TRPs and Pain

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Abstract

Pain usually occurs as a result of tissue damage and has a role in healing and protection. However, in certain conditions it has no functional purpose and can become chronic and debilitating. A demand for more effective treatments to deal with this highly prevalent problem requires a better understanding of the underlying mechanisms. TRP channels are associated with numerous sensory functions across a wide range of species. Investigation into the expression patterns, electrophysiological properties and the effects of channel deletion in transgenic animal models have produced a great deal of evidence linking these channels to transduction of noxious stimuli as well as signalling within the pain system.

Keywords

TRP channels • Pain • Nociception • Inflammation • Neuropathy • Analgesia

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1 Pain and Nociception

Pain is a complex phenomenon which has been described by the International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (http://www.iasp-pain.org). The perception of pain is usually the result of tissue damage caused by a noxious stimulus and as such has a protective function as well as being important for allowing healing of damaged tissue. Specialised damage-sensing neurons that innervate the skin, muscle and viscera are activated by noxious stimuli, and this initial transduction of pain-producing stimuli is known as nociception. Noxious stimuli can be mechanical, thermal or chemical, and they activate nociceptors, a type of sensory afferent neuron whose cell bodies lie in the dorsal and trigeminal root ganglia. The two main categories of nociceptor are Aδ and C fibres which are myelinated and unmyelinated, respectively. As a result of their myelination state and their larger diameter, Aδ fibres have a greater conduction velocity than C fibres and are responsible for the so-called first pain, a pinprick sensation which precedes the burning sensation, and the 'second pain' mediated by small-diameter unmyelinated C fibres. C fibres can be subdivided into peptidergic and non-peptidergic sets according to their expression profiles; peptidergic C fibres express the TrkA receptor and respond to nerve growth factor (NGF), while non-peptidergic nociceptors bind the lectin IB4 and are sensitive to glial-derived neurotrophic factor (GDNF) acting through the c-Ret receptor. Each subtype of sensory neurons expresses a different subset of transient receptor potential (TRP) channels which are linked to a variety of functions (Table 1).

Although pain usually arises from a stimulus, it can occur without noxious input or outlast the initial insult and become chronic. A large-scale survey estimated that approximately 19 % of people in Europe suffer from chronic pain (http://www.britishpainsociety.org/Pain%20in%20Europ%20survey%20report.pdf, British Pain Society 2003). The comorbidities associated with chronic pain are numerous and debilitating, including depression, anxiety and insomnia. It was also reported that 1 in 5 sufferers in Europe have lost, or had to leave, their job as a result of their pain. Chronic pain can occur as a result of either inflammatory or neuropathic processes.

Inflammation associated with sensitisation (reduced pain thresholds) is characterised by redness, swelling and tenderness. Following tissue damage peripheral leucocytes, Schwann cells and endothelia release proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1), which leads to an increase in NGF production by macrophages. In turn, NGF forms part of a positive feedback loop whereby it binds to receptors such as TrkA on the peripheral terminals of nociceptors. As a consequence, tyrosine kinases phosphorylate TRPV1 which then is trafficked into the plasma membrane (Zhang et al. 2005a, b). NGF also activates mast cells which release mediators such as prostaglandins, bradykinin, ATP and serotonin (5-HT), adding to the inflammatory milieu. This cycle of events via its effect on TRPV1 function leads to nociceptor sensitisation as well as increased excitability at central terminals resulting in symptoms such as thermal and mechanical hyperalgesia. When these proinflammatory effects persist, chronic

Table 1 Summary of TRP channel expression in sensory neurons and the potential roles in pain

TRP	Peripheral sensory neuron expression	Possible role in pain
TRPV1	Peptidergic small- and medium-diameter sensory neurons (Caterina et al. 1997)	Inflammatory hyperalgesia
TRPV2	Peptidergic small-diameter and medium-diameter fibres (Caterina et al. 1999)	Appears to be upregulated in DRG in certain models of inflammatory pain, though functional significance unclear
TRPV3	Peptidergic small- and medium-diameter sensory neurons (in a subset of TRPV1+ neurons) (Smith et al. 2002); keratinocytes (Peier et al. 2002a, b)	Acute noxious heat
TRPV4	Small- and medium-diameter sensory neurons (Facer et al. 2007)	Inflammatory mechanical and thermal hyperalgesia
TRPA1	Peptidergic small- and medium-diameter sensory neurons (co-expressed with TRPV1) (Story et al. 2003)	Acute noxious cold mechanosensation
TRPM8	Small-diameter, capsaicin-insensitive neurons (higher expression in TG than DRG) (McKemy et al. 2002)	Innocuous cold, noxious cold activated by temperatures 8 °C–28 °C.
TRPC1	Peripheral sensory neurons (Elg et al. 2007). Co-expressed with TRPV4 and TRPC6 (Alessandri-Haber et al. 2009)	Mechanical hyperalgesia
TRPC6	Most peripheral sensory neurons (Quick et al. 2012) co-expressed with TRPV4 and TRPC1 in peripheral sensory neurons (Alessandri-Haber et al. 2009)	Mechanical hyperalgesia

pain can occur and is seen, for example, in conditions such as osteoarthritis where ongoing pain and increased sensitivity in the affected joints are highly detrimental to normal life.

