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REVIEW

Transient receptor potential ion channels in primary sensory neurons as targets for novel analgesics

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The last decade has witnessed an explosion in novel findings relating to the molecules involved in mediating the sensation of pain in humans. Transient receptor potential (TRP) ion channels emerged as the greatest group of molecules involved in the transduction of various physical stimuli into neuronal signals in primary sensory neurons, as well as, in the development of pain. Here, we review the role of TRP ion channels in primary sensory neurons in the development of pain associated with peripheral pathologies and possible strategies to translate preclinical data into the development of effective new analgesics. Based on available evidence, we argue that nociception-related TRP channels on primary sensory neurons provide highly valuable targets for the development of novel analgesics and that, in order to reduce possible undesirable side effects, novel analgesics should prevent the translocation from the cytoplasm to the cell membrane and the sensitization of the channels rather than blocking the channel pore or binding sites for exogenous or endogenous activators.

LINKED ARTICLES
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Abbreviations
AKAP79/150, A kinase anchoring protein 79/159; CB_1, cannabinoid type 1; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; HCN2, hyperpolarization-activated cyclic nucleotide-gated K^+ channel 2; IB4, *Griffonia simplicifolia lectin;* mGlu receptor, metabotropic glutamate receptor; PSN, primary sensory neuron; siRNA, small interfering RNA; TG, trigeminal ganglion; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin type 1 ion channel; TRPC1, transient receptor potential canonical type 1 ion channel; TRPM2, transient receptor potential melastatin type 2 ion channel; TRPV1, transient receptor potential vanilloid type 1 ion channel

Introduction

Attempts to satisfactorily control chronic pain conditions remain unsuccessful in many contexts notwithstanding the myriad of scientific discoveries that have been made concerning the molecular basis of pain during the past decade. This inability to provide effective analgesia to patients suffering from severe chronic pain exacts an indescribable toll on the patient concerned, the extent of which is brought into relief by the observation that, in rodent models of neuropathic pain, animals may seek relief from their condition even by autotomy (self-mutilation) of an afflicted limb. Unrelenting severe pain is destructive of human dignity and has traditionally been feared even more than death itself. In addition to the burden of human suffering, chronic pain conditions impose a huge financial burden on health systems and society.

The great majority of cases involving chronic pain are associated with altered activity and excitability of peripheral nerves due either to inflammatory processes initiated by tissue damage or physical, chemical (e.g. anticancer drugs) or biological (e.g. metabolic diseases or infections) injury of the peripheral nerves themselves (Scholz and Woolf, 2002; Woolf, 2010). Increased excitation of primary sensory neurons (PSN) occasioned by these pathologies, particularly of the nociceptive subclass of PSN, which respond to noxious stimuli, results in nociceptive signalling to the CNS. That

signalling, following multiple processing, results in the perception of pain.

Transducer molecules in nociceptive signalling

A variety of molecules that function in peripheral pain signalling to the brain have been identified in the last two decades at different levels of the pain processing system. These include mediators, intracellular signalling molecules, voltage-gated ion channels, GPCRs, tyrosine kinase receptors and transducer molecules (White and Miller, 2010; Heinzmann and Mcmahon, 2011; Ji *et al.*, 2011; Lötsch and Geisslinger, 2011; Myers and Shubayev, 2011; Takeda *et al.*, 2011; Eijkelkamp *et al.*, 2012; Nicotra *et al.*, 2012; Petho and Reeh, 2012; Piscitelli and Di Marzo, 2012; Tsuda *et al.*, 2012; Vay *et al.*, 2012; Vink and Alewood, 2012; Wemmie *et al.*, 2013). Transducers in the peripheral terminals of nociceptive PSN convert noxious stimuli, such as thermal, mechanical or chemical, into excitation of those cells which, through the pain processing system may ultimately result in the sensation of pain. These transducers may be particularly valuable targets for drug therapy aimed at producing analgesia, since they are understood to be pivotal for the expression of the most common modalities of pain sensation, namely, burning, freezing and mechanical pain. For example, the transient receptor potential vanilloid type 1 ion channel (TRPV1) is the target receptor of capsaicin and mediates the pungent sensation induced by capsaicin, which is found in hot peppers (Caterina *et al.*, 1997). TRPV1 was the first noxious heat-sensitive transducer molecule identified as being present on a subset of PSN (Caterina *et al.*, 1997) and it is essential for the development of the burning pain sensation (heat hyperalgesia), which results from tissue inflammation or physical injury (Caterina *et al.*, 2000; Davis *et al.*, 2000; Pogatzki-Zahn *et al.*, 2005).

Transient receptor potential (TRP) channels, signal transduction and nociceptive processing

TRP ion channels constitute the largest group of transducer molecules thus far known to be involved in the generation of pain sensations in mammals. TRP channels are tetrameric in structure and form a conserved family of molecules, which are grouped into seven subfamilies (Table 1) (Nilius and Owsianik, 2011). TRP channels act as sensors for a range of innocuous and noxious physical stimuli such as heat, cold, touch and stretch across the spectrum of species (Nilius and Owsianik, 2011). Ten members from four subfamilies of TRP channels have been reported to be involved in nociceptive processing so far (Table 1): TRPV1 (Caterina *et al.*, 1997; 2000; Davis *et al.*, 2000), the vanilloid type 2 (TRPV2) (Caterina *et al.*, 1999; Nagy and Rang, 1999; Ahluwalia *et al.*, 2002), the vanilloid type 3 (TRPV3) (Peier *et al.*, 2002; Smith *et al.*, 2002; Xu *et al.*, 2002; Moqrich *et al.*, 2005), the vanilloid type 4 (TRPV4) (Liedtke *et al.*, 2000; Strotmann *et al.*, 2000; Delany *et al.*, 2001; Alessandri-Haber *et al.*, 2003), the ankyrin type 1 (TRPA1) (Story *et al.*, 2003; Bandell *et al.*, 2004; Jordt *et al.*, 2004; Obata *et al.*, 2005; da Costa *et al.*, 2010), the melastatin type 2 (TRPM2) (Kudoh *et al.*, 1997; Haraguchi *et al.*, 2012), the melastatin type 3 (TRPM3) (Lee *et al.*, 2003; Vriens *et al.*, 2011), the melastatin type 8 (TRPM8) (Tsavaler *et al.*, 2001; McKemy *et al.*, 2002; Bautista *et al.*, 2007; Colburn *et al.*, 2007; Knowlton *et al.*, 2010; 2011), the canonical type 1 (TRPC1) (Zitt *et al.*, 1996; Alessandri-Haber *et al.*, 2009) and the canonical type 6 (TRPC6) (Boulay *et al.*, 1997; Alessandri-Haber *et al.*, 2009).

