pharmacol Exp Ther 314: 410–421.

Hu HZ, Gu Q, Wang C, Colton CK, Tang J, Kinoshita-Kawada M *et al.* (2004). 2-aminoethoxydiphenyl borate is a common activator of TRPV1, TRPV2, and TRPV3. J Biol Chem 279: 35741–35748.

Huang SM, Bisogno T, Trevisani M, Al-Hayani A, De Petrocellis L, Fezza F *et al.* (2002). An endogenous capsaicin-like substance with high potency at recombinant and native vanilloid VR1 receptors. Proc Natl Acad Sci U S A 99: 8400–8405.

Huh D, Leslie DC, Matthews BD, Fraser JP, Jurek S, Hamilton GA *et al.* (2012). A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-chip microdevice. Sci Transl Med 4: 159ra147.

Hwang SW, Cho H, Kwak J, Lee SY, Kang CJ, Jung J *et al.* (2000). Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances. Proc Natl Acad Sci U S A 97: 6155–6160.

Iadarola MJ, Gonnella GL (2013). Resiniferatoxin for pain treatment: an interventional approach to personalized pain medicine. Open Pain J 6: 95–107.

Iadarola MJ, Mannes AJ (2011). The vanilloid agonist resiniferatoxin for interventional-based pain control. Curr Top Med Chem 11: 2171–2179.

Igarashi P, Somlo S (2002). Genetics and pathogenesis of polycystic kidney disease. J Am Soc Nephrol 13: 2384–2398.

Imamachi N, Park GH, Lee H, Anderson DJ, Simon MI, Basbaum AI *et al.* (2009). TRPV1-expressing primary afferents generate behavioral responses to pruritogens via multiple mechanisms. Proc Natl Acad Sci U S A 106: 11330–11335.

Ishii M, Shimizu S, Hagiwara T, Wajima T, Miyazaki A, Mori Y *et al.* (2006). Extracellular-added ADP-ribose increases intracellular free Ca2+ concentration through Ca2+ release from stores, but not through TRPM2-mediated Ca2+ entry, in rat beta-cell line RIN-5F. J Pharmacol Sci 101: 174–178.

Izzo AA, Capasso R, Aviello G, Borrelli F, Romano B, Piscitelli F *et al.* (2012). Inhibitory effect of cannabichromene, a major non-psychotropic cannabinoid extracted from Cannabis sativa, on inflammation-induced hypermotility in mice. Br J Pharmacol 166: 1444–1460.

Jeske NA, Patwardhan AM, Ruparel NB, Akopian AN, Shapiro MS, Henry MA (2009). A-kinase anchoring protein 150 controls protein kinase C-mediated phosphorylation and sensitization of TRPV1. Pain 146: 301–307.

Jia Y, Zhou J, Tai Y, Wang Y (2007). TRPC channels promote cerebellar granule neuron survival. Nat Neurosci 10: 559–567.

Jian MY, King JA, Al-Mehdi AB, Liedtke W, Townsley MI (2008). High vascular pressure-induced lung injury requires P450 epoxygenase-dependent activation of TRPV4. Am J Respir Cell Mol Biol 38: 386–392.

Jiang LH, Yang W, Zou J, Beech DJ (2010). TRPM2 channel properties, functions and therapeutic potentials. Expert Opin Ther Targets 14: 973–988.

Jimenez-Andrade JM, Mantyh P (2010). TRPV1 and bone cancer pain. In: Gomtsyan A, Faltynek C (eds). Vanilloid Receptor TRPV1 in Drug Discovery. Targeting Pain and Other Pathological Disorders. John Wiley & Sons: Hoboken, NJ, pp. 191–205.

Jordt SE, Bautista DM, Chuang HH, McKemy DD, Zygmunt PM, Högestätt ED *et al.* (2004). Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature 427: 260–265.

Joshi SK, Honore P (2010). The role of TRPV1 receptors in osteoarthritic pain. In: Gomtsyan A, Faltynek C (eds). Vanilloid Receptor TRPV1 in Drug Discovery. Targeting Pain and Other Pathological Disorders. John Wiley & Sons: Hoboken, NJ, pp. 175–190.

Kaczmarek JS, Riccio A, Clapham DE (2012). Calpain cleaves and activates the TRPC5 channel to participate in semaphorin 3A-induced neuronal growth cone collapse. Proc Natl Acad Sci USA 109: 7888–7892.

Kaneko Y, Szallasi A (2013). TRP channels as therapeutic targets. Curr Top Med Chem 13: 241–243.

Keszthelyi D, Troost FJ, Jonkers DM, Helyes Z, Hamer HM, Ludidi S *et al.* (2013). Alterations in mucosal neuropeptides in patients with irritable bowel syndrome and ulcerative colitis in remission: a role in pain symptom generation? Eur J Pain 17: 1299–1306.

Ketterer C, Müssig K, Heni M, Dudziak K, Randrianarisoa E, Wagner R *et al.* (2011). Genetic variation within the TRPM5 locus associates with prediabetic phenotypes in subjects at increased risk for type 2 diabetes. Metabolism 60: 1325–1333.

Khairatkar-Joshi N, Maharaj N, Thomas A (2010). The TRPV3 receptor as a pain target: a therapeutic promise or just some more new biology? Open Drug Discov J 2: 89–97.

Kida N, Sokabe T, Kashio M, Haruna K, Mizuno Y, Suga Y *et al.* (2012). Importance of transient receptor potential vanilloid 4 (TRPV4) in epidermal barrier function in human skin keratinocytes. Pflugers Arch 463: 715–725.

Kitaguchi T, Swartz KJ (2005). An inhibitor of TRPV1 channels isolated from funnel web spider venom. Biochemistry 44: 15544–15549.

Kiyonaka S, Kato K, Nishida M, Mio K, Numaga T, Sawaguchi Y *et al.* (2009). Selective and direct inhibition of TRPC3 channels underlies biological activities of a pyrazole compound. Proc Natl Acad Sci U S A 106: 5400–5405.

Klausen TK, Pagani A, Minassi A, Ech-Chahad A, Prenen J, Owsianik G *et al.* (2009). Modulation of the transient receptor potential vanilloid channel TRPV4 by 4α-phorbol esters: a structure-activity study. J Med Chem 52: 2933–2939.

Klose C, Straub I, Riehle M, Ranta F, Krautwurst D, Ullrich S *et al.* (2011). Fenamates as TRP channel blockers: mefenamic acid selectively blocks TRPM3. Br J Pharmacol 162: 1757–1769.

Knotkova H, Pappagallo M, Szallasi A (2008). Capsaicin (TRPV1 agonist) therapy for pain relief: farewell or revival? Clin J Pain 24: 142–154.

Knowlton WM, McKemy DD (2011). TRPM8: from cold to cancer, peppermint to pain. Curr Pharm Biotechnol 12: 68–77.

Kobayashi K, Fukuoka T, Obata K, Yamanaka H, Dai Y, Tokunaga A *et al.* (2005). Distinct expression of TRPM8, TRPA1, and TRPV1 mRNAs in rat primary afferent neurons with adelta/c-fibers and colocalization with trk receptors. J Comp Neurol 493: 596–606.

Koivisto A, Hukkanen M, Saarnilehto M, Chapman H, Kuokkanen K, Wei H *et al.* (2012). Inhibiting TRPA1 ion channel reduces loss of cutaneous nerve fiber function in diabetic animals: sustained activation of the TRPA1 channel contributes to the pathogenesis of peripheral diabetic neuropathy. Pharmacol Res 65: 149–158.

Kolisek M, Beck A, Fleig A, Penner R (2005). Cyclic ADP-ribose and hydrogen peroxide synergize with ADP-ribose in the activation of TRPM2 channels. Mol Cell 18: 61–69.

Kollarik M, Undem BJ (2004). Activation of bronchopulmonary vagal afferent nerves with bradykinin, acid and vanilloid receptor agonists in wild-type and TRPV1–/– mice. J Physiol 555: 115–123.

Köttgen M, Buchholz B, Garcia-Gonzalez MA, Kotsis F, Fu X, Doerken M *et al*. (2008). TRPP2 and TRPV4 form a polymodal sensory channel complex. J Cell Biol 182: 437–447.