Neuropathic pain is the result of damage, disease or dysfunction within the nervous system. When damage occurs, several key events follow which can lead to spontaneous pain, hyperalgesia (enhanced sensitivity to a noxious stimulus) and allodynia (pain from a normally non-noxious stimulus). For example, there is a loss of trophic support; usually, NGF and other growth factors such as GDNF are taken up by peripheral neurons and retrogradely transported to the cell somata. When peripheral neurons are damaged, the portion of the cell distal to the injury begins to degenerate, and consequently, the peripheral receptors can no longer respond appropriately to growth factor inputs. Further, the contents of the cell, including growth factors and neurotransmitters, are released into the surrounding area. As a result, not only is there aberrant activity and ectopic transduction in the damaged neuron itself, but there is also an increase in excitability of surrounding neurons. Peripheral nociceptors themselves also undergo an increase in excitability and response to a wider range of stimulus intensities. The barrage of peripheral activity which occurs following damage to the nervous system also leads to sensitisation centrally. It is important to note, however, that while animal models of neuropathic pain (Fig. 1) have elucidated many details of underlying mechanisms of pain

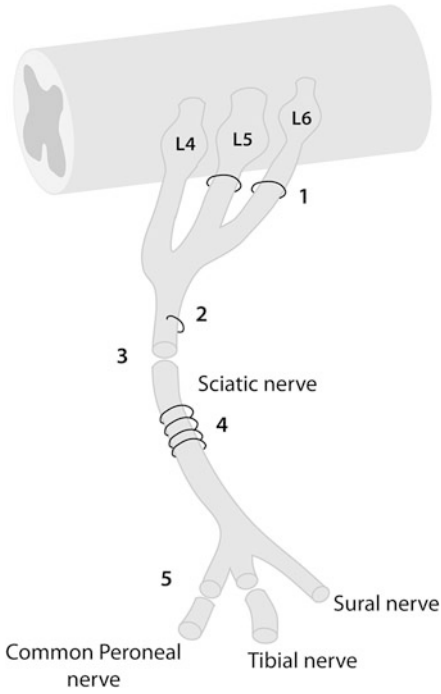

Fig. 1 Models of neuropathic pain. (1) *SNL* spinal nerve ligation; tight ligation of L5 and L6 spinal nerves. (2) *PSNL* partial sciatic nerve ligation; tight ligation of between one third and one half of the sciatic nerve. (3) *SNT* sciatic nerve transection; complete transection of sciatic nerve. (4) *CCI* chronic constriction injury; 3–4 loose ligatures around nerve. (5) *SNI* spared nerve injury; tibial and common peroneal branches of the sciatic nerve are transected distal to its trifurcation

consequent to nerve damage, they have also highlighted that each model can undergo different molecular and cellular changes, albeit with an apparently similar nociceptive phenotype (Koltzenburg and Scadding 2001).

Existing analgesics, centred around opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), are limited in their efficacy and are frequently associated with undesirable side effects and can induce dependence. The development of new, more effective analgesics therefore requires new potential targets and a better understanding of the underlying mechanisms of pain.

2 Heat

A number of TRP channels have been linked to noxious heat and cold transduction. When TRPV1 was first identified, it was named vanilloid receptor subtype 1 (VR1) because of its response to capsaicin, a component of capsicum peppers which is the active ingredient in spicy foods (Caterina et al. 1997). TRPV1 has repeatedly been shown to be activated by noxious thermal stimuli (temperatures >43 °C) and low pH (Caterina et al. 1997, 2000). Interestingly, however, while mice lacking the TRPV1 receptor lose sensitivity to capsaicin as well as low pH, they exhibit almost no loss of sensitivity to acute noxious heat (Davis et al. 2000; Caterina et al. 2000; Woodbury et al. 2004). In contrast, in models of inflammatory pain induced by

carrageenan or complete Freund's adjuvant (CFA), thermal hyperalgesia is lost (Caterina et al. 2000; Davis et al. 2000). Consistent with a deficit in inflammation-induced thermal hyperalgesia in TRPV1 null mice, tissue damage leads to elevated TRPV1 expression in sensory neurons of the dorsal root ganglia (DRG) and in lamina I and II of the spinal cord (Amaya et al. 2003; Luo et al. 2004). Following these findings, Mishra et al. (2011) developed a conditional mouse model and found that selective ablation by diphtheria toxin of TRPV1-expressing sensory neurons results in loss of both sensitivity to acute noxious heat and thermal hyperalgesia. Thus the population of TRPV1 expressing neurons is involved in heat sensing, and TRPV1 is principally involved in inflammatory pain.

As TRPV1 has no role in sensing acute noxious heat (Davis et al. 2000), other members of the TRPV family were considered potential candidates for this function. TRPV2, though insensitive to capsaicin, confers sensitivity to high temperatures >52 °C in Xenopus oocytes (Caterina et al. 1999), although the relevance of this finding to mammalian cells has not been demonstrated. TRPV3 and TRPV4 are activated at 33–39 °C and 25–34 °C, respectively, and are expressed in sensory neurons (TRPV3 is co-expressed with TRPV1) and keratinocytes (Liedtke et al. 2000; Smith et al. 2002; Xu et al. 2002; Peier et al. 2002b; Chung et al. 2004). TRPV4 is sensitive to capsaicin, but TRPV3 is not (Smith et al. 2002), and instead it responds the phenylpropanoid eugenol (which is also detected by TRPV1 and TRPV3).