All of the 10 TRP channels known to participate in nociception are ligand-gated cationic channels (Nilius and Owsianik, 2011), which are also often referred to as 'ionotropic receptors'. Ionotropic receptors, like voltage-gated ion channels, are responsible for mediating the fast changes in membrane conductance by transiently increasing the permeability of the neuronal membrane to particular ions. When activated, TRP channels are permeable only to cations, but their selectivity is limited. Hence, activated TRP channels are permeable to all major cations (Na^+, K^+, and Ca^{2+}) found in the extra- and intracellular fluids. Consequently, activation of the nociception-related TRP channels expressed by excitable membranes, such as those in PSN, produces a net inward current, which depolarizes the membrane and increases the probability of action potential generation. In addition, Ca^{2+} influx increases the release of various mediators (Parnas and Parnas, 2010), which then induce excitation in postsynaptic neurons, or indeed, if the release occurs from peripheral non-neuronal cells, in PSN. Therefore, it is expected that blocking nociception-related TRP channels in a selective and specific

Table 1

Human transient receptor potential (TRP) channel family

TRP subfamily channels:	Canonical type – TRPC	Melastatin type – TRPM	Vanilloid type – TRPV	Ankyrin type – TRPA	Mucolipin type – TRPML	Polycystic type – TRPP
	TRPC1-7	TRPM1-8	TRPV1-6	TRPA1	TRPML1-3	TRPP2 TRPP3 TRPP5
TRP channels involved in nociception	TRPC1 TRPC6	TRPM2 TRPM3 TRPM8	TRPV1 TRPV2 TRPV3 TRPV4	TRPA1		

manner should result in a reduction in the excitation of PSN, thereby providing significant pain relief.

PSN may constitute a preferable site for interfering with nociception-related TRP channels

There are several sites for possible intervention to inhibit or reduce nociceptive signalling within the nociceptive processing system (Scholz and Woolf, 2002). However, it is generally believed that pain sensations of peripheral origin may be most efficiently controlled by modulating the activity of molecules comprised on, or in PSN (Patapoutian *et al.*, 2009). Important nociception-related TRP channels are found in various tissues (Table 2; Fernandes *et al.*, 2012). However, all of these molecules are expressed by PSN and/or by some nociception-relevant non-neuronal cells at the periphery (see at Expression of nociception-related TRP channels). Crucially, affecting the activity of these molecules at the periphery reduces the risk of inducing undesirable CNS-mediated side effects. Nevertheless, targeting nociception-related TRP channels in the CNS is still worth considering, as highlighted by data summarized in some excellent recent reviews (Giordano *et al.*, 2012; Palazzo *et al.*, 2012; Barrière *et al.*, 2013; Köles *et al.*, 2013). Detailed discussion of these data is out of the scope of this review and readers are referred to these reviews.

Intervention at the level of the PSN evokes its own complications, because these neurons, particularly the nociceptive cells, are involved in a complex local regulatory system that participates in the modulation of vascular, inflammatory, immune, protective, restorative and trophic processes, both in somatic and visceral tissues (Belvisi, 2003; Geppetti *et al.*, 2008; Aubdool and Brain, 2011; Andreev *et al.*, 2012). Some nociception-related TRP channels appear to be intimately involved in these homeostatic functions (Belvisi, 2003; Geppetti *et al.*, 2008; Aubdool and Brain, 2011; Andreev *et al.*, 2012). Hence, activation of nociception-related TRP channels in PSN results in the release of transmitters and neuropeptides including glutamate, calcitonin gene-related peptide (CGRP) and substance P from the peripheral terminals of these neurons (Aubdool and Brain, 2011; Andreev *et al.*, 2012). These mediators, in turn, act on immunocompetent, smooth muscle and endothelial cells at the periphery (Belvisi, 2003; Geppetti *et al.*, 2008; Aubdool and Brain, 2011; Andreev *et al.*, 2012) and their actions induce the development of a local reaction referred to as neurogenic inflammatory response. During this response, immunocompetent cells release substances, such as histamine, 5-HT and nerve growth factor, which by acting on their cognate receptors, as well as inducing sensitization that increases TRP channel responsiveness (Belvisi, 2003; Nagy, 2004; Nagy *et al.*, 2004; Geppetti *et al.*, 2008; Aubdool and Brain, 2011; Andreev *et al.*, 2012), further increase the activity of PSN. Hence, activation of nociception-related TRP channels on PSN either by direct physical stimuli or by agents produced and released during tissue damage results in continuous/reverberating activation of TRP channels and indeed PSN. Obviously, this process significantly increases the spinal nociceptive input, and ultimately results in the sensation of pain by the brain. Consequently, blocking nociception-related TRP channels in PSN intervenes with the development of this reverberating activation, and may significantly contribute to pain relief. However, due to the possible interference with PSN-mediated homeostatic functions, it is important to understand that there are constraints on the extent to which one may intervene to modulate these ion channels without doing more harm than good.

Expression of nociception-related TRP channels

PSN form three morphologically, physiologically and pharmacologically distinct subpopulations, namely, large diameter non-nociceptive cells with fast-conducting myelinated fibres (Aβ-fibres) and small diameter nociceptive neurons with slow-conducting thinly myelinated (Aδ-fibres) or unmyelinated fibres (C-fibres) (Nagy, 2004). The majority of nociception-related TRP channels are widely expressed by

Table 2

Expression pattern of nociception-related TRP channels in different tissue in mammals

TRPV1	TRPV2	TRPV3	TRPV4	TRPC1	TRPC6	TRPM2	TRPM3	TRPM8	TRPA1
PSN	PSN	PSN	PSN	PSN	PSN	PSN	PSN	PSN	PSN
Brain?	Brain	Brain	Brain	Brain	Brain	Glial cells	Brain		
Skin?	Spinal cord	Spinal cord	Skin	Heart	Heart	Immune cells	Kidney		
	Lung	Skin	Kidney	Testis	Testis				
	Liver	Stomach	Lung	Ovaries	Ovaries				
	Spleen	Colon	Inner Ear						
	Colon		Urothelium						

PSN, primary sensory neurons.
? indicates inconsistent data.

these neurons, which originate from dorsal root ganglia (DRG) and trigeminal ganglia (TG), outside the CNS and terminate by synapsing with second-order neurons in the spinal dorsal horn. Vandewauw *et al*. (2013) have shown that TRPV1, TRPV2, TRPV4, TRPA1, TRPM2, TRPM3, TRPM8 and TRPC1 are expressed by DRG and the TG (Vandewauw *et al*., 2013). Alessandri-Haber *et al*. (2009) have reported TRPC6 expression in PSN (Alessandri-Haber *et al*., 2009). Within DRG and TG, TRPV1, TRPV4, TRPA1 and TRPM8 are expressed predominantly by small diameter neurons, which express the nociceptive cell markers CGRP or/and a binding site for the lectin *Griffonia simplicifolia* (IB4) (Caterina *et al*., 1999; Guo *et al*., 1999; Michael and Priestley, 1999; Ahluwalia *et al*., 2000; 2002; Ma, 2001; Alessandri-Haber *et al*., 2003; Patapoutian *et al*., 2003; Story *et al*., 2003; Jordt *et al*., 2004; Lewinter *et al*., 2004; Kobayashi *et al*., 2005; Neeper *et al*., 2007; Cao *et al*., 2009; Chen *et al*., 2013). Neither TRPV2 nor TRPC1 are found on neurons that express the IB4-binding site. However, the neurons on which these channels are found express the 200 kDa neurofilament, which is a marker for the cells that Aβ and Aδ-fibres originate from (Lawson and Waddell, 1991; Caterina *et al*., 1999; Ichikawa and Sugimoto, 2000; Lewinter *et al*., 2004; Elg *et al*., 2007; Bachy *et al*., 2011). TRPV2-expressing neurons express CGRP (Caterina *et al*., 1999; Ichikawa and Sugimoto, 2000; Lewinter *et al*., 2004). The relationship of TRPC6, TRPM2 and TRPM3 in DRG or TG with the major PSN markers is not known at present, although the co-expression of TRPV1 with TRPM3 (Vriens *et al*., 2011) suggests that TRPM3 may exhibit a certain co-expression with CGRP and/or IB4.