Kovacs G, Montalbetti N, Simonin A, Danko T, Balazs B, Zsembery A *et al*. (2012). Inhibition of the human epithelial calcium channel TRPV6 by 2-aminoethoxydiphenyl borate (2-APB). Cell Calcium 52: 468–480.

Kraft R, Grimm C, Frenzel H, Harteneck C (2006). Inhibition of TRPM2 cation channels by N-(p-amylcinnamoyl)anthranilic acid. Br J Pharmacol 148: 264–273.

Krall P, Canales CP, Kairath P, Carmona-Mora P, Molina J, Carpio JD *et al*. (2010). Podocyte-specific overexpression of wild type or mutant trpc6 in mice is sufficient to cause glomerular disease. PLoS One 5: e12859.

Krarup AL, Ny L, Astrand M, Bajor A, Hvid-Jensen F, Hansen MB *et al*. (2011). Randomised clinical trial: the efficacy of a transient receptor potential vanilloid 1 antagonist AZD1386 in human oesophageal pain. Pharmacol Ther 33: 1113–1122.

Kremeyer B, Lopera F, Cox JJ, Momin A, Rugiero F, Marsh S *et al*. (2010). A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome. Neuron 66: 671–680.

Kruse M, Schulze-Bahr E, Corfield V, Beckmann A, Stallmeyer B, Kurtbay G *et al*. (2009). Impaired endocytosis of the ion channel TRPM4 is associated with human progressive familial heart block type I. J Clin Invest 119: 2737–2744.

Kusudo T, Wang Z, Mizuno A, Suzuki M, Yamashita H (2012). TRPV4 deficiency increases skeletal muscle metabolic capacity and resistance against diet-induced obesity. Appl Physiol 112: 1223–1232.

Kuwahara K, Wang Y, McAnally J, Richardson JA, Bassel-Duby R, Hill JA *et al*. (2006). TRPC6 fulfills a calcineurin signaling circuit during pathologic cardiac remodeling. J Clin Invest 116: 3114–3126.

Kyriazis GA, Soundarapandian MM, Tyrberg B (2012). Sweet taste receptor signaling in beta cells mediates fructose-induced potentiation of glucose-stimulated insulin secretion. Proc Natl Acad Sci U S A 109: E524–E532.

Lai-Cheong JE, Sethuraman G, Ramam M, Stone K, Simpson MA, McGrath JA (2012). Recurrent heterozygous missense mutation, p.Gly573Ser, in the TRPV3 gene in an Indian boy with sporadic Olmsted syndrome. Br J Dermatol 167: 440–442.

Landourè G, Zdebik AA, Martinez TL, Burnett BG, Stanescu HC, Inada H *et al*. (2010). Mutations in TRPV4 cause Charcot–Marie–Tooth disease type 2C. Nature Genet 42: 170–174.

Lange I, Yamamoto S, Partida-Sanchez S, Mori Y, Fleig A, Penner R (2009). TRPM2 functions as a lysosomal Ca2+-release channel in beta cells. Sci Signal 2: ra23.

LaPlante JM, Ye CP, Quinn SJ, Goldin E, Brown EM, Slaugenhaupt SA *et al*. (2004). Functional links between mucolipin-1 and Ca2+-dependent membrane trafficking in mucolipidosis IV. Biochem Biophys Res Commun 322: 1384–1391.

Lashinger ES, Steiginga MS, Hieble JP, Leon LA, Gardner SD, Nagilla R *et al*. (2008). AMTB, a TRPM8 channel blocker: evidence in rats for activity in overactive bladder and painful bladder syndrome. Am J Physiol Renal Physiol 295: F803–F810.

Leamy AW, Shukla P, McAlexander MA, Carr MJ, Ghatta S (2011). Curcumin ((E,E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) activates and desensitizes the nociceptor ion channel TRPA1. Neurosci Lett 503: 157–162.

Lee SP, Buber MT, Yang Q, Cerne R, Cortés RY, Sprous DG *et al*. (2008). Thymol and related alkyl phenols activate the hTRPA1 channel. Br J Pharmacol 153: 1739–1749.

Lee YM, Kim YK, Chung JH (2009). Increased expression of TRPV1 channel in intrinsically aged and photoaged human skin *in vivo*. Exp Dermatol 18: 431–436.

Lee YM, Kang SM, Lee SR, Kong KH, Lee JY, Kim EJ *et al*. (2011). Inhibitory effects of TRPV1 blocker on UV-induced responses in the hairless mice. Arch Dermatol Res 303: 727–736.

Lehen'kyi V, Prevarskaya N (2011). Oncogenic TRP channels. Adv Exp Med Biol 704: 929–945.

Lei Z, Ishizuka O, Imamura T, Noguchi W, Yamagishi T, Yokoyama H *et al*. (2013). Functional roles of transient receptor potential melastatin 8 (TRPM8) channels in the cold stress-induced detrusor overactivity pathways in conscious rats. Neurourol Urodyn 32: 500–504.

Leuenroth SJ, Okuhara D, Shotwell JD, Markowitz GS, Yu Z, Somlo S *et al*. (2007). Triptolide is a traditional Chinese medicine-derived inhibitor of polycystic kidney disease. Proc Natl Acad Sci U S A 104: 4389–4394.

Leuner K, Kazanski V, Müller M, Essin K, Henke B, Gollasch M *et al*. (2007). Hyperforin, a key constituent of St. John's wort, specifically activates TRPC6 channels. FASEB J 21: 4101–4111.

Leuner K, Heiser JH, Derksen S, Mladenov MI, Fehske CJ, Schubert R *et al*. (2010). Simple 2,4-diacylphloroglucinols as classic transient receptor potential-6 activators-identification of a novel pharmacophore. Mol Pharmacol 77: 368–377.

Li J, Kanju P, Patterson M, Chew WL, Cho SH, Gilmour I *et al*. (2011b). TRPV4-mediated calcium influx into human bronchial epithelia upon exposure to diesel exhaust particles. Environ Health Perspect 119: 784–793.

Li M, Jiang J, Yue L (2006). Functional characterization of homo- and heteromeric channel kinases TRPM6 and TRPM7. J Gen Physiol 127: 525–537.

Li M, Li Q, Yang G, Kolosov VP, Perelman JM, Zhou XD (2011a). Cold temperature induces mucin hypersecretion from normal human bronchial epithelial cells *in vitro* through a transient receptor potential melastatin 8 (TRPM8)-mediated mechanism. J Allergy Clin Immunol 128: 626–634.

Li Y, Jia YC, Cui K, Li N, Zheng ZY, Wang YZ *et al*. (2005). Essential role of TRPC channels in the guidance of nerve growth cones by brain-derived neurotrophic factor. Nature 434: 894–898.

Liang J, Xiao G, Ji W (2011). Capsaicin induces reflex scratching in inflamed skin. Pharmacology 2011: 82–87.

Liberati S, Morelli MB, Nabissi M, Santoni M, Santoni G (2013). Oncogenic and anti-oncogenic effects of transient receptor potential channels. Curr Top Med Chem 13: 344–366.

Lin Z, Chen Q, Lee M, Cao X, Zhang J, Ma D *et al*. (2012). Exome sequencing reveals mutations in TRPV3 as a cause of Olmsted syndrome. Am J Hum Genet 90: 558–564.

Liu BC, Song X, Lu XY, Li DT, Eaton DC, Shen BZ *et al*. (2013). High glucose induces podocyte apoptosis by stimulating TRPC6 via elevation of reactive oxygen species. Biochim Biophys Acta 1833: 1434–1442.

Liu H, El Zein L, Kruse M, Guinamard R, Beckmann A, Bozio A *et al*. (2010). Gain-of-function mutations in TRPM4 cause autosomal dominant isolated cardiac conduction disease. Circ Cardiovasc Genet 3: 374–385.

Liu L, Welch JM, Erickson RP, Reinhart PH, Simon SA (2000). Different responses to repeated applications of zingerone in behavioral studies, recordings from intact and cultured TG neurons, and from VR1 receptors. Physiol Behav 69: 177–186.