TRPV2 has been studied less intensively than TRPV1, and TRPV2 knockout mice have been available only since 2011 (Park et al. 2011). In these animals (which have reduced viability and survival into adulthood) no hyperalgesia develops after inflammation or spinal nerve ligation. Further evidence against an acute heat-sensing role for TRPV2 is provided by the fact that 82 % of heat-sensitive neurons in TRPV1 null mice do not express TRPV2 (Woodbury et al. 2004). Moreover, in TRPV1 neuron-depleted mice, TRPV2 expression was still found in spite of the complete loss of heat sensitivity (Mishra et al. 2011).

TRPV3 shows the unusual property of hysteresis. Current is progressively activated at temperatures above 28 °C, but if the preparation is cooled even slightly during the experiment, the current deactivates sharply. Moreover, the channel itself undergoes sensitisation after a train of stimuli, whereby the current is evoked more reliably after the temperature is stepped repeatedly from 21 °C to 45 °C (Liu et al. 2011; Peier et al. 2002b). TRPV3 also supports a secondary current, which develops after channel sensitisation, with increased amplitude, loss of rectification and altered permeability to cations (Chung et al. 2005). These observations plausibly account for some features of peripheral sensitisation; however since the expression of TRPV3 is higher in keratinocytes than in nervous tissue, some of the behavioural effects might be only indirectly neuronal. TRPV3 null mice show deficits in detection of noxious heat but not a complete loss of sensitivity, and mice develop thermal hyperalgesia induced by bradykinin and CFA in the same way as wild-type controls (Moqrich et al. 2005).

TRPV4 is the mammalian homologue of the *C. elegans* osmosensor *osm-9*. Osmolar and pH changes occur as a result of inflammation, motivating a study

(Alessandri-Haber et al. 2003) on single fibres of rat sensory nerve in hypotonic solution. This treatment activated a proportion of the fibres, an effect that was enhanced by application of the inflammatory mediator prostaglandin but was reduced by antisense to TRPV4. Knockout mice showed a reduced sensitivity to protons and altered thermal preference, whereas response to noxious heat was unimpaired, and thresholds of mechanical sensation were increased (Liedtke and Friedman 2003). The channel is sensitised by an agonist of protease-activated receptor 2/PAR2, which elicits mechanical hyperalgesia in mice but not in TRPV4 knockout animals. In rat spinal cord, PAR2 agonist stimulated release from the dorsal horn of the nociceptive neuropeptide, substance P, an effect presumed to depend on the expression of TRPV4, though this was not shown directly (Grant et al. 2007). In expression systems, TRPV4 is activated by heat, and the extent of activation is increased in hypotonic conditions (Güler et al. 2002) of the kind that might prevail during inflammation.

Since TRPV3 and TRPV4 have overlapping temperature response profiles, Huang et al. (2011) developed TRPV3/TRPV4 double knockout mice. They found no significant differences in the acute thermal responses or in various thermal preference paradigms between wild-type (WT) and TRPV3/4 null mice. Similarly, minimal differences were seen in null mice treated with a TRPV1 antagonist in both acute and inflammatory models of thermal pain suggesting this channel does not mask a role of TRPV3 and TRPV4 (Huang et al. 2011).

Inflammatory mediators (including bradykinin, ATP, cytokines) are released from endothelium and cells of the immune system in the neighbourhood of the nociceptor, and via receptors on the neuron surface, these factors can engage second messengers that act on TRP channels (Amadesi et al. 2006). Since TRPV1 null mice have deficits in thermal hyperalgesia, the role of TRPV1 in inflammatory pain states has been widely investigated. Pro-inflammatory mediators sensitise TRPV1, leading to induction and maintenance of thermal hyperalgesia, via protein kinase A (PKA) and PKA-mediated phosphorylation of the C-terminal. PKA accomplishes this in a process mediated by PKA-anchoring proteins (AKAP) leading to enhanced gating and increased TRPV1 translocation to the membrane; for example, inhibition of the AKAP79/150 protein prevents sensitisation of TRPV1 by bradykinin and PGE2 (Zhang et al. 2008). Protein kinase C (PKC) is able to reduce the activation threshold via phosphorylation of TRPV1 leading to enhanced gating and potentiation of channel activity (Premkumar and Ahern 2000; Vellani et al. 2001) and is upregulated in DRG during inflammation (Zhou et al. 2003).