CGRP-containing and IB4-binding neurons differ both in the type of tissue they innervate and in their role in nociceptive processing (Bennett *et al*., 1996; Breese *et al*., 2005; Todd, 2010). Thus, while peptidergic cells predominantly innervate visceral tissues, IB4-binding cells predominantly innervate somatic tissue. Further, peptidergic and IB4-binding cells seem to respond differently to peripheral inflammation (Breese *et al*., 2005). Hence, different patterns of expression of the several nociception-related TRP channels in the two major subtypes of nociceptive PSN may be related to their respective functions and role in the development of pain of various origins. This may be important in the context of the known overlap in the sensitivity of nociception-related TRP channels to physical and particularly chemical activators.

TRP channels are likely to be expressed in the perikarya, central and peripheral processes; hence application of specific selective activators of nociception-related TRP channels on peripheral or central processes and the DRG results in similar excitatory effects. Thus, TRPV1, TRPV2, TRPV4, TRPA1 and TRPM8 have been demonstrated to exist in the peripheral and/or spinal terminals of PSN in various tissues as well as in the superficial laminae of the spinal dorsal horn (Guo *et al*., 1999; Valtschanoff *et al*., 2001; Avelino *et al*., 2002; Lewinter *et al*., 2004; Dinis *et al*., 2005; Du *et al*., 2007; Dhaka *et al*., 2008; Streng *et al*., 2008; Cao *et al*., 2009; Kim *et al*., 2010). The proportion of PSN that express nociception-related TRP channels varies: TRPM3 shows the highest expression (~70–80% of the total population of neurons) (Vriens *et al*., 2011) followed by TRPV1 (~40%) (Guo *et al*., 1999; Michael and Priestley, 1999), TRPA1 (~40%) (Kobayashi *et al*., 2005), TRPV4 (~35%) (Alessandri-Haber *et al*., 2003), TRPM8 (~20%) (Kobayashi *et al*., 2005) and TRPV2 (~10–20%) (Ahluwalia *et al*., 2002; Greffrath *et al*., 2003; Lewinter *et al*., 2004). At present, the proportion of neurons expressing TRPM2 is not known.

The proportion of neurons expressing nociception-related TRP channels as well as the co-expression of these TRP channels with various cell markers suggest that TRPs may exhibit extensive co-expression in PSN. Indeed, TRPV4, TRPA1, TRPM3 and TRPC6 show a high degree of co-expression with TRPV1 (Alessandri-Haber *et al*., 2003; Kress *et al*., 2008; Cao *et al*., 2009; Vriens *et al*., 2011; Zimmermann *et al*., 2011; Chen *et al*., 2013). Further, TRPC1, TRPC6 and TRPV4 also show extensive co-expression in PSN (Alessandri-Haber *et al*., 2009). In contrast, TRPV1- and TRPV2-expression appears to be completely segregated (Ahluwalia *et al*., 2002; Lewinter *et al*., 2004), although some authors have reported limited co-expression of these two channels (Greffrath *et al*., 2003). Similarly, TRPV1 and TRPM8 show very little co-expression (Kobayashi *et al*., 2005).

The co-expression of various nociception-related TRP channels may enable neurons to function as mediators of several pain sensations (e.g. burning and cold sensations). In addition, TRP molecules can form functional heterotetramers, the response properties of which are significantly different from those of homotetrameric structures (Cheng *et al*., 2007; 2012). Further, various TRP channels may form signalling complexes, in which the channels can affect each other's respective responses. TRPV4 and TRPC6 have recently been suggested to be involved in forming such signalling complexes (Alessandri-Haber *et al*., 2009).

Nociception-related TRP channels have been found in neurons other than PSN both inside and outside the CNS (Table 2; Fernandes *et al*., 2012). These neurons include peripheral autonomic neurons, hippocampal neurons (Delany *et al*., 2001; Shibasaki *et al*., 2007), spinal cord and periaqueductal gray neurons (Mezey *et al*., 2000; Valtschanoff *et al*., 2001; Roberts *et al*., 2004; Kim *et al*., 2012); however, some observations challenge this broader distribution (Mishra *et al*., 2010; Cavanaugh *et al*., 2011). Although, when first identified, TRPV3 was found in nociceptive PSN (Smith *et al*., 2002; Xu *et al*., 2002), later studies have found scant evidence of the expression of this ion channel in these cells (Peier *et al*., 2002; Vriens *et al*., 2011). Instead, TRPV3 is found in keratinocytes (Peier *et al*., 2002; Moqrich *et al*., 2005; Huang *et al*., 2008; Mandadi *et al*., 2009; Yamada *et al*., 2010). Other peripheral cells and tissues which have been reported to express nociception-related TRP channels include trachea, lung, salivary glands, cochlear hair cells, transitional epithelium and immunocompetent cells (Delany *et al*., 2001; Chen *et al*., 2003; Corey *et al*., 2004; Nagasawa *et al*., 2006; Mizoguchi *et al*., 2008; Charrua *et al*., 2009; Hamanaka *et al*., 2010; Wu *et al*., 2011; Yu *et al*., 2011; Haraguchi *et al*., 2012; Sobhan *et al*., 2013). While the functional role of nociception-related TRP channels in PSN has been identified (see below), little is known about the role of these channels in other neurons and non-neuronal cells. However, it is likely that TRP channels in many areas of the periphery, such as the viscera, may perform important func-

tions. Therefore, it is imperative that analgesic agents acting on nociception-related TRP channels do not affect those functions.

Inhibiting the activity of nociception-related TRP channels is associated with reduced nociceptive responses

It has been shown, by inhibiting or deleting nociception-related TRP channels, that heat-, cold- and mechanotransducers play an important role in the development of burning, freezing and mechanical pain sensations, respectively, during inflammation or nerve injury (Table 3).

Inflammatory heat hyperalgesia

Deletion of the noxious heat-sensitive TRPV1 and TRPM3 channels results in reduced inflammatory heat hyperalgesia (Caterina *et al.*, 2000; Davis *et al.*, 2000; Vriens *et al.*, 2011). TRPM2 is not a heat transducer, but the development of inflammatory heat hyperalgesia also depends on the expression and functioning of this channel (Haraguchi *et al.*, 2012). Although TRPM2 is expressed by PSN (Vandewauw *et al.*, 2013), it appears that this channel, which mediates inflammatory heat hyperalgesia, is activated in immunocompetent cells rather than in PSN. Activated immunocompetent cells then release mediators, such as chemokine ligand-2, which act on PSN (Haraguchi *et al.*, 2012).