Liu T, Ji RR (2012). Oxidative stress induces itch via activation of transient receptor potential subtype ankyrin 1 in mice. Neurosci Bull 28: 145–154.

Lysy J, Sistiery-Ittah M, Israelit Y, Shmueli A, Strauss-Liviatan N, Mindrul V *et al*. (2003). Topical capsaicin-a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. Gut 52: 1323–1326.

Ma S, Yu H, Zhao Z, Luo Z, Chen J, Ni Y *et al*. (2012b). Activation of the cold-sensing TRPM8 channel triggers UCP1-dependent thermogenesis and prevents obesity. J Mol Cell Biol 4: 88–96.

Ma X, He D, Ru X, Chen Y, Cai Y, Bruce IC *et al*. (2012a). Apigenin, a plant-derived flavone, activates transient receptor potential vanilloid 4 cation channel. Br J Pharmacol 166: 349–358.

Macpherson LJ, Hwang SW, Miyamoto T, Dubin AE, Patapoutian A, Story GM (2006). More than cool: promiscuous relationships of menthol and other sensory compounds. Mol Cell Neurosci 32: 335–343.

Maggi CA, Barbanti G, Santicioli P, Beneforti P, Misuri D, Meli A *et al*. (1989). Cystometric evidence that capsaicin-sensitive nerves modulate the afferent branch of micturition reflex in humans. J Urol 142: 150–154.

Majeed Y, Bahnasi Y, Seymour VA, Wilson LA, Milligan CJ, Agarwal AK *et al*. (2011a). Rapid and contrasting effects of rosiglitazone on transient receptor potential TRPM3 and TRPC5 channels. Mol Pharmacol 79: 1023–1030.

Majeed Y, Amer MS, Agarwal AK, McKeown L, Porter KE, O'Regan DJ *et al*. (2011b). Stereo-selective inhibition of transient receptor potential TRPC5 cation channels by neuroactive steroids. Br J Pharmacol 162: 1509–1520.

Majeed Y, Tumova S, Green BL, Seymour VA, Woods DM, Agarwal AK *et al*. (2012). Pregnenolone sulphate-independent inhibition of TRPM3 channels by progesterone. Cell Calcium 51: 1–11.

Malek S, Sample SJ, Schwartz Z, Nemke B, Jacobson PB, Cozzi EM *et al*. (2012). Effect of analgesic therapy on clinical outcome measures in a randomized controlled trial using client-owned dogs with hip osteoarthritis. BMC Vet Res 8: 185–191.

Marsch R, Foeller E, Rammes G, Bunck M, Kössl M, Holsboer F *et al*. (2007). Reduced anxiety, conditioned fear, and hippocampal long-term potentiation in transient receptor potential vanilloid type 1 receptor-deficient mice. J Neurosci 27: 832–839.

Marshall NJ, Liang L, Bodkin J, Dessapt-Baradez C, Nandi M, Collot-Teixeira S *et al*. (2013). A role for TRPV1 in influencing the onset of cardiovascular disease in obesity. Hypertension 61: 246–252.

Materazzi S, Nassini R, Andrè E, Campi B, Amadesi S, Trevisani M *et al*. (2008). Cox-dependent fatty acid metabolites cause pain through activation of the irritant receptor TRPA1. Proc Natl Acad Sci U S A 105: 12045–12050.

Mathar I, Vennekens R, Meissner M, Kees F, Van der Mieren G, Camacho Londoño JE *et al*. (2010). Increased catecholamine secretion contributes to hypertension in TRPM4-deficient mice. J Clin Invest 120: 3267–3279.

Matthews JM, Qin N, Colburn RW, Dax SL *et al*. (2012). The design and synthesis of novel, phosphonate-containing transient receptor potential melastatin 8 (TRPM8) antagonists. Bioorg Med Chem Lett 22: 2922–2926.

Matthews PJ, Aziz Q, Facer P, Davis JB, Thompson DG, Anand P (2004). Increased capsaicin receptor TRPV1 nerve fibers in the inflamed human oesophagus. Eur J Gastroenterol Hepatol 16: 897–902.

McGaraughty S, Chu KL, Perner RJ, Didomenico S, Kort ME, Kym PR (2010). TRPA1 modulation of spontaneous and mechanically evoked firing of spinal neurons in uninjured, osteoarthritic, and inflamed rats. Mol Pain 6: 14.

McKemy DD, Neuhausser WM, Julius D (2002). Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 416: 52–58.

McNamara CR, Mandel-Brehm J, Bautista DM, Siemens J, Deranian KL, Zhao M *et al*. (2007). TRPA1 mediates formalin-induced pain. Proc Natl Acad Sci U S A 104: 13525–13530.

McNamara FN, Randall A, Gunthorpe MJ (2005). Effects of piperine, the pungent component of black pepper, at the human vanilloid receptor (TRPV1). Br J Pharmacol 144: 781–790.

Meotti FC, Forner S, Lima-Garcia JF, Viana AF, Calixto JB (2013). Antagonism of the transient receptor potential ankyrin 1 (TRPA1) attenuates hyperalgesia and urinary bladder overactivity in cyclophosphamide-induced haemorrhagic cystitis. Chem Biol Interact 203: 440–447.

Miller BA, Zhang W (2011). TRP channels as mediators of oxidative stress. Adv Exp Med Biol 704: 531–544.

Miller M, Shi J, Zhu Y, Kustov M, Tian JB, Stevens A *et al*. (2011). Identification of ML204, a novel potent antagonist that selectively modulates native TRPC4/C5 ion channels. J Biol Chem 286: 33436–33446.

Millqvist E (2011). The airway sensory hyperreactivity syndrome. Pulm Pharmacol 24: 263–266.

Minke B (2010). The history of the *Drosophila* TRP channel: the birth of a new channel superfamily. J Neurogenet 24: 216–233.

Miranda A, Nordstrom E, Mannem A, Smith C, Banerjee B, Sengupta JN (2007). The role of transient receptor potential vanilloid 1 in mechanical and chemical visceral hyperalgesia following experimental colitis. Neuroscience 148: 1021–1032.

Mochizuki T, Wu G, Hayashi T, Xenophontos SL, Veldhuisen B, Saris JJ *et al*. (1996). PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science 272: 1339–1342.

Mochizuki T, Sokabe T, Araki I, Fujishita K, Shibasaki K, Uchida K *et al*. (2009). The TRPV4 cation channel mediates stretch-evoked Ca2+ influx and ATP release in primary urothelial cell cultures. J Biol Chem 284: 21257–21264.

Möller CC, Wei C, Altintas MM, Li J, Greka A, Ohse T *et al*. (2007). Induction of TRPC6 channel in acquired forms of proteinuric kidney disease. J Am Soc Nephrol 18: 29–36.

Monet M, Gkika D, Lehen'kyi V, Pourtier A, Vanden Abeele F, Bidaux G *et al*. (2009). Lysophospholipids stimulate prostate cancer cell migration via TRPV2 channel activation. Biochim Biophys Acta 1793: 528–539.

Montell C (2003). Mg^{2+} homeostasis: the Mg^{2+}nificent TRPM chanzymes. Curr Biol 13: R799–R801.

Montell C, Rubin GM (1989). Molecular characterization of the *Drosophila trp* locus: a putative integral membrane protein required for phototransduction. Neuron 2: 1313–1323.

Moqrich A, Hwang SW, Earley TJ, Petrus MJ, Murray AN, Spencer KS *et al*. (2005). Impaired thermosensation in mice lacking TRPV3, a heat and camphor sensor in the skin. Science 307: 1468–1472.

Moran MM, McAlexander MA, Bíró T, Szallasi A (2011). Transient receptor potential channels as therapeutic targets. Nat Rev Drug Discov 10: 601–620.

Morelli MB, Amantini C, Liberati S, Santoni M, Nabissi M (2013). TRP channels: new potential therapeutic approaches in CNS neuropathies. CNS Neurol Disord Drug Targets 12: 274–293.

Motter AL, Ahern GP (2008). TRPV1-null mice are protected from diet-induced obesity. FEBS Lett 582: 2257–2262.