PGE2 and PGI2, released following tissue damage, sensitise TRPV1 via PKC- and PKA-dependent mechanisms and are able to reduce the thermal threshold of TRPV1 to ~35 °C (Moriyama et al. 2005). By a similar mechanism of sensitisation, injection of the chemokine CCL3 in mice-induced thermal hyperalgesia (Zhang et al. 2005a, b), while treating cultured trigeminal ganglia (TG) neurons with 5-HT, also potentiates TRPV1 activity (Loyd et al. 2011). Bradykinin-mediated thermal hyperalgesia can be inhibited by administration of the TRPV1 antagonist, capsazepine, as well as by blocking activity of phospholipase C (PLC), PKC and PKA (Ferreira et al. 2004). Interestingly, TRPA1 null mice, and neurons in culture,

also show attenuated sensitivity to bradykinin in a similar way to TRPV1 null TG cultures and animal models (Bautista et al. 2006). TRPV1 and TRPV4 are both sensitised by ATP, a known mediator of inflammation. ATP reduces the sensitivity of TRPV3 whereas it has no effects on TRPV2 (Phelps et al. 2010). TRPV3 activation in keratinocytes, by agonists or heat, leads to release of PGE2 and appears to cause increased sensitivity to acute noxious heat and thermal hyperalgesia in a TRPV1-independent manner (Huang et al. 2008). Recruitment of 'silent' afferents which previously did not respond is a feature of sensitisation evoked by inflammation; there appears to be a single report on the role of TRP channels in this process, which concluded, on the basis of work in null mutant mice, that TRPV1 is not involved (Koerber et al. 2010). NGF can increase TRPV1 expression by upregulating its transcription and also via PKC-mediated phosphorylation of the channel (Ji et al. 2002); PI3K can also potentiate its activity and induce thermal hyperalgesia (Zhuang et al. 2004), and this requires tyrosine phosphorylation by Src family kinases (Zhang et al. 2005a, b). When retrogradely transported to the DRG, NGF activates the MAP kinase p38 which increases translation and transport of TRPV1 to the periphery where it contributes to maintenance of thermal hyperalgesia in inflammatory and neuropathic pain states (Ji et al. 2002).

TRPV1 expression is downregulated in damaged neurons following partial or total spinal nerve ligation (SNL) and in sciatic nerve transection (SNT), models of neuropathic pain (Hudson et al. 2001; Fukuoka et al. 2002). It is also upregulated in surrounding, undamaged neurons, for example, in L4 neurons following SNL of L5 (Fukuoka et al. 2002). This upregulation correlates with the thermal hypersensitivity profile observed after SNL (Fukuoka et al. 2002). Thermal nocifensive behaviour is reduced by block of NGF following chronic constriction injury (CCI) (Wilson-Gerwing et al. 2005), an effect which might depend on reduced levels of TRPV1. TRPV1 expression is also altered in human painful neuropathies; a loss of TRPV1-positive neurons in peripheral and sural nerves and in the skin was observed in diabetic and motor neuropathies (Lauria et al. 2006; Facer et al. 2007). An increase in TRPV1 and TRPV3 expression is seen in intact nerves after injury while TRPV4 appears to be unaltered (Facer et al. 2007).

3 Cold

Recently cell ablation studies have highlighted TRPM8-positive neurons as the key cell types involved in noxious cold perception in mice (Pogorzala et al. 2013). The threshold for noxious cold, as distinct from innocuous cool, is considered to occur at temperatures $<15\ ^{\circ}C$. TRPM8 is sensitive to menthol (a cooling compound) and cold, with a threshold of ~25 °C, and is activated by temperatures encompassing the innocuous cool and noxious cold range (McKemy et al. 2002; Peier et al. 2002a). TRPM8 is expressed in a subset of capsaicin-insensitive, small-diameter neurons in both dorsal root and trigeminal ganglia, though at higher levels in the latter (7.4 % vs. 14.8 %), consistent with greater cold sensitivity in structures of the face and

head (McKemy et al. 2002). Since TRPV1 expression is often considered a marker for nociceptors, this would suggest that TRPM8 is not involved in detection of noxious stimuli. Indeed, the use of TRPM8 null mice has firmly established a role for the channel in detection of innocuous cold though its role in detection of noxious stimuli is less conclusive. Knowlton et al. (2013) suggested that the cold-plate technique of measuring cold hypersensitivity, used in many of these investigations, was highly variable across earlier studies. Two groups found there was no difference in the nocifensive responses of TRPM8 null mice when compared to WT in a noxious cold-plate test (Bautista et al. 2007; Dhaka et al. 2007). However these same two groups showed a significant decrease in the response of these mice to application of the noxious cooling chemical acetone on the hind paw. Colburn et al. (2007) found a deficit in cold sensitivity in both of these assays, but this deficit was not reversed upon administration of TRPM8 antisense oligonucleotides.

It has emerged more recently that TRPM8 is upregulated in experimental bowel inflammation and that the TRPM8 agonist icilin, which attenuates chemically induced colitis in normal mice, presumably because the channel mediates a local cooling, brings no relief in the knockout animals (Ramachandran et al. 2013). In other circumstances, however, TRPM8 agonists lead to increases of core temperature, an effect that suggests coupling of central channels to the homeostatic mechanisms, whereas a TRPM8 blocker induces hypothermia (Ma et al. 2012; Knowlton et al. 2011). Once again, this example illustrates the apparently paradoxical effect of channels on somatosensation, when they are activated in different tissues by different experimental paradigms. Because TRPV1 is expressed in TRPM8-positive neurons during development but subsequently downregulated, conditional knockout of TRPV1 in sensory neurons also caused ablation of TRPM8. These animals showed significant deficits in responses to acute noxious cold (Mishra et al. 2011).