Inflammatory cold hyperalgesia

After some debate (Bautista *et al.*, 2006; Kwan *et al.*, 2006), recent publications have provided solid evidence that TRPA1 is a key mediator of cold sensitivity (Karashima *et al.*, 2009; del Camino *et al.*, 2010). In addition to its involvement in acute cold sensation, the development of inflammatory cold hyperalgesia also appears to be dependent on the expression and function of this channel (Obata *et al.*, 2005; da Costa *et al.*, 2010). TRPM8 is also a cold transducer molecule and deleting or blocking this channel results in reduced inflammation-induced cold hypersensitivity (Colburn *et al.*, 2007; Knowlton *et al.*, 2011). However, TRPM8 is also responsible for the cooling-induced analgesia in inflammation (Dhaka *et al.*, 2008).

Inflammatory mechanical hyperalgesia

Consistent with exhibiting reduced responses to mechanical stimuli (Kwan *et al.*, 2006), TRPA1$^{-/-}$ mice show deficits in the development of inflammatory mechanical hyperalgesia (da Costa *et al.*, 2010; Fernandes *et al.*, 2011). Likewise, TRPV4$^{-/-}$ mice also exhibit reduced responses to mechanical stimuli (Suzuki *et al.*, 2004), and either alone (Segond von Banchet *et al.*, 2002; Chen *et al.*, 2013; Ota *et al.*, 2013) or together with TRPC1 and/or TRPC6 (Alessandri-Haber *et al.*, 2009), TRPV4 channels might play a pivotal role in the development of inflammatory mechanical hyperalgesia. The TRPV4 channel is also expressed and activated in the epidermis. It has recently been shown that UV-B irradiation activates TRPV4 channels in epidermal cells, and that through the release of mediators which act on PSN, also contributes to the development of increased mechanical sensitivity following

Table 3

Pain modalities mediated by different nociceptive-related TRP channels in inflammation or following peripheral nerve injury

Inflammation			Nerve Injury		
Heat hyperalgesia	**Cold hyperalgesia**	**Mechanical hyperalgesia**	**Heat hyperalgesia**	**Cold allodynia**	**Mechanical allodynia**
TRPV1 (Caterina *et al.*, 2000; Davis *et al.*, 2000)		TRPV1 (Walker *et al.*, 2003)	TRPV1 (Vilceanu *et al.*, 2010)		TRPV1 (Walker *et al.*, 2003)
TRPM2 (Haraguchi *et al.*, 2012)		TRPM2 (Haraguchi *et al.*, 2012)	TRPM2 (Haraguchi *et al.*, 2012)		TRPM2 (Haraguchi *et al.*, 2012)
TRPM3 (Vriens *et al.*, 2011)					
	TRPA1 (Obata *et al.*, 2005)	TRPA1 (Eid *et al.*, 2008; da Costa *et al.*, 2010)		TRPA1 (Obata *et al.*, 2005)	TRPA1 (Eid *et al.*, 2008)
	TRPM8 (Colburn *et al.*, 2007)			TRPM8 (Colburn *et al.*, 2007)	
		TRPV4 (Alessandri-Haber *et al.*, 2006)			TRPV4 (Alessandri-Haber *et al.*, 2004)
		TRPC1 (Alessandri-Haber *et al.*, 2009)			
		TRPC6 (Alessandri-Haber *et al.*, 2009)			

sunburn (Moore *et al.*, 2013). Although mechanical responsiveness, when probed with punctate stimuli on the paw is not affected in TRPV1$^{-/-}$ mice (Caterina *et al.*, 2000), inhibiting TRPV1 activity has been reported to reduce inflammatory mechanical hyperalgesia (Walker *et al.*, 2003). Furthermore, while TRPV1 is not involved in burn injury-associated spontaneous nociceptive processing, it has been shown to contribute to mechanical stimulation-evoked pain-related behaviour following burn injury (Green *et al.*, 2013). TRPM2 also appears to play an important role in the development of mechanical hyperalgesia in inflammatory conditions (Haraguchi *et al.*, 2012).

Visceral pain associated with inflammation

TRP channels are also involved in the development of visceral inflammation, hyperreflexia and pain associated with such inflammation. TRPV1 plays a pivotal role in the development of increased bladder activity and pain in cystitis (Birder *et al.*, 2001; Dinis *et al.*, 2004a; Charrua *et al.*, 2007). TRPA1 has been reported to be involved in the development of colitis and associated pain through neurogenic inflammation (Engel *et al.*, 2011). The contribution of TRPA1 to enteral inflammation is further supported by the finding that TRPA1 mRNA expression is increased in rodent gut during inflammation (Izzo *et al.*, 2012). TRPV4 is also associated with colitis and visceral hypersensitivity during inflammation (Cenac *et al.*, 2008; Fichna *et al.*, 2012).

Mechanical allodynia associated with peripheral nerve injury

Peripheral nerve injury is also most often associated with the development of mechanical and thermal pain (Scholz and Woolf, 2002; Woolf, 2010). TRPV4 has been shown to play a critical role in the development of mechanical allodynia in chemotherapy-associated neuropathy (Alessandri-Haber *et al.*, 2004). TRPM2, activated in immunocompetent cells during nerve injury both in the periphery and in the spinal cord, is also involved in the development of nerve injury-induced mechanical allodynia (Haraguchi *et al.*, 2012; Isami *et al.*, 2013). Blocking TRPV1 activity reduces nerve injury-induced mechanical allodynia (Walker *et al.*, 2003; Kanai *et al.*, 2005). When the TRPV1 antagonist is applied intrathecally, the analgesic effect could be mediated by postsynaptic, rather than presynaptic TRPV1, which have recently been shown to be expressed by some GABA-expressing interneurons in the spinal dorsal horn (Kim *et al.*, 2012; but see Mishra *et al.*, 2010; Cavanaugh *et al.*, 2011). Finally, TRPA1 antagonists have also been shown to produce analgesic effects, when assessed by measuring mechanical responsiveness following peripheral nerve injury (Eid *et al.*, 2008).

Cold allodynia associated with peripheral nerve injury

TRPA1, in addition to contributing to the development of inflammatory cold pain, is also involved in the development of cold allodynia following nerve injury (Obata *et al.*, 2005). Blocking TRPM8 has been found to be associated with a reduction in nerve injury-induced cold hypersensitivity (Knowlton *et al.*, 2011). Importantly, however, TRPM8 activation seems to have an analgesic effect in neuropathy-associated pain (Proudfoot *et al.*, 2006).

Heat hyperalgesia associated with peripheral nerve injury

TRPM2 (Haraguchi *et al.*, 2012) and TRPV1 (Vilceanu *et al.*, 2010) have both been implicated in the development of heat hyperalgesia following peripheral nerve injury.

Nociception-related TRP channels which are involved in the detection of noxious stimuli but have not been shown to contribute to the development of pathological pain

Although TRPV2 is responsive to temperatures above 50°C, TRPV2$^{-/-}$ mice show no deficits in responses to heat stimuli (Park *et al.*, 2011a). Furthermore, TRPV2 has not yet been shown to be involved in the development of pain associated with peripheral pathologies.