Moussaieff A, Rimmerman N, Bregman T, Straiker A, Felder CC, Shoham S *et al.* (2008). Incensole acetate, an incense component, elicits psychoactivity by activating TRPV3 channels in the brain. FASEB J 22: 3024–3034.

Mukerji G, Yiangou Y, Corcoran SL, Selmer IS, Smith GD, Benham CD *et al.* (2006a). Cool and menthol receptor TRPM8 in human urinary bladder disorders and clinical correlations. BMC Urol 6: 6.

Mukerji G, Waters J, Chessell IP, Bountra C, Agarwal SK, Anand P (2006b). Pain during ice water test distinguishes clinical bladder hypersensitivity from overactivity disorders. BMC Urol 6: 31.

Mukhopadhyay I, Gomes P, Aranake S, Shetty M, Karnik P, Damle M *et al.* (2011). Expression of functional TRPA1 receptor on human lung fibroblasts and epithelial cells. J Recept Signal Transduct Res 31: 350–358.

Nakayama H, Wilkin BJ, Bodi I, Molkentin JD (2006). Calcineurin-dependent cardiomyopathy is activated by TRPC in the adult mouse heart. FASEB J 20: 1660–1670.

Nassini R, Materazzi S, Vriens J, Prenen J, Benemei S, De Siena G *et al.* (2012a). The 'headache tree' via umbellulone and TRPA1 activates the trigeminovascular system. Brain 135: 376–390.

Nassini R, Pedretti P, Moretto N, Fusi C, Carnini C, Facchinetti F *et al.* (2012b). Transient receptor potential ankyrin 1 channel localized to non-neuronal airway cells promotes non-neurogenic inflammation. PLoS One 7: e42454.

Nassini R, Benemei S, Fusi C, Trevisan dos Santos G, Materazzi S (2013). Transient receptor potential channels in chemotherapy-induced neuropathy. Open Pain J 5: 32–37.

Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X *et al.* (2003). Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. Nat Genet 33: 129–137.

Naylor J, Milligan CJ, Zeng F, Jones C, Beech DJ (2008). Production of a specific extracellular inhibitor of TRPM3 channels. Br J Pharmacol 155: 567–573.

Naziroğlu M, Lückhoff A, Jüngling E (2007). Antagonist effect of flufenamic acid on TRPM2 cation channels activated by hydrogen peroxide. Cell Biochem Funct 25: 383–387.

Nelson PL, Beck A, Chen H (2011). Transient receptor proteins illuminated: current views on TRPs and disease. Vet J 187: 153–164.

Nieto-Posadas A, Jara-Oseguera A, Rosenbaum T (2011a). TRP channel gating physiology. Curr Top Med Chem 11: 2131–2150.

Nieto-Posadas A, Picazo-Juárez G, Llorente I, Jara-Oseguera A, Morales-Lázaro S, Escalante-Alcalde D *et al.* (2011b). Lysophosphatidic acid directly activates TRPV1 through a C-terminal binding site. Nat Chem Biol 8: 78–85.

Nilius B (2013). Transient receptor potential TRP channels as therapeutic drug targets: next round! Curr Top Med Chem 13: 244–246.

Nilius B, Appendino G (2013). Spices: the savory and beneficial science of pungency. Rev Physiol Biochem Pharmacol 164: 1–76.

Nilius B, Bíró T (2013). TRPV3: a 'more than skinny' channel. Exp Dermatol 22: 447–452.

Nilius B, Owsianik G (2010). Transient receptor potential channelopathies. Pflugers Arch 460: 437–450.

Nilius B, Owsianik G (2011). The transient receptor potential family of ion channels. Genome Biol 12: 218–229.

Nilius B, Voets T (2013). The puzzle of TRPV4 channelopathies. EMBO Rep 14: 152–163.

Nilius B, Prenen J, Owsianik G (2011). Irritating channels: the case of TRPA1. J Physiol 589: 1543–1549.

Nomoto Y, Yoshida A, Ikeda S, Kamikawa Y, Harada K, Ohwatashi A *et al.* (2008). Effect of menthol on detrusor smooth-muscle contraction and the micturition reflex in rats. Urology 72: 701–705.

Nyman E, Franzén B, Nolting A, Klement G, Liu G, Nilsson M *et al.* (2013). *In vitro* pharmacological characterization of a novel TRPA1 antagonist and proof of mechanism in a human dental pulp model. J Pain Res 6: 59–70.

O'Conor CJ, Griffin TM, Liedtke W, Guilak F (2013). Increased susceptibility of Trpv4-deficient mice to obesity and obesity-induced osteoarthritis with very high-fat diet. Ann Rheum Dis 72: 300–304.

Ohba T, Watanabe H, Murakami M, Takahashi Y (2007). Upregulation of TRPC1 in the development of cardiac hypertrophy. J Mol Cell Cardiol 42: 498–507.

Ohkawara S, Tanaka-Kagawa T, Furukawa Y, Jinno H (2012). Methylglyoxal activates the human transient receptor potential ankyrin 1 channel. J Toxicol Sci 37: 831–835.

Okun A, Liu P, Davis P, Ren J, Remeniuk B, Brion T *et al.* (2012). Afferent drive elicits ongoing pain in a model of advanced osteoarthritis. Pain 153: 924–933.

Onohara N, Nishida M, Inoue R, Kobayashi H, Sumimoto H, Sato Y *et al.* (2006). TRPC3 and TRPC6 are essential for angiotensin II-induced cardiac hypertrophy. EMBO J 25: 5305–5316.

Owsianik G, D'hoedt D, Voets T, Nilius B (2006). Structure-function relationship of the TRP channel superfamily. Rev Physiol Biochem Pharmacol 156: 61–90.

Palmer RK, Atwal K, Bakaj I, Carlucci-Derbyshire S, Buber MT, Cerne R *et al.* (2010). Triphenylphosphine oxide is a potent and selective inhibitor of the transient receptor potential melastatin-5 ion channel. Assay Drug Dev Technol 8: 703–713.

Park CK, Xu ZZ, Liu T, Lü N, Serhan CN, Ji RR (2011a). Resolvin D2 is a potent endogenous inhibitor for transient receptor potential subtype V1/A1, inflammatory pain, and spinal cord synaptic plasticity in mice: distinct roles of resolvin D1, D2, and E1. J Neurosci 31: 18433–18438.

Park HW, Kim JY, Choi SK, Lee YH, Zeng W, Kim KH *et al.* (2011b). Serine-threonine kinase with-no-lysine 4 (WNK4) controls blood pressure via transient receptor potential canonical 3 (TRPC3) in the vasculature. Proc Natl Acad Sci U S A 108: 10750–11075.

Parks DJ, Parsons WH, Colburn RW, Meegalla SK, Ballentine SK, Illig CR *et al.* (2011). Design and optimization of benzimidazole-containing transient receptor potential melastatin 8 (TRPM8) antagonists. J Med Chem 54: 233–247.

Parnas M, Peters M, Dadon D, Lev S, Vertkin I, Slutsky I *et al.* (2009). Carvacrol is a novel inhibitor of Drosophila TRPL and mammalian TRPM7 channels. Cell Calcium 45: 300–309.

Patapoutian A, Tate S, Woolf CJ (2009). Transient receptor potential channels: targeting pain at the source. Nat Rev Drug Discov 8: 55–69.

Patwardhan AM, Scotland PE, Akopian AN, Hargreaves KM (2009). Activation of TRPV1 in the spinal cord by oxidized linoleic acid metabolites contributes to inflammatory hyperalgesia. Proc Natl Acad Sci U S A 106: 18820–18824.

Pearce LV, Petukhov PA, Szabo T, Kedei N, Bizik F, Kozikowski AP *et al.* (2004). Evodiamine functions as an agonist for the vanilloid receptor TRPV1. Org Biomol Chem 2: 2281–2286.

Pedersen SF, Nilius B (2007). Transient receptor potential channels in mechanosensing and cell volume regulation. Methods Enzymol 428: 183–207.

Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM *et al.* (2002a). A TRP channel that senses cold stimuli and menthol. Cell 108: 705–715.