TRPA1 was the first candidate cold-sensing TRP channel. This channel is expressed in a subset of capsaicin-sensitive, calcitonin gene-related peptide (CGRP) positive neurons and has an activation threshold of 17 °C (Story et al. 2003) which is close to the cold temperature considered to be painful. Interestingly these neurons do not appear to co-express TRPM8 (Story et al. 2003).

TRPA1 is also activated by chemicals such as mustard oil (allyl isothiocyanate) which, when applied to the skin, elicits a burning or pricking sensation and causes aversive behaviour which is lost in TRPA1 null mice (Jordt et al. 2004; Bandell et al. 2004; Bautista et al. 2006; Kwan et al. 2006). Jordt et al. (2004) found that the majority (96 %) of cultured trigeminal neurons from rat which were sensitive to the mustard oil component allyl isothiocyanate (AITC) were insensitive to cold and that the remaining 4 % were sensitive to menthol, suggesting a role for TRPM8 in their cold sensitivity (Jordt et al. 2004). Also, when human embryonic kidney (HEK293) cells were transfected with TRPA1, although a response to mustard oil (AITC) was clearly observed, no responses to cold temperature of 5 °C were seen. Furthermore, it was shown that 5 % of the cold-sensitive neurons in culture were insensitive to both menthol and AITC, something corroborated by Babes

et al. (2004), indicating another mechanism for noxious cold sensitivity, independent of TRPA1 and TRPM8.

Kwan et al. (2006) reported that mice lacking the TRPA1 channel showed decreased responsiveness to noxious cold temperatures on a cold plate and reduced sensitivity to acetone application when compared with WT mice. Using the same behavioural assays, Bautista et al. (2006) observed no such difference. Furthermore, Bautista et al. (2006) cultured WT and TRPA1 null trigeminal neurons and found there was no difference in the magnitude of current in response to application of a noxious cold stimulus. It has been proposed that this discrepancy may be the result of different techniques and experimental setup (Kwan et al. found a greater deficit in the response of female mice while Bautista et al. only used males). Also, when considering the conflicting evidence provided by these models, the design of the knockout model must be considered. For example, some knockout constructs involve deletion of an entire gene while others may merely result in insertion of a cassette or premature stop codon. The latter may lead to generation of a truncated form of the protein. As a result, two knockout models of the same gene may vary substantially in their expression of that gene which may potentially impact upon the phenotype exhibited by each model. Indeed, TRP channels are known to heteromultimerise, and since the TRPA1 'null' mice used by both aforementioned groups are believed to express a truncated form of the channel, it has been suggested that this truncated form may exert an effect on other implicated channels, thus affecting the phenotype of the null mice (Foulkes and Wood 2007).

The difficulty in clarifying the role of TRPA1 in noxious cold detection led to investigations of its underlying properties. The release of Ca^{2+} from intracellular stores activates TRPA1 by a PLC-dependent mechanism, while the presence of extracellular Ca^{2+} is able to augment the response of TRPA1 to agonists such as AITC (Jordt et al. 2004). Zurborg et al. (2007) investigated this further and found that an EF-hand domain within the channel subunit is required for intracellular Ca^{2+}-mediated activation of TRPA1. They demonstrated that cells expressing TRPA1 showed responses to cold; however, in EF-hand domain mutants, responses to cold were not abolished but rather were reduced to levels of control cells which did not express TRPA1. They reasoned, therefore, that TRPA1 is activated by an increase in intracellular Ca^{2+} seen upon cooling rather than being directly activated by cold thus providing a potential explanation for the inconsistencies seen in vitro and in vivo. Subsequently, however, Karashima et al. (2009) used heterologous expression studies to argue that TRPA1 could be activated by cold in the absence of both intra- and extracellular Ca^{2+}.

Cold hyperalgesia is a symptom of diseases such as rheumatoid arthritis (Jahanshaki et al. 1989), and cold allodynia is a common feature of many neuropathic pain states including those caused by traumatic nerve injury and postherpetic neuralgia (Jørum et al. 2003). Since TRPM8 and TRPA1 have both been implicated in sensitivity to innocuous and noxious cold, their roles in these phenomena have been investigated. Caspani et al. (2009) reported nociceptive behaviour in response to menthol, a TRPM8 agonist, in mice following CCI surgery, suggesting a normally cool stimulus mediating a noxious effect via