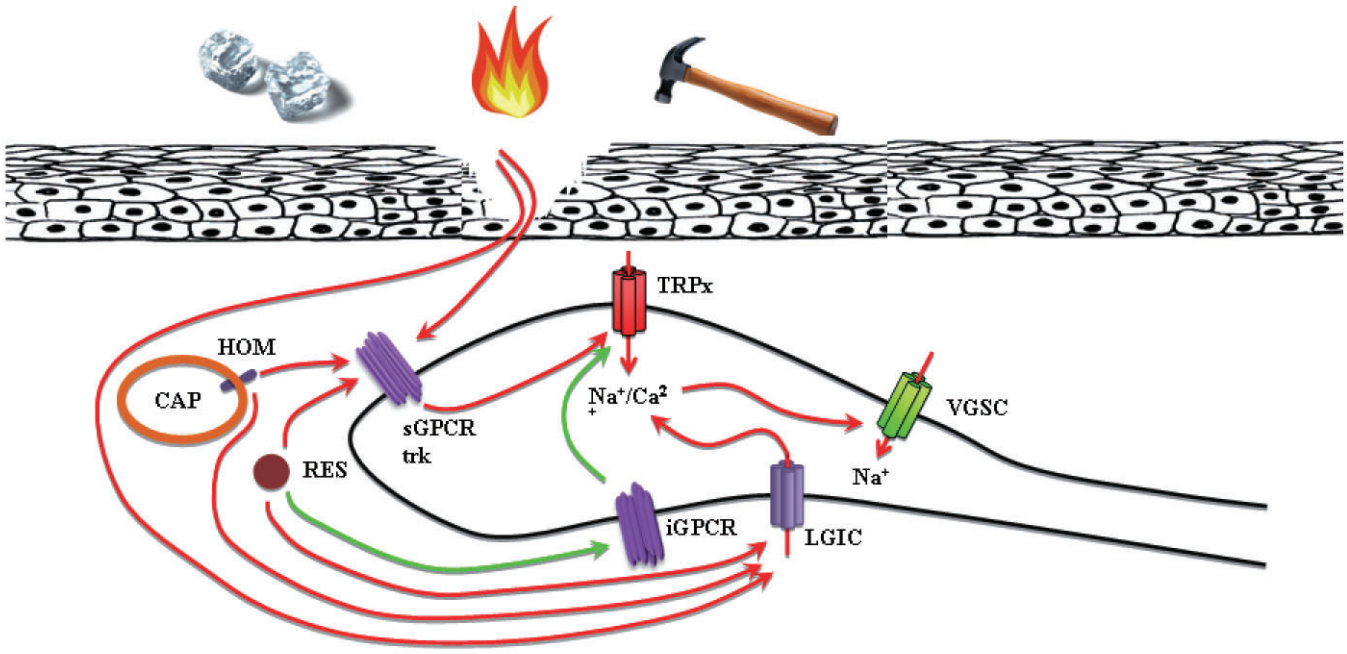
Moqrich *et al.* (2005) have reported that TRPV3$^{-/-}$ mice exhibit a significant change in temperature preference and lack of responses to noxious heat stimuli. Hence, these authors concluded that TRPV3, which is expressed in keratinocytes rather than sensory neurons (Peier *et al.*, 2002), plays a specific role in both noxious and innocuous thermal sensation. However, others found no obvious differences in temperature preference or noxious heat-evoked responses in TRPV3$^{-/-}$ mice, although these behavioural responses may depend on the background strain of the knockout animals (Huang *et al.*, 2011). Nevertheless, several specific antagonists have been developed for TRPV3 (Reilly and Kym, 2011). Yet, due to unresolved discrepancies in tissue distribution and species differences, recognition of TRPV3 as a desirable target for pain treatment is problematic (Reilly and Kym, 2011).

Interestingly, TRPV3 single nucleotide polymorphism has been associated with migraine in a small population case-control genetic association study (Freilinger *et al.*, 2012; Carreño *et al.*, 2011). In addition to TRPV2, TRPM8 may also have an important role in the development of migraine (Esserlind *et al.*, 2013). Finally, TRPA1 seems to significantly contribute to the development of headache following exposure to environmental irritants including cigarette smoke (Kunkler *et al.*, 2011).

Based on the pattern of expression and the effect of deleting or blocking nociception-related TRP channels, TRPV1, TRPV4, TRPA1, TRPM2, TRPM3 and TRPM8 may provide particularly valuable targets for the development of novel analgesics to control chronic pain of inflammatory or peripheral nerve injury origin. These data also suggest that while several channels could be targeted for the control of a given modality of pain in a given pathology, a 'magic bullet' approach is unlikely to work. Interestingly, while TRPV1, TRPV4, TRPA1, TRPM2 and TRPM3 activity must be reduced in PSN to produce an analgesic effect, the direction of change in TRPM8 activity for producing analgesia may depend on the nature of the peripheral pathological process. Based on our present knowledge, multiple nociception-related TRP channels may be involved in the development of a particular pain modality, necessitating the potential targeting of several different channel types to induce analgesia.

Strategies to modulate nociception-related TRP channels

In normal physiological conditions, nociception-related TRP channels in PSN function primarily as proteins designed to detect potentially harmful, tissue-damaging physical or chemical contacts, and it is important that this function is maintained during targeting the channels in peripheral pathologies. In pathological conditions, nociception-related TRP channels become sensitized and produce larger responses, which are initiated at lower stimulus strength (Patapoutian *et al.*, 2009; Stein *et al.*, 2009; Boesmans *et al.*, 2011; Holzer, 2011; Vay *et al.*, 2012). As a result, the depolarization produced by the activation of sensitized TRP channels becomes larger and longer-lasting, upon which neurons generate more action potentials than in the physiological state. This sensitization process is supported by increased transcription and translation, post-translational modification and increased membrane expression of the TRP channels (Patapoutian *et al.*, 2009; Holzer, 2011; Vay *et al.*, 2012). These changes are initiated by substances produced during the pathological process (Patapoutian *et al.*, 2009; Stein *et al.*, 2009; Holzer, 2011; Vay *et al.*, 2012). In addition to pronociceptive agents, tissue damage is also associated with the production of antinociceptive molecules, such as resolvins (Bang *et al.*, 2010c; Ji *et al.*, 2011). Furthermore, several receptors and ion channels are expressed by PSN that are, potentially, able to reduce the activity of nociception-related TRP channels. Hence, there are five main approaches to reduce the activity of PSN in which nociception-related TRP channels are involved (Figure 1). These are: (i) the reduction of the production, release and action of agents on PSN which initiate and/or maintain the sensitization process; (ii) the reduction of channel activity by antinociceptive molecules produced during the tissue damage; (iii) activation



Reduction of the production, release and action of agents on PSN which initiate and/or maintain the sensitization process (e.g. inflammatory mediators)

The use of naturally occurring inhibitory molecules (e.g. resolvin)

Activation of inhibitory receptors (e.g. CB_1 receptor)

Reduction of action potential generation and propagation (e.g. VGSC, HCN2)

Reduction of nociception-related TRP channel activity
- desensitization
- inhibition of the activation and/or the activity of the channel