Peier AM, Reeve AJ, Andersson DA, Moqrich A, Earley TJ, Hergarden AC *et al.* (2002b). A heat-sensitive TRP channel expressed in keratinocytes. Science 296: 2046–2049.

Perraud AL, Takanishi CL, Shen B, Kang S, Smith MK, Schmitz C *et al.* (2005). Accumulation of free ADP-ribose from mitochondria mediates oxidative stress-induced gating of TRPM2 cation channels. J Biol Chem 280: 6138–6148.

Peters DJ, Spruit L, Saris JJ, Ravine D, Sandkuijl LA, Fossdal R *et al.* (1993). Chromosome 4 localization of a second gene for autosomal dominant polycystic kidney disease. Nat Genet 5: 359–362.

Petrus M, Peier AM, Bandell M, Hwang SW, Huynh T, Olney N *et al.* (2007). A role of TRPA1 in mechanical hyperalgesia is revealed by pharmacological inhibition. Mol Pain 3: 40.

Pingle SC, Matta JA, Ahern GP (2007). Capsaicin receptor: TRPV1 a promiscuous TRP channel. Handb Exp Pharmacol 179: 155–171.

Planells-Cases R, Ferrer-Montiel A (2007). TRP channel trafficking. In: Liedtke WB, Heller S (eds). TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades. CRC Press, Taylor & Francis: Boca Raton, FL, pp. 319–330.

Plato CC, Galasko D, Garruto RM, Plato M, Gamst A, Craig UK *et al.* (2002). ALS and PDC of Guam: 40-year follow-up. Neurology 58: 765–773.

Preti D, Szallasi A, Patacchini R (2012). TRP channels as therapeutic targets in airway disorders: a patent review. Expert Opin Ther Pat 22: 663–695.

Puttfarcken PS, Han P, Joshi SK, Neelands TR, Gauvin DM, Baker SJ *et al.* (2010). A-995662 [R-8-(4-methyl-5-(4-(trifluoromethyl)phenyl) oxazol-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol], a novel, selective TRPV1 receptor antagonist, reduces spinal release of glutamate and CGRP in a rat knee joint pain model. Pain 150: 319–326.

Qin N, Neeper MP, Liu Y, Hutchinson TL, Lubin ML, Flores CM (2008). TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. J Neurosci 28: 6231–6238.

Qin X, Yue Z, Sun B, Yang W, Xie J, Ni E *et al.* (2013). Sphingosine and FTY720 are potent inhibitors of the transient receptor potential melastatin 7 (TRPM7) channels. Br J Pharmacol 168: 1294–1312.

Ramachandran R, Hyun E, Zhao L, Lapointe TK, Chapman K, Hirota CL *et al.* (2013). TRPM8 activation attenuates inflammatory responses in mouse models of colitis. Proc Natl Acad Sci USA 110: 7476–7481.

Raychowdhury MK, González-Perrett S, Montalbetti N, Timpanaro GA, Chasan B, Goldmann WH *et al.* (2004). Molecular pathophysiology of mucolipidosis type IV: pH dysregulation of the mucolipin-1 cation channel. Hum Mol Genet 13: 617–627.

Razavi R, Chan Y, Afifiyan FN, Liu XJ, Wan X, Yantha J *et al.* (2006). TRPV1+ sensory neurons control beta cell stress and islet inflammation in autoimmune diabetes. Cell 127: 1123–1135.

Reiser J, Polu KR, Möller CC, Kenlan P, Altintas MM, Wei C *et al.* (2005). TRPC6 is a glomerular slit diaphragm-associated channel required for normal renal function. Nat Genet 37: 739–744.

Riccio A, Li Y, Moon J, Kim KS, Smith KS, Rudolph U *et al.* (2009). Essential role for TRPC5 in amygdala function and fear-related behavior. Cell 137: 761–772.

Romano B, Borrelli F, Fasolino I, Capasso R, Piscitelli F, Cascio M *et al.* (2013). The cannabinoid TRPA1 agonist cannabichromene inhibits nitric oxide production in macrophages and ameliorates murine colitis. Br J Pharmacol 169: 213–229.

Romero JR, Germer S, Castonguay AJ, Barton NS, Martin M, Zee RY (2010). Gene variation of the transient receptor potential cation channel, subfamily M, member 2 (TRPM2) and type 2 diabetes mellitus: a case-control study. Clin Chim Acta 411: 1437–1440.

Round P, Priestly A, Robinson J (2011). An investigation of the safety and pharmacokinetics of the novel TRPV1 antagonist XEN-D0501 in healthy subject. Br J Clin Pharmacol 72: 921–931.

Rowbotham MC, Nothaft W, Duan WR, Wang Y, Faltynek C, McGaraughty S *et al.* (2011). Oral and cutaneous thermosensory profile of selective TRPV1 inhibition by ABT-102 in a randomized healthy volunteer trial. Pain 152: 1192–1200.

Ryckmans T, Aubdool AA, Bodkin JV, Cox P, Brain SD, Dupont T *et al.* (2011). Design and pharmacological evaluation of PF-4840154, a non-electrophilic reference agonist of the TrpA1 channel. Bioorg Med Chem Lett 21: 4857–4859.

Saldanha SA, Grimm C, Mercer BA, Choi JY, Allais C, Roush WR *et al.* (2010–2009). Campaign to Identify Agonists of Transient Receptor Potential Channels 3 and 2 (TRPML3 & TRPML2). Reports from the NIH Molecular Libraries Program [Internet]. National Center for Biotechnology Information (US): Bethesda, MD.

Santoni G, Farfariello V (2011). TRP channels and cancer: new targets for diagnosis and chemotherapy. Endocr Metab Immune Disord Drug Targets 11: 54–67.

Santos-Silva A, Charrua A, Cruz CD, Gharat L, Avelino A, Cruz F (2012). Rat detrusor overactivity induced by chronic spinalization can be abolished by a transient receptor potential vanilloid 1 (TRPV1) antagonist. Auton Neurosci 166: 35–38.

Schattling B, Steinbach K, Thies E, Kruse M, Menigoz A, Ufer F *et al.* (2012). TRPM4 cation channel mediates axonal and neuronal degeneration in experimental autoimmune encephalomyelitis and multiple sclerosis. Nat Med 18: 1805–1811.

Schleifer H, Doleschal B, Lichtenegger M, Oppenrieder R, Derler I, Frischauf I *et al.* (2012). Novel pyrazole compounds for pharmacological discrimination between receptor-operated and store-operated Ca(2+) entry pathways. Br J Pharmacol 167: 1712–1722.

Schulze A, Oehler B, Urban N, Schaefer M, Hill K (2013). Apomorphine is a bimodal modulator of TRPA1 channels. Mol Pharmacol 83: 542–551.

Schwartz EC, Wolfs MJ, Tonner S, Wenning AS, Quintana A, Griesemer D *et al.* (2007). TRP channels in lymphocytes. Hand Exp Pharmacol 179: 445–456.

Seabrook GR, Sutton KG, Jarolimek W, Hollingworth GJ, Teague S, Webb J *et al.* (2002). Functional properties of the high-affinity TRPV1 (VR1) vanilloid receptor antagonist (4-hydroxy-5-iodo-3-methoxyphenylacetate ester) iodo-resiniferatoxin. J Pharmacol Exp Ther 303: 1052–1060.

Seth M, Zhang ZS, Mao L, Graham V, Burch J, Stiber J *et al*. (2009). TRPC1 channels are critical for hypertrophic signaling in the heart. Circ Res 105: 1023–1030.

Shen D, Wang X, Li X, Zhang X, Yao Z, Dibble S *et al*. (2012). Lipid storage disorders block lysosomal trafficking by inhibiting a TRP channel and lysosomal calcium release. Nat Commun 3: 731.

Sherkheli MA, Vogt-Eisele AK, Bura D, Beltrán Márques LR, Gisselmann G, Hatt H (2010). Characterization of selective TRPM8 ligands and their structure activity response (S.A.R.) relationship. J Pharm Pharm Sci 13: 242–253.