TRPM8 in a neuropathic pain model. Similarly, Colburn et al. (2007) found that acetone application resulted in a reduced response in TRPM8 null mice after CCI surgery and CFA injection when compared to WT; an even greater allodynic phenotype was seen after CCI in mice with ablation of TRPM8 expressing sensory neurons (Knowlton et al. 2013). In spite of this, reports of changes in TRPM8 expression after CCI surgery remain contentious (Proudfoot et al. 2006; Caspani et al. 2009), and no changes in expression following CFA-induced inflammation were seen in one report (Obata et al. 2005). No upregulation of TRPM8 mRNA or protein was seen following SNL, and administration of antisense oligonucleotides to TRPM8 had no effect on SNL-induced cold hyperalgesia, although antisense oligonucleotide block of TRPA1 was able to attenuate this behaviour (Obata et al. 2005; Katsura et al. 2006; Stucky et al. 2009). Indeed, though TRPA1 expression is decreased in rats and mice after CCI (Caspani et al. 2009) and in injured L5 nerves in SNL, it is upregulated in intact L4 nerves and DRG in this model (Obata et al. 2005; Katsura et al. 2006). Cold allodynia resulting from spared nerve injury (SNI) surgery and CFA injection in rats was diminished by administration of TRPA1 antagonists (Stucky et al. 2009; del Camino et al. 2010). TRPA1 null mice exhibited reduced nocifensive responses to formalin, a chemical inducer of inflammation (Macpherson et al. 2007; McNamara et al. 2007; Stucky et al. 2009) and TG cultures from null mice show attenuated responses to bradykinin (Bautista et al. 2006).

Using HEK293 and cultured neurons as well as behavioural models, del Camino et al. (2010) found that even noxious cold temperatures were, alone, unable to evoke significant channel activity but that in the presence of an agonist, such as AITC, even low levels of innocuous cool evoked large currents and nocifensive responses. Moreover, the responses to noxious cold plate were comparable in WT and TRPA1 null mice (del Camino et al. 2010) suggesting that TRPA1 may play a role in mediating cold sensitivity only in pathological conditions, such as those mimicked in animal models of inflammatory and neuropathic pain.

4 Mechanical

The role of TRP channels in mechanosensation has been summarised in a recent review (Eijkelkamp et al. 2013). Very interestingly, TRPV1 global and conditional knockout mice show normal responses to mechanical stimulation even in models of inflammatory pain. A CCI model of neuropathic pain in rats, however, showed ipsilateral upregulation of TRPV1 protein in lamina I and II of the spinal cord and mechanical allodynia behaviour which was attenuated by a specific TRPV1 antagonist, BCTC (Kanai et al. 2005). TRPV3 null mice show no deficits in mechanical responses nor any differences in mechanical hyperalgesia induced by CFA or bradykinin compared to WTs (Moqrich et al. 2005). Though it does not respond to stretching of the membrane in vitro, and thus may not be gated by mechanical stimulation (Strotmann et al. 2000), TRPV4 does appear to play a role in mechanical hyperalgesia in inflammatory and neuropathic pain. In a variety of rat models of

neuropathic pain, including diabetic and peripheral neuropathies, the reduction in mechanical threshold was reversed by intrathecal administration of TRPV4 antisense oligonucleotides while TRPV4 null mice did not exhibit mechanical hypersensitivity to the same extent as WTs (Alessandri-Haber et al. 2008). Interestingly, however, the expression of TRPV4 does not appear to be upregulated in these rat models of neuropathic pain. TRPV4 is frequently co-expressed with TRPC1 and TRPC6 in DRG, and it has been proposed that the channels may act in concert to mediate mechanical hyperalgesia in sensitised nociceptive neurons. Induction of mechanical hyperalgesia in inflammatory and neuropathic pain models was reversed by administration of antisense oligonucleotides to TRPC6 and, in certain models, TRPC1 (Alessandri-Haber et al. 2009). In contrast with this it has recently been shown that TRPC3 and TRPC6 double knockout mice do not have deficits in sensitivity to noxious mechanical pressure (Quick et al. 2012).

Drosophila larvae lacking expression of the TRPA1 homologue, *painless*, are insensitive to noxious mechanical stimuli (Tracey et al. 2003); similar to its role in noxious cold, however, the role of TRPA1 in transduction of noxious mechanical stimuli is in debate. Kwan et al. (2006) found a deficit in response to repeated application of 'high force' innocuous and noxious mechanical stimulation in TRPA1 null mice though Bautista et al. (2006) focus on their finding that there is no variation in the mechanical thresholds of these mice. A loss of slowly and intermediate adapting currents in small-diameter, non-peptidergic fibres was seen in DRG neurons taken from TRPA1 null mice (Vilceanu and Stucky 2010; Brierley et al. 2011); it had previously been suggested that slowly adapting currents from such neurons are associated with noxious mechanosensation (Drew et al. 2007). Mustard oil-induced mechanical hyperalgesia was inhibited by TRPA1 antisense oligonucleotides and TRPA1 antagonists (Perin-Martins et al. 2013), while CFA- and SNL-induced mechanical hyperalgesia is attenuated by TRPA1 antagonists (Petrus et al. 2007; Eid et al. 2008) but not by antisense oligonucleotides (Obata et al. 2005). On the basis of transfection of HEK293 cells with TRPA1, however, it seemed that the channel alone is not sufficient to confer mechanical sensitivity (Vilceanu and Stucky 2010); hence, it is possible that TRPA1 does not contribute to acute noxious mechanosensitivity but rather to the maintenance of mechanical hyperalgesia (Petrus et al. 2007). Alternatively, Brierley et al. (2011) suggest that TRPA1 confers mechanical sensitivity to a specific set of small-diameter fibres and that there are other DRG neurons which do not require the channel to confer mechanosensitivity.