Figure 1

Schematic drawing of peripheral processes that could serve as targets for reducing the activity of nociception-related TRP channels. Red arrows indicate sensitizing processes that could be inhibited, while green arrows indicate inhibitory processes, which could be activated in order to reduce the activity of nociception-related TRP channels. Abbreviations: CAP, capillary; HCN2, hyperpolarization-activated cyclic nucleotide-gated K^+ channel 2; HOM, homing immunocompetent cell; LGIC, nociception-related TRP channel-sensitizing ligand-gated ion channel; PSN, primary sensory neuron; RES, resident immunocompetent cells; sGPCR, nociception-related TRP channel-sensitizing GPCR; trk, nociception-related TRP channel-sensitizing tyrosine kinase-coupled receptor; TRP, transient receptor potential ion channel; TRPx, nociception-related TRP channel; VGSC, voltage-gated sodium channel.

of inhibitory receptors, which are co-expressed with nociception-related TRP channels in PSN; (iv) the reduction of action potential generation and propagation; and finally, (v) the reduction of nociception-related TRP channel activity. Of these five possibilities, due to space limitations, we will give a short summary of (i)–(iv) in the succeeding paragraphs, followed by a detailed discussion of approaches for (v).

A large number of agents are known to sensitize TRP channels, including bradykinin, nerve growth factor, PGE_2, phosphatidylinositol phosphates and TNF-α (Tabata *et al.*, 2002; Nilius *et al.*, 2007; Zhang *et al.*, 2008; Adcock, 2009). All of the above have been targets for producing analgesic effects; more detailed descriptions of these trials are provided in recent reviews (Dray, 2008; Schumacher, 2010; Vay *et al.*, 2012).

The ultimate result of the activation/activity of nociception-related TRP channels is the generation and propagation of action potentials in sensory pathways to pain centres in the brain. Hence, blocking the activity of ion channels involved in action potential generation and propagation is also a promising means of reducing pain initiated by the activity of nociception-related TRP channels. Voltage-gated Na^+ channels, which are specifically expressed in nociceptive PSN, constitute one of the main choices of targets for this approach (Dray, 2008). Three of the nine voltage-gated Na^+ channels, $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$ are expressed specifically by nociceptive PSN (Krafte and Bannon, 2008; Liu and Wood, 2011). Based on promising preclinical data, several clinical trials have been initiated with novel sodium channel blockers (Heinzmann and McMahon, 2011). Progress has been slow but initial results with selective $Na_V1.7$ blockers are encouraging (Chowdhury *et al.*, 2011; Dib-Hajj *et al.*, 2012).

A fascinating approach to block voltage-gated Na^+ channels in PSN has recently been proposed. This approach uses capsaicin to activate TRPV1 to introduce the membrane-impermeant derivative of the local anaesthetic lidocaine QX-314 to the intracellular binding site on sodium channels (Binshtok *et al.*, 2007). QX-314 then blocks action potential generation only in TRPV1-expressing PSN. Hence, any unwanted action of a drug on non-nociceptive sensory, autonomic and motor neurons can be avoided. This targeted delivery technique approach should be further explored.

Another way to reduce the action potential generation in PSN has recently been reported; this involves a reduction in the activity of the hyperpolarization-activated cyclic nucleotide-gated K^+ channel 2 (HCN2; Emery *et al.*, 2011). HCN2 is expressed in small diameter PSN (Momin *et al.*, 2008) and its activity contributes to action potential generation and the development of pain-related behaviour in inflammatory conditions as well as following peripheral nerve injury (Emery *et al.*, 2011). Based on preclinical data, HCN2 is a very promising target to reduce action potential generation and propagation initiated by the activity of nociception-related TRP channels in PSN.

As mentioned above, inflammation is associated with the production of anti-inflammatory and antinociceptive agents, such as resolvins, which are omega-3 fatty acid derivatives (Serhan and Chiang, 2013). Resolvin D1, D2 and E1 have been shown to inhibit responses mediated by TRPV1, TRPV3, TRPV4 and/or TRPA1 and reduce pain (Bang *et al.*, 2010c; 2012b; Park *et al.*, 2011b). Resolvins produce their inhibitory effects through GPCRs, and the signalling involves the mitogen-activated kinase pathway (Xu *et al.*, 2010; Park *et al.*, 2011b). Again, based on these preclinical data, resolvins seem to be promising to reduce the activity of at least some of the nociception-related TRP channels.

Nociceptive PSN express various GPCRs, including the cannabinoid type 1 (CB_1) receptor, the $GABA_B$ receptor, the M_2 ACh receptor, the NPY Y_2 receptor, several opioid, 5-HT, α-adrenoceptors, histamine and metabotropic-glutamate (mGlu) receptors (Ji *et al.*, 1995; Chen *et al.*, 1998; Ongioco *et al.*, 2000; Tata *et al.*, 2000; Towers *et al.*, 2000; Brumovsky *et al.*, 2005; Chiechio *et al.*, 2006; Carlton and Hargett, 2007; Medhurst *et al.*, 2008; Carlton *et al.*, 2009; 2011; Strakhova *et al.*, 2009; Govea *et al.*, 2012; De Angelis *et al.*, 2013). Activation of these receptors results in the inhibition of adenylate cyclase activity (Sharman *et al.*, 2013), which sensitizes several nociception-related TRP channels including TRPV1, TRPV4, TRPM8 and TRPA1 (Table 4). Therefore, activation of these GPCRs may produce an analgesic effect by reducing the activity of nociception-related TRP channels. Indeed, activation of the μ-, κ- and δ-opioid receptors, the CB_1 receptor, the α_{2C}-adrenoceptor, group II mGlu receptors ($mGlu_2$ and $mGlu_3$) and the $mGlu_8$-receptor have been shown to reduce TRPV1-, TRPM8- and TRPA1-mediated cellular and/or behavioural responses (Ma *et al.*, 2005; Vetter *et al.*, 2006; Werkheiser *et al.*, 2006; De Petrocellis *et al.*, 2007; Endres-Becker *et al.*, 2007; Fischbach *et al.*, 2007; Carlton *et al.*, 2009; Mahmud *et al.*, 2009; Santha *et al.*, 2010; Wrigley *et al.*, 2010; Govea *et al.*, 2012; Shapovalov *et al.*, 2013).

With regard to targeting nociception-related TRP channels directly for the control of pain, there are two main approaches (Figure 1). The first approach utilizes desensitization, the principle characteristics of certain nociception-related TRP channels. The second approach entails inhibiting the activation and/or activity of the channel.