Shibata Y, Ugawa S, Imura M, Kubota Y, Ueda T, Kojima Y *et al*. (2011). TRPM8-expressing dorsal root ganglion neurons project dichotomizing axons to both skin and bladder in rats. Neuroreport 22: 61–67.

Shim WS, Tak MH, Lee MH, Kim M, Kim M, Koo JY *et al*. (2007). TRPV1 mediates histamine-induced itching via the activation of phospholipase A2 and 12-lipoxygenase. J Neurosci 27: 2331–2337.

Shintaku K, Uchida K, Suzuki Y, Zhou Y, Fushiki T, Watanabe T *et al*. (2012). Activation of transient receptor potential A1 by a non-pungent capsaicin-like compound, capsiate. Br J Pharmacol 165: 1476–1486.

Siemens J, Zhou S, Piskorowski R, Nikai T, Lumpkin EA, Basbaum AI *et al*. (2006). Spider toxins activate the capsaicin receptor to produce inflammatory pain. Nature 444: 208–212.

Singh BB, Pabelick CM, Prakash YS (2012). Canonical transient receptor potential channel expression, regulation and function. TRP Channels in Drug Discovery. Szallasi A, Bíró T. Methods in Pharmacology and Toxicology, Springer Protocols. Humana Press/Springer: New York, Heidelberg, Dordrecht, London, pp. 61–88.

Siroky BJ, Ferguson WB, Fuson AL, Xie Y, Fintha A, Komlosi P *et al*. (2006). Loss of primary cilia results in deregulated and unabated apical calcium entry in ARPKD collecting duct cells. Am J Physiol Renal Physiol 290: F1320–F1328.

Skryma R, Prevarskaya N, Gkika D, Shuba Y (2011). From urgency to frequency: facts and controversies of TRPs in the lower urinary tract. Nat Rev Urol 8: 617–630.

Smit LA, Kogevinas M, Antó JM, Bouzigon E, González JR, Le Moual N *et al*. (2012). Transient receptor potential genes, smoking, occupational exposures and cough in adults. Respir Res 13: 26.

Smith AC, Parajuli SP, Hristov KL, Cheng Q, Soder RP, Afeli SA *et al*. (2013a). TRPM4 channel: a new player in urinary bladder smooth muscle function in rats. Am J Physiol Renal Physiol 304: F918–F929.

Smith AC, Hristov KL, Cheng Q, Xin W, Parajuli SP, Earley S *et al*. (2013b). Novel role for the transient potential receptor melastatin 4 channel in guinea pig detrusor smooth muscle physiology. Am J Physiol Cell Physiol 304: C467–C477.

Smith PK, Nilius B (2013). Transient receptor potentials (TRPs) and anaphylaxis. Curr Allergy Asthma Res 13: 93–100.

Smith PL, Maloney KN, Pothen RG, Clardy J, Clapham DE (2006). Bisandrographolide from Andrographis paniculata activates TRPV4 channels. J Biol Chem 281: 29897–29904.

Spassova MA, Hewavitharana T, Xu W, Soboloff J, Gill DL (2006). A common mechanism underlies stretch activation and receptor activation of TRPC6 channels. Proc Natl Acad Sci U S A 103: 16586–16591.

Spina D, Page CP (2013). Regulating cough through modulation of sensory nerve function in the airways. Pulm Pharmacol Ther 26: 486–490.

Stallmeyer B, Zumhagen S, Denjoy I, Duthoit G, Hébert JL, Ferrer X *et al*. (2012). Mutational spectrum in the Ca(2+)-activated cation channel gene TRPM4 in patients with cardiac conductance disturbances. Hum Mutat 33: 109–117.

Stokes A, Wakano C, Koblan-Huberson M, Adra CN, Fleig A, Turner H (2006). TRPA1 is a substrate for de-ubiquitination by the tumor suppressor CYLD. Cell Signal 18: 1584–1594.

Story GM, Peier AM, Reeve AJ, Eid SR, Mosbacher J, Hricik TR *et al*. (2003). ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell 112: 819–829.

Straub I, Mohr F, Stab J, Konrad M, Philipp SE, Oberwinkler J *et al*. (2013). Citrus fruit and fabacea secondary metabolites potently and selectively block TRPM3. Br J Pharmacol 168: 1835–1850.

Streng T, Axelsson HE, Hedlund P, Andersson DA, Jordt SE, Bevan S *et al*. (2008). Distribution and function of the hydrogen sulfide-sensitive TRPA1 ion channel in rat urinary bladder. Eur Urol 53: 391–399.

Sun HS, Jackson MF, Martin LJ, Jansen K, Teves L, Cui H *et al*. (2009). Suppression of hippocampal TRPM7 protein prevents delayed neuronal death in brain ischemia. Nat Neurosci 12: 1300–1307.

Sun M, Goldin E, Stahl S, Falardeau JL, Kennedy JC, Acierno JS Jr *et al*. (2000). Mucolipidosis type IV is caused by mutations in a gene encoding a novel transient receptor potential channel. Hum Mol Genet 9: 2471–2478.

Suri A, Szallasi A (2008). The emerging role of TRPV1 in diabetes and obesity. Trends Pharmacol Sci 29: 29–36.

Suzuki M, Mizuno A, Kodaira K, Imai M (2003). Impaired pressure sensation in mice lacking TRPV4. J Biol Chem 278: 22664–22668.

Szabó A, Helyes Z, Sándor K, Bite A, Pintér E, Németh J *et al*. (2005). Role of transient receptor potential vanilloid 1 receptors in adjuvant-induced chronic arthritis: *in vivo* study using gene-deficient mice. J Pharmacol Exp Ther 314: 111–119.

Szallasi A, Blumberg PM (1989). Resiniferatoxin, a phorbol-related diterpene, acts as an ultrapotent analog of capsaicin, the irritant constituent in red pepper. Neuroscience 30: 515–520.

Szallasi A, Blumberg PM (1999). Vanilloid (Capsaicin) receptors and mechanisms. Pharmacol Rev 51: 159–212.

Szallasi A, Blumberg PM (2006). Complex regulation of TRPV1 by vanilloids. In: Heller S, Liedtke W (eds). TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades. CRC Press: Boca Raton, FL, pp. 85–104.

Szallasi A, Sheta M (2012). Targeting TRPV1 for pain relief: limits, losers and laurels. Expert Opin Investig Drugs 21: 1351–1369.

Szallasi A, Cortright DN, Bloom CA, Eid SR (2007). The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. Nat Rev Drug Discov 6: 357–372.

Szolcsányi J, Sándor Z (2012). Multisteric TRPV1 nocisensor: a target for analgesics. Trends Pharmacol Sci 33: 646–655.

Tai Y, Feng S, Ge R, Du W, Zhang X, He Z *et al*. (2008). TRPC6 channels promote dendritic growth via the CaMKIV-CREB pathway. J Cell Sci 121: 2301–2307.

Takezawa R, Cheng H, Beck A, Ishikawa J, Launay P, Kubota H *et al*. (2006). A pyrazole derivative potently inhibits lymphocyte Ca2+ influx and cytokine production by facilitating transient receptor potential melastatin 4 channel activity. Mol Pharmacol 69: 1413–1420.

Tamayo NA, Bo Y, Gore V, Ma V, Nishimura N, Tang P *et al*. (2012). Fused piperidines as a novel class of potent and orally available transient receptor potential melastatin type 8 (TRPM8) antagonists. J Med Chem 55: 1593–1611.

Tanaka H, Shimaya A, Kiso T, Kuramochi T, Shimokawa T, Shibasaki M (2011). Enhanced insulin secretion and sensitization in diabetic mice on chronic treatment with a transient receptor potential vanilloid 1 antagonist. Life Sci 88: 559–563.

Taylor-Clark TE, Undem BJ (2010). Ozone activates airway nerves via the selective stimulation of TRPA1 ion channels. J Physiol 588: 423–433.

Taylor-Clark TE, Undem BJ, Macglashan DW Jr, Ghatta S, Carr MJ, McAlexander MA (2008a). Prostaglandin-induced activation of nociceptive neurons via direct interaction with transient receptor potential A1 (TRPA1). Mol Pharmacol 73: 274–281.