A point mutation (N855S) in the S4 transmembrane segment of TRPA1 causes an autosomal dominant heritable pain condition known as familial episodic pain syndrome (FEPS) (Kremeyer et al. 2010). This mutation leads to greater inward currents following channel activation at resting neuronal membrane potentials and manifests as crippling upper body pain which begins in infancy and consists of attacks with a duration of ~1.5 h. Interestingly, the attacks are described as involving a sensation of mechanical pain which is initiated by a number of factors including cold.

5 Central Pain Pathways

The architecture of the central pain-processing pathway is generally agreed (Ossipov et al. 2010; Perl 2011), although refinements of the wiring have been proposed to account for the range of pain sensations evoked by different stimuli (Craig 2003). The primary afferent nociceptor terminates centrally on relay neurons and interneurons of the dorsal horn in the spinal cord, mostly in laminae I and II. Most of these terminals are glutamatergic, but some are peptidergic. Relay neurons within the cord project to spinothalamic neurons, which course through the brainstem and midbrain, and synapse onto different nuclei of the thalamus (Fig. 2). Lateral branches of the ascending pathway also terminate within brainstem structures, the periaqueductal grey (PAG) and the rostroventral medulla (RVM). Thalamic neurons are wired to cortical regions mediating sensory and emotive aspects of pain, respectively, the somatosensory cortex and anterior cingulate cortex. A spinoparabrachial pathway travels from the spinal cord to limbic structures. Descending pathways (Fig. 2) originating in the cortex and amygdala, and modulated by outputs of the PAG, medial RVM and locus ceruleus, affect the activity of the dorsal horn neurons via neurotransmitters including GABA and serotonin, which can antagonise or facilitate the sensation of pain, in some cases leading to the generation of efferent signals along the nociceptor into the periphery.

TRP channels of the A, C, V and M subfamilies are detectable in the spinal cord and brain. Topical and systemic application of capsaicin dominates the study of central TRP channels. TRPV1 may occur postsynaptically in lamina II of the dorsal horn, especially in lumbar segments, in glia as well as in neurons, and co-localises with substance P (Spicarová and Palecek 2008). TRPV1 activity in the cord causes release of substance P, ultimately antagonising peripheral inputs by activating interneurons (Ferrini et al. 2007). The inflammatory mediator bradykinin is released from endothelia and glia following injury (Hausmann 2003) and mediates pain via sensitisation of TRPA1 co-localised with B2R receptors on DRG neurons (Wang et al. 2008), but there is no report of a similar co-expression in central neurons.

TRPV1 shows robust in vitro response to inflammatory mediators, but the special characteristics of the central nervous system (CNS) immune response—generally weaker, involving a different repertoire of cell types and excluding many serum proteins by reason of the blood–spinal cord and blood–brain barriers—imply that the signalling pathways will differ from those in the periphery (Hausmann 2003). Nonetheless, microglial activation has been correlated with peripheral pain states including those caused by peripheral nerve trauma and bone cancer pain (Watkins et al. 2001a, b; Xu et al. 2006), and TRPV1 activity leads to microglial cell death (Kim et al. 2006), suggesting a coupling of central pain and inflammatory pathways. In the same way, spinal cord trauma leads to release of factors, some of which are not found after peripheral nerve damage, to mediate oxidative stress, inflammatory, energetic, apoptotic and lipid metabolic change (Kuner 2010; Yip and Malaspina 2012). It is not clear which if any of these factors subserve nociceptive functions by acting on TRP channels or in which direction the effect occurs. TRPV1 may stand upstream of some inflammatory responses, as suggested by the

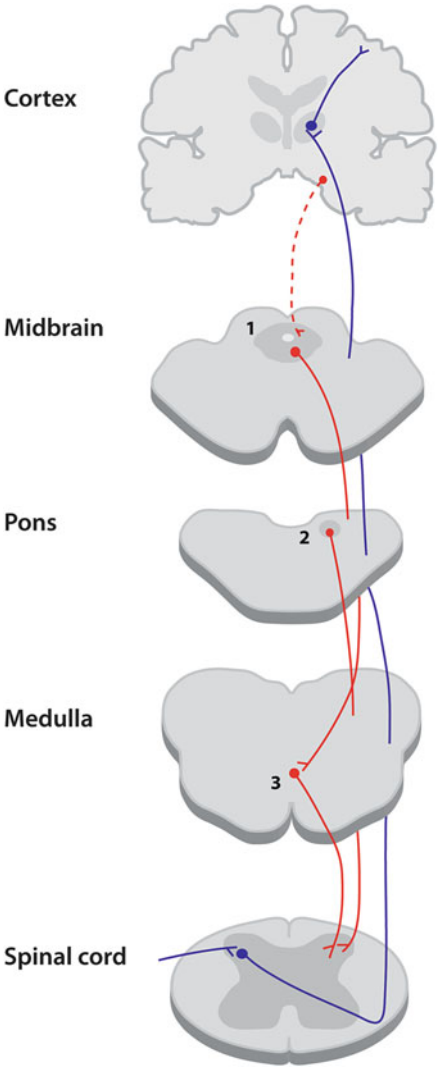

Fig. 2 Central pain processing. Ascending tracts (*blue*) and their peripheral inputs. Descending tracts (*red*) and modulatory pathways. (1) PAG; (2) Locus ceruleus; (3) RVM