Desensitization

Excessive activation of TRP channels including some of those that are involved in nociception induces desensitization (Porszasz and Jancso, 1959; Caterina *et al.*, 1997; McKemy *et al.*, 2002; Xu *et al.*, 2005; Gordon-Shaag *et al.*, 2008). Hence, inducing excessive channel activation, if this process is not unduly painful, may offer analgesia through targeting nociception-related TRP channels in PSN. This approach has long been employed via the use of capsaicin, resiniferatoxin or camphor for desensitizing TRPV1. However, these agents may produce initial irritation and require multiple applications. Therefore, attempts have been made to develop activators, which do not produce pain but desensitize the channel. Thus far, no such compound has been introduced into clinical practice. It appears that the main reason for this failure is the limited efficacy of these compounds. Another limitation of this approach is that the desensitization often results in complete unresponsiveness to noxious stimuli of the area supplied by the desensitized nerve, which may present a significant risk of tissue injury. In addition, excessive activation may result in degeneration of the affected sensory nerve fibres (Jancsó *et al.*, 1977; 1985; Jancsó and Lawson, 1990). While degeneration of small peripheral terminals of sensory

Table 4

Endogenous activators/sensitizers of nociception-related TRP channels

TRP channel	Endogenous activators/ sensitizers	References
TRPV1	AEA, OEA, PEA	Zygmunt *et al.* (1999); Ahern (2003); Ambrosino *et al.* (2013)
	NADA and OLDA	Huang *et al.* (2002); Chu *et al.* (2003)
	AA LOX products	Hwang *et al.* (2000)
	LPA	Nieto-Posadas *et al.* (2011)
	PIP_2	Chuang *et al.* (2001) but see Liu *et al.* (2005); Stein *et al.* (2006)
	DAG	Woo *et al.* (2008)
	PKC	Numazaki (2002); Bhave *et al.* (2003); Studer and McNaughton (2010)
	CaM(–)	Lishko *et al.* (2007)
	Ca^{2+}	Ahern *et al.* (2005)
	CaMKII	Jung *et al.* (2004)
	PKA(+/–)	Rathee *et al.* (2002) but see Bhave *et al.* (2002); Mohapatra and Nau (2003)
TRPV2	CaMKII	Boels *et al.* (2001)
	PKA	Stokes *et al.* (2004)
TRPV3	Farnesyl pyrophosphate 17R-RvD1	Bang *et al.* (2010b) Bang *et al.* (2012a)
	AA	Hu *et al.* (2006)
	CaM(–)	Xiao *et al.* (2008)
	Ca^{2+}	Xiao *et al.* (2008)
TRPV4	AEA	Watanabe *et al.* (2003)
	AA and AA EPOX products	Watanabe *et al.* (2003)
	NAT	Saghatelian *et al.* (2006)
	DMAPP	Bang *et al.* (2012b)
	PKC	Fan *et al.* (2009)
	CaM (–)	Strotmann *et al.* (2003)
	Ca^{2+}	Strotmann *et al.* (2010)
	PKA	Fan *et al.* (2009)
TRPC1	PIP2	Saleh *et al.* (2009)
	DAG	Lintschinger *et al.* (2000)
	PKC	Ahmmed *et al.* (2004)
	CaM	Kwon *et al.* (2007)
	Ca^{2+}	Zitt *et al.* (1996)
	CaMKII	Cuddapah *et al.* (2013)
TRPC6	$PIP_{2/3}$	Kwon *et al.* (2007)
	DAG	Hofmann *et al.* (1999)
	PKC(–)	Bousquet *et al.* (2010)
	CaM(–)	Kwon *et al.* (2007)
	Ca^{2+}	Boulay (2002)
	CaMKII	Shi *et al.* (2013)
TRPM2	ADP	Perraud *et al.* (2001)
	cADP	Kolisek *et al.* (2005)
	NAADP	Beck *et al.* (2006)
	ROS	Nagamine *et al.* (1998)
	PIP_2	Toth *et al.* (2009)
	PKC	Nazıroğlu and Özgül (2013)
	CaM	Tong *et al.* (2006)
	Ca^{2+}	Starkus *et al.* (2007)

Table 4

Continued

TRP channel	Endogenous activators/ sensitizers	References
TRPM3	Sphingosine	Grimm *et al.* (2005)
	Pregnenolone sulphate	Wagner *et al.* (2008)
	PIP_2	Holakovska *et al.* (2012)
	CaM(–)	Holakovska *et al.* (2012)
	Ca^{2+}	Lee *et al.* (2003)
TRPM8	Lysophospholipids	Vanden Abeele *et al.* (2006); Andersson *et al.* (2007)
	Cyclopentenone PG	Taylor-Clark *et al.* (2007); Andersson *et al.* (2008); Cruz-Orengo *et al.* (2008); Materazzi *et al.* (2008)
	AA(–)	Andersson *et al.* (2007)
	PIP_2	Liu *et al.* (2005); Rohács *et al.* (2005)
	PKC(–)	Abe *et al.* (2006)
	CaM	Sarria and Gu (2010)
	Ca^{2+}(–)	McKemy *et al.* (2002)
	CaMKII(–)	Sarria and Gu (2010)
	PKA(–)	De Petrocellis *et al.* (2007)
TRPA1	AA, AA LOX and AA EPOX Hydrogen sulfide	Bandell *et al.* (2004) Brenneis *et al.* (2011); Gregus *et al.* (2012); Sisignano *et al.* (2012) Okubo *et al.* (2012)
	PIP_2 (–)	Dai *et al.* (2007); Kim *et al.* (2008)
	DAG	Bandell *et al.* (2004)
	PKC	Wang *et al.* (2007)
	Ca^{2+}	Doerner *et al.* (2007)
	PKA	Wang *et al.* (2007)

17R-RvD1, 17(R)-resolvin D1; AA, arachidonic acid; AEA, anandamide; cADP, cyclic adenosine diphosphate ribose; CaM, calmodulin; CaMKII, Ca2+/calmodulin-dependent protein kinase II; DMAPP, dimethylallyl pyrophosphate; EPOX, epoxygenases; LOX, lipoxygenase; LPA, lysophosphatidic acid; NAADP, nicotinamide adenine dinucleotide phosphate; NADA, N-arachidonoyldomanine; NAT, N-acyl taurine; OEA, oleoylethanolamine; OLDA, N-oleaoyldomine; PEA, palmitoylethanolamine; PIP_2, phosphotidylinositol (4,5) bisphosphate, ROS, reactive oxygen species.
(–) indicates negative effect.
(+/–) indicates debated effect.

neurons is not permanent, desensitization might not be an attractive approach for many because of the presence of anaesthesia for a longer time. Nevertheless, desensitization of nociception-related TRP channels in PSN – particularly for TRPV1 – is an existing and effective means of pain control (Apostolidis *et al.*, 2006; Anand and Bley, 2011; Iadarola and Mannes, 2011). At present, a dermal patch containing 8% capsaicin is available for the treatment of postherpetic neuralgia and human immunodeficiency virus infection-associated pain (Center for Drug Evaluation and Research, 2009). Other formulations, such as a spray from Winston Pharmaceuticals (Vernon Hills, IL, USA), to tackle postherpetic neuralgia and other painful conditions affecting the area of innervation by the trigeminal nerve are under development (Mandadi and Roufogalis, 2008).

Blocking of nociception-related TRP channel activity

Nociception-related TRP channels are polymodal receptors, which respond to various physical stimuli as well as endogenous agents (Table 4). The endogenous agents, which either directly activate or sensitize the channel, include second messengers, inflammatory mediators and their metabolites, and membrane constituents and their metabolites (Mandadi and Roufogalis, 2008) (Table 4). Hence, there are several activation and sensitization sites in nociception-related TRP channels and some of these, particularly those for second messengers such as PKA or PKC, TKs or non-receptor TKs may not be specific for a given channel. A further complication regarding activation and sensitization sites is that a second messenger that positively modulates the activity of one channel may have a negative effect on another channel. For example, calmodulin has a negative modulatory effect on TRPV1 but has a sensitizing effect on TRPC1, TRPC6 and TRPM3 (Numazaki *et al.*, 2003; Kwon *et al.*, 2007; Holakovska *et al.*, 2012).