Taylor-Clark TE, McAlexander MA, Nassenstein C, Sheardown SA, Wilson S, Thornton J *et al*. (2008b). Relative contributions of TRPA1 and TRPV1 channels in the activation of vagal bronchopulmonary C-fibres by the endogenous autacoid 4-oxononenal. J Physiol 586: 3447–3459.

Taylor-Clark TE, Ghatta S, Bettner W, Undem BJ (2009). Nitrooleic acid, an endogenous product of nitrative stress, activates nociceptive sensory nerves via the direct activation of TRPA1. Mol Pharmacol 75: 820–829.

Ternesten-Hassèus E, Larsson C, Bende M, Millqvist E (2008). Capsaicin provocation using two different inhalation devices. Respir Med 102: 1784–1790.

Thilo F, Loddenkemper C, Berg E, Zidek W, Tepel M (2009). Increased TRPC3 expression in vascular endothelium of patients with malignant hypertension. Mod Pathol 22: 426–430.

Thorneloe KS, Sulpizio AC, Lin Z, Figueroa DJ, Clouse AK, McCafferty GP *et al*. (2008). N-((1S)-1-{[4-((2S)-2-{ [(2,4-dichlorophenyl)sulfonyl]amino}-3-hydroxypropanoyl)-1-piperazinyl]carbonyl}-3-methylbutyl)-1-benzothiophene-2-carboxamide (GSK1016790A), a novel and potent transient receptor potential vanilloid 4 channel agonist induces urinary bladder contraction and hyperactivity: part I. J Pharmacol Exp Ther 326: 432–442.

Thorneloe KS, Cheung M, Bao W, Alsaid H, Lenhard S, Jian MY *et al*. (2012). An orally active TRPV4 channel blocker prevents and resolves pulmonary edema induced by heart failure. Sci Transl Med 4: 159ra148.

Tian D, Jacobo SM, Billing D, Rozkalne A, Gage SD, Anagnostou T *et al*. (2010). Antagonistic regulation of actin dynamics and cell motility by TRPC5 and TRPC6 channels. Sci Signal 3: ra77.

Todaka H, Taniguchi J, Satoh J, Mizuno A, Suzuki M (2004). Warm temperature-sensitive transient receptor potential vanilloid 4 (TRPV4) plays an essential role in thermal hyperalgesia. J Biol Chem 279: 35133–35138.

Togashi K, Inada H, Tominaga M (2008). Inhibition of the transient receptor potential cation channel TRPM2 by 2-aminoethoxydiphenyl borate (2-APB). Br J Pharmacol 153: 1324–1330.

Tominaga M (2007). The role of TRP channels in thermosensation. In: Liedtke WB, Heller S (eds). TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades. CRC Press, Taylor & Francis: Boca Raton, FL, pp. 271–286.

Toth A, Kedei N, Szabo T, Wang Y, Blumberg PM (2002). Thapsigargin binds to and inhibits the cloned vanilloid receptor-1. Biochem Biophys Res Commun 293: 777–782.

Tóth BI, Dobrosi N, Dajnoki A, Czifra G, Oláh A, Szöllosi AG *et al*. (2011). Endocannabinoids modulate human epidermal keratinocyte proliferation and survival via the sequential engagement of cannabinoid receptor-1 and transient receptor potential vanilloid-1. J Invest Dermatol 131: 1095–1104.

Trevisani M, Patacchini R, Nicoletti P, Gatti R, Gazzieri D, Lissi N *et al*. (2005). Hydrogen sulfide causes vanilloid receptor 1-mediated neurogenic inflammation in the airways. Br J Pharmacol 145: 1123–1131.

Trevisani M, Siemens J, Materazzi S, Bautista DM, Nassini R, Campi B *et al*. (2007). 4-Hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1. Proc Natl Acad Sci U S A 104: 13519–13524.

Tsui H, Razavi R, Chan Y, Yantha J, Dosch HM (2007). 'Sensing' autoimmunity in type 1 diabetes. Trends Mol Med 13: 405–413.

Tsui H, Paltser G, Chan Y, Dorfman R, Dosch HM (2011). 'Sensing' the link between type 1 and type 2 diabetes. Diabetes Metab Res Rev 27: 913–918.

Uchida K, Dezaki K, Damdindorj B, Inada H, Shiuchi T, Mori Y *et al*. (2011). Lack of TRPM2 impaired insulin secretion and glucose metabolisms in mice. Diabetes 60: 119–126.

Valdes AM, De Wilde G, Doherty SA, Lories RJ, Vaughn FL, Laslett LL *et al*. (2011). The Ile585Val TRPV1 variant is involved in risk of painful knee osteoarthritis. Ann Rheum Dis 70: 1556–1561.

Valenzano KJ, Grant ER, Wu G, Hachicha M, Schmid L, Tafesse L *et al*. (2003). N-(4-tertiarybutylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2H)-carbox-amide (BCTC), a novel, orally effective vanilloid receptor 1 antagonist with analgesic properties: I. *in vitro* characterization and pharmacokinetic properties. J Pharmacol Exp Ther 306: 377–386.

Vay L, Gu C, McNaughton PA (2012). The thermoTRP ion channel family: properties and therapeutic implications. Br J Pharmacol 165: 787–801.

Vennekens R, Menigoz A, Nilius B (2012). TRPs in the brain. Rev Physiol Biochem Pharmacol 163: 27–64.

Vergarajauregui S, Puertollano R (2008). Mucolipidosis type IV: the importance of functional lysosomes for efficient autophagy. Autophagy 4: 832–834.

Vetter I, Touska F, Hess A, Hinsbey R, Sattler S, Lampert A *et al*. (2012). Ciguatoxins activate cold pathways to elicit burning pain from cooling. EMBO J 31: 3795–3808.

Vincent F, Acevedo A, Nguyen MT, Dourado M, DeFalco J, Gustafson A *et al*. (2009). Identification and characterization of novel TRPV4 modulators. Biochem Biophys Res Commun 389: 490–494.

Vindis C, D'Angelo R, Mucher E, Nègre-Salvayre A, Parini A, Mialet-Perez J (2010). Essential role of TRPC1 channels in cardiomyoblasts hypertrophy mediated by 5-HT2A serotonin receptors. Biochem Biophys Res Commun 391: 979–983.

Vogt-Eisele AK, Weber K, Sherkheli MA, Vielhaber G, Panten J, Gisselmann G *et al*. (2007). Monoterpenoid agonists of TRPV3. Br J Pharmacol 151: 530–540.

Vriens J, Nilius B, Vennekens R (2008). Herbal compounds and toxins modulating TRP channels. Curr Neuropharmacol 6: 79–96.

Vriens J, Owsianik G, Hofmann T, Philipp SE, Stab J, Chen X *et al*. (2011). TRPM3 is a nociceptor channel involved in the detection of noxious heat. Neuron 70: 482–494.

Wagner TF, Loch S, Lambert S, Straub I, Mannebach S, Mathar I *et al.* (2008). Transient receptor potential M3 channels are ionotropic steroid receptors in pancreatic beta cells. Nat Cell Biol 10: 1421–1430.

Wang P, Yan Z, Zhong J, Chen J, Ni Y, Li L *et al.* (2012). Transient receptor potential vanilloid 1 activation enhances gut glucagon-like peptide-1 secretion and improves glucose homeostasis. Diabetes 61: 2155–2165.

Wang X, Miyares RL, Ahern GP (2005). Oleoylethanolamide excites vagal sensory neurones, induces visceral pain and reduces short-term food intake in mice via capsaicin receptor TRPV1. J Physiol 564: 541–547.

Wang Y, Jarad G, Tripathi P, Pan M, Cunningham J, Martin DR *et al.* (2010). Activation of NFAT signaling in podocytes causes glomerulosclerosis. J Am Soc Nephrol 21: 1657–1666.

Wang ZY, Wang P, Merriam FV, Bjorling DE (2008). Lack of TRPV1 inhibits cystitis-induced increased mechanical sensitivity in mice. Pain 139: 158–167.