Among the activation sites, one may regard those which respond to heat, cold or mechanical stimuli as being particularly useful targets for drug therapy, because due to sensitization-induced changes, ambient temperature or low

intensity mechanical stimuli can activate these sites. However, at present, our understanding of the molecular identity of these sites, as well as, their mechanism of action is very limited (Nilius *et al.*, 2005; Brauchi *et al.*, 2006; Voets *et al.*, 2007). As already mentioned, nociception-related TRP channels belong to a warning system, which aims to prevent tissue damage, whereas some of the temperature-sensitive TRP channels – as has been shown using TRPV1, TRPV3, TRPM8 and TRPA1 antagonists – are involved in the regulation of body temperature (Masamoto *et al.*, 2009). Hence, inhibition of these channels may result in the disruption of thermoregulatory processes or the detection of accidental tissue damage, as demonstrated during clinical trials with novel TRPV1 antagonists (Rawls and Benamar, 2011; Kort and Kym, 2012). Similar undesirable side effects can be expected from directly blocking other nociception-related ion channels.

Endogenous activators produced during a pathological process are also believed to contribute to enhanced activity of nociception-related TRP channels (McVey *et al.*, 2003; Dinis *et al.*, 2004b; Bang *et al.*, 2010a). Hence, another strategy to inhibit nociception-related TRP channels entails inhibiting either the synthesis and/or the release of endogenous activators for these channels or inhibiting the binding site for these agents. However, these approaches are complicated by the apparent existence of multiple endogenous activators for the majority of channels (Zygmunt *et al.*, 1999; Watanabe *et al.*, 2003; Bandell *et al.*, 2004; Taylor-Clark *et al.*, 2007; Andersson *et al.*, 2008; Urban *et al.*, 2011). Again, blocking the binding site of endogenous activators must not affect sites that respond to physical stimuli. This separation of effects necessitates a much better understanding of the mechanism of actions of, and the relationship and communication between, the various parts of the ion channels.

The involvement of nociception-related TRP channels in pain signalling relies on their sensitization status (Patapoutian *et al.*, 2009; Stein *et al.*, 2009; Holzer, 2011; Vay *et al.*, 2012). Therefore, as also noted by Holzer (2008) and Boesmans *et al.* (2011), a more realistic intervention would involve specifically inhibiting the activation of sensitized nociception-related TRP channels without reducing the activity of non-sensitized channels. This could be achieved by preventing the sensitization event itself. As noted above, sensitization involves increased transcription and translation, various post-translational changes as well as translocation of the ion channel from the cytoplasm to the cell membrane (Patapoutian *et al.*, 2009; Holzer, 2011; Vay *et al.*, 2012). Hence, there are three possibilities to prevent or at least reduce sensitization of nociception-related TRP channels in PSN.

Firstly, up-regulation of nociception-related TRP channel transcription could be targeted at several sites along the regulatory process of gene transcription and translation. One possibility is to deliver small interfering RNA (siRNA) or antisense oligonucleotides to the cell body of PSN, for example, through intrathecal administration of these molecules. In fact, reducing TRPV1 expression by such approaches has been shown to attenuate visceral and neuropathic pain in rats (Christoph *et al.*, 2006; 2007). Delivering siRNA into PSN has not yet been properly developed, although a recent report from Samad *et al.* (2012) shows that intraganglionic injection of a small hairpin RNA-adeno-associated viral construct provides a highly efficient and targeted route for delivery. However, this approach would interfere with the expression of TRP channels in unaffected neurons in the ganglia and, hence, increase the risk of side effects.

The next possibility to intervene with sensitization of nociception-related TRP channels is to inhibit channel trafficking from cytosolic compartments to the cell membrane, so as to reduce the availability of TRP channels on the cell surface. It has been well documented that TRPV1, TRPV4 and TRPA1 translocate rapidly from the cytoplasm to the cytoplasmic membrane following various post-translational modifications such as phosphorylation or glycosylation induced by mediators found in injured/inflamed tissues (Morenilla-Palao *et al.*, 2004; Van Buren *et al.*, 2005; Zhang *et al.*, 2005; Cuajungco *et al.*, 2006; Stein *et al.*, 2006; Xu *et al.*, 2006; D'hoedt *et al.*, 2008; Schmidt *et al.*, 2009). It appears that the molecular basis for this translocation is different for the various nociception-related TRP channels, which may provide specificity for targeting. For example, while TRPV1 translocation involves synaptosomal-associated protein 25 receptor proteins, TRPV4 translocation requires association with PKC and casein kinase substrate in neurons protein 3 (Morenilla-Palao *et al.*, 2004; Cuajungco *et al.*, 2006). However, utilization of this attractive approach requires detailed elucidation of the regulation of translocation for all nociception-related TRP channels, as well as the development of agents which interfere with the translocation process and an effective and preferably non-invasive intracellular delivery of those novel agents.

The third possibility to inhibit or reduce sensitization of nociception-related TRP channels is blocking the site of the channel that is pivotal in the sensitization process. Recently, Zhang *et al.* (2008) have identified the molecular complex formed between TRPV1, the A kinase anchoring protein 79/159 (AKAP79/150), and PKA, PKC and calcineurin, which all modulate TRPV1 activity, as the 'final common element' of TRPV1 sensitization and the development of inflammatory heat hyperalgesia. Fischer *et al.* (2013) identified the binding site for AKAP79/150 on TRPV1 and designed a small peptide to interact with that site. They have reported that blocking the interaction between TRPV1 and AKAP79/150 indeed results in reduced TRPV1 sensitization and inflammatory pain without affecting physiological TRPV1-mediated responses (Fischer *et al.*, 2013). Hence, this approach may provide a selective and specific way to reduce the activity of sensitized nociception-related TRP channels in PSN. However, the adoption of this approach for other nociception-related TRP channels requires the identification of specific sequences involved in the sensitization process of each channel type and the design of drugs with good bioavailability, preferable pharmacodynamics and pharmacokinetics.

Conclusions

In summary, nociception-related TRP channels expressed by PSN play important roles in the development of pain originating in various peripheral pathologies. Hence, they may offer highly valuable targets for the development of novel analgesics. While several approaches are available to target

nociception-related TRP channels in PSN for drug therapy, there are various serious difficulties involved in attempting to translate apparently satisfactory laboratory results into novel analgesics suitable for clinical use. Of these approaches, targeting of translocation of TRP channels from the cytoplasm to the cell membrane or targeting of specific sensitization sites of the relevant channel may prove the most effective control of pain without intolerable side effects. However, implementing these approaches requires the identification of the molecular basis of channel translocation and/or the main sensitization sites in various channels and the development of specific and selective agents with good bioavailability properties. Until these agents become available for clinical use, clinicians are compelled to rely upon techniques that involve the blocking of nociception-related TRP channels by desensitization.

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Conflict of interest

The authors declare no conflict of interest.

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