Watanabe H, Vriens J, Prenen J, Droogmans G, Voets T, Nilius B (2003). Anandamide and arachidonic acid use epoxyeicosatrienoic acids to activate TRPV4 channels. Nature 424: 434–438.

Watanabe H, Iino K, Ohba T, Ito H (2013). Possible involvement of TRP channels in cardiac hypertrophy and arrhythmia. Curr Top Med Chem 13: 283–294.

Wei H, Hämäläinen MM, Saarnilehto M, Koivisto A, Pertovaara A (2009). Attenuation of mechanical hypersensitivity by an antagonist of the TRPA1 ion channel in diabetic animals. Anesthesiology 111: 147–154.

Weissmann N, Dietrich A, Fuchs B, Kalwa H, Ay M, Dumitrascu R *et al.* (2006). Classical transient receptor potential channel 6 (TRPC6) is essential for hypoxic pulmonary vasoconstriction and alveolar gas exchange. Proc Natl Acad Sci U S A 103: 19093–19098.

Weissmann N, Sydykov A, Kalwa H, Storch U, Fuchs B, Mederos y Schnitzler M *et al.* (2012). Activation of TRPC6 channels is essential for lung ischaemia-reperfusion induced oedema in mice. Nat Commun 3: 649.

Wes PD, Chevesich J, Jeromin A, Rosenberg C, Stetten G, Montell C (1995). TRPC1, a human homolog of a *Drosophila* store-operated channel. Proc Natl Acad Sci USA 92: 9652–9656.

Willette RN, Bao W, Nerurkar S, Yue TL, Doe CP, Stankus G *et al.* (2008). Systemic activation of the transient receptor potential vanilloid subtype 4 channel causes endothelial failure and circulatory collapse: part 2. J Pharmacol Exp Ther 326: 443–452.

Willis DN, Liu B, Ha MA, Jordt SE, Morris JB (2011). Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. FASEB J 25: 4434–4444.

Wilson SR, Gerhold KA, Bifolck-Fisher A, Liu Q, Patel KN *et al.* (2011). TRPA1 is required for histamine-independent, Mas-related G protein-coupled receptor-mediated itch. Nat Neurosci 14: 595–602.

Winn MP, Conlon PJ, Lynn KL, Farrington MK, Creazzo T, Hawkins AF *et al.* (2005). A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. Science 308: 1801–1804.

Wu LJ, Sweet TB, Clapham DE (2010). International Union of Basic and Clinical Pharmacology. LXXVI. Current progress in the mammalian TRP ion channel family. Pharmacol Rev 62: 381–404.

Xing H, Ling JX, Chen M, Johnson RD, Tominaga M, Wang CY *et al.* (2008). TRPM8 mechanism of autonomic nerve response to cold in respiratory airway. Mol Pain 4: 22.

Xu H, Ramsey IS, Kotecha SA, Moran MM, Chong JA, Lawson D *et al.* (2002). TRPV3 is a calcium-permeable temperature-sensitive cation channel. Nature 418: 181–186.

Xu H, Blair NT, Clapham DE (2005). Camphor activates and strongly desensitizes the transient receptor potential vanilloid subtype 1 channel in a vanilloid-independent mechanism. J Neurosci 25: 8924–8937.

Xu H, Delling M, Jun JC, Clapham DE (2006a). Oregano, thyme and clove-derived flavors and skin sensitizers activate specific TRP channels. Nat Neurosci 9: 628–635.

Xu SZ, Muraki K, Zeng F, Li J, Sukumar P, Shah S *et al.* (2006b). A sphingosine-1-phosphate-activated calcium channel controlling vascular smooth muscle cell motility. Circ Res 98: 1381–1389.

Yamaguchi T, Hempson SJ, Reif GA, Hedge AM, Wallace DP (2006). Calcium restores a normal proliferation phenotype in human polycystic kidney disease epithelial cells. J Am Soc Nephrol 17: 178–187.

Yang H, Zhao B, Liao C, Zhang R, Meng K, Xu J *et al.* (2013). High glucose-induced apoptosis in cultured podocytes involves TRPC6-dependent calcium entry via the RhoA/ROCK pathway. Biochem Biophys Res Commun 434: 394–400.

Yang J, Li Y, Zuo X, Zhen Y, Yu Y, Gao L (2008). Transient receptor potential ankyrin-1 participates in visceral hyperalgesia following experimental colitis. Neurosci Lett 440: 237–241.

Ye L, Kleiner S, Wu J, Sah R, Gupta RK, Banks AS *et al.* (2012). TRPV4 is a regulator of adipose oxidative metabolism, inflammation, and energy homeostasis. Cell 151: 96–110.

Yiangou Y, Facer P, Dyer NH, Chan NL, Knowles C, Williams NS *et al.* (2001). Vanilloid receptor 1 immunoreactivity in inflamed human bowel. Lancet 357: 1338–1339.

Yoshioka T, Imura K, Asakawa M, Suzuki M, Oshima I, Hirasawa T *et al.* (2009). Impact of the Gly573Ser substitution in TRPV3 on the development of allergic and pruritic dermatitis in mice. J Invest Dermatol 129: 714–722.

Yu W, Hill WG, Apodaca G, Zeidel ML (2011). Expression and distribution of transient receptor potential (TRP) channels in bladder epithelium. Am J Physiol Renal Physiol 300: F49–F59.

Yu Y, Fantozzi I, Remillard CV, Landsberg JW, Kunichika N, Platoshyn O *et al.* (2004). Enhanced expression of transient receptor potential channels in idiopathic pulmonary arterial hypertension. Proc Natl Acad Sci U S A 101: 13861–13866.

Yu Y, Keller SH, Remillard CV, Safrina O, Nicholson A, Zhang SL *et al.* (2009a). A functional single-nucleotide polymorphism in the TRPC6 gene promoter associated with idiopathic pulmonary arterial hypertension. Circulation 119: 2313–2322.

Yu Y, Ulbrich MH, Li MH, Buraei Z, Chen XZ, Ong AC *et al.* (2009b). Structural and molecular basis of the assembly of the TRPP2/PKD1 complex. Proc Natl Acad Sci U S A 106: 11558–11563.

Zhang X, Li L, McNaughton PA (2008). Proinflammatory mediators modulate the heat-activated ion channel TRPV1 via the scaffolding protein AKAP79/150. Neuron 59: 450–461.

Zhou J, Du W, Zhou K, Tai Y, Yao H, Jia Y *et al.* (2008). Critical role of TRPC6 channels in the formation of excitatory synapses. Nat Neurosci 11: 741–743.

Zhu B, Xia M, Xu X, Ludovici DW, Tennakoon M, Youngman MA *et al.* (2013). Arylglycine derivatives as potent transient receptor potential melastatin 8 (TRPM8) antagonists. Bioorg Med Chem Lett 23: 2234–2237.

Zhu G, ICGN Investigators, Gulsvik A, Bakke P, Ghatta S, Anderson W, Lomas DA *et al*. (2009). Association of TRPV4 gene polymorphisms with chronic obstructive pulmonary disease. Hum Mol Genet 18: 2053–2062.

Zhu X, Chu PB, Peyton M, Birnbaumer L (1995). Molecular cloning of a widely expressed human homologue for the *Drosophila trp* gene. FEBS Lett 373: 193–198.

Zhu Z, Luo Z, Ma S, Liu D (2011). TRP channels and their implications in metabolic diseases. Pflugers Arch 461: 211–223.

Zierler S, Yao G, Zhang Z, Kuo WC, Pörzgen P, Penner R *et al*. (2011). Waixenicin A inhibits cell proliferation through magnesium-dependent block of transient receptor potential melastatin 7 (TRPM7) channels. J Biol Chem 286: 39328–39335.

Zimmermann K, Lennerz JK, Hein A, Link AS, Kaczmarek JS, Delling M *et al*. (2011). Transient receptor potential channel, subfamily C, member 5 (TRPC5) is a cold-transducer in the peripheral nervous system. Proc Natl Acad Sci USA 108: 18114–18119.

Zygmunt PM, Petersson J, Andersson DA, Chuang H, Sørgård M, Di Marzo V *et al*. (1999). Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 400: 452–457.