finding that systemic capsaicin upregulated B1R expression on spinal cord microglia (Talbot et al. 2012). The secondary injury to the blood capillaries that follows spinal cord trauma is preceded by upregulation of the TRPM4 channel on the vessels (Gerzanich et al. 2009). Capillary fragmentation does not necessarily contribute to pain sensation, though it impairs neurological function. This channel overexpressed in HEK293 cells shows a graduated response to temperatures between 15 °C and 35 °C (Talavera et al. 2005) but must respond to other, unidentified outputs from injury in vivo to mediate the reported effects on

haemorrhage. TRPV1 is implicated in the central response to a plantar injection of Freund's adjuvant; within substantia gelatinosa of spinal cord isolated after CFA treatment, synaptic transmission is inhibited by a TRPV1-selective antagonist, as though the channel had become activated by the inflammatory stimulus (Lappin et al. 2006). Intrathecal application of TRV1 antagonists alleviates the response to paw injection of formalin (Kanai et al. 2006), supporting the same conclusion. Oral administration of TRPV1 antagonists with different degrees of CNS permeance shows that central TRP channels contribute to pain responses (Cui et al. 2006). Intrathecal application of the TRPV1 agonist RTX produces analgesia, attributable to selective ablation of TRPV1-expressing central nerve terminals (Jeffry et al. 2009).

TRPV1 channels at the central terminals of nociceptors are exposed to CNS modulators of activity. The endogenous ligands of TRPV1 include 12-HPETE (an arachidonic acid derivative), AEA (anandamide) and NADA (*N*-arachidonoyl dopamine) (O'Neill et al. 2012). The endocannabinoid anandamide promotes calcium entry through TRPV1, via a mechanism that differs from that of capsaicin (Fischbach et al. 2007). The affinity of anandamide for the CB1 receptor is higher, and it is unclear what sequence of events would lead to effects on TRPV1 function in situ.

Neurotransmitters and peptides (e.g. substance P) with modulatory effect on the circuitry of relay neurons and interneurons are released by the central terminals of nociceptors. A family of lipid mediators, the resolvins, lowers transmission probability across spinal synapses via effects on TRPV1 and TRPA1 (Park et al. 2011). Activation of central TRPV1 channels by capsaicin is correlated with altered spinal plasticity as well as hyperalgesic behaviour. This altered plasticity is a likely component of central sensitisation, whereby innocuous inputs are interpreted as noxious (Willis 2009). Sensitisation of spinal—and perhaps supraspinal—responses is proposed to account for a sensation of pain that persists beyond the initial stimulus (Park et al. 1995: Sang et al. 1996). This pain might be ectopic (secondary hyperalgesia) or evoked in response to innocuous stimuli (allodynia). The injured afferent may additionally re-route, projecting to a synapse on a different lumbar segment, to facilitate input from undamaged afferents (Campbell and Meyer 2006). The relevant biological mechanism leading to facilitation is likely to be nociceptor burst activity, repeatedly stimulating the central synapse, following peripheral injury (Campbell and Meyer 2006); this proposed peripheral origin does not exclude the action of mediators within the cord sensitising TRP channels. Following synaptic plasticity, upregulation of cyclooxygenase (COX)-2 and other neuronal signalling pathways leads to ongoing pain beyond the initial stimulus (Rivat et al. 2010). Distinct features of central sensitisation include secondary hyperalgesia and mechanical allodynia, whereby the abnormally enhanced response occurs in undamaged tissue. The TRPV1 agonist gingerol can relieve secondary hyperalgesia after central application in rat model of spinal nerve injury (Gauthier et al. 2012).

The reactive metabolite methylglyoxal (MG) occurs in all cell types as a by-product of glycolysis and lipid peroxidation and might be an endogenous ligand

of the TRPA1 channel. MG is normally detoxified by a glyoxalase pathway, but deficiency of this route is suggested by the high MG plasma levels in diabetes mellitus patients. The effect of MG on depressing the compound action potential of the sciatic nerve preparation is abolished in TRPA1 null mice (Eberhardt et al. 2012). While diabetes patients show reduced conduction velocity in the peroneal nerve (Hyllienmark et al. 2013), and patients with diabetic neuropathy can experience an increase in sensitivity to mechanical and thermal stimuli, the relevance of the MG observations to pathology is currently unclear.

Pain-associated plastic changes are best documented in spinothalamic tract neurons of the spinal cord (Willis 2002), but thalamic and cortical plasticity also is believed to contribute to sensitisation (Fu et al. 2008). Although potentiation of spinal transmission can be demonstrated, this is not conclusively a cellular analogue of pain sensation. Nonetheless, the data of Hjornevik et al. (2010) suggest that high-frequency stimulation of the spine produces both LTP and alterations in opioid receptor activity in higher brain areas.

Supraspinal involvement of TRP channels in pain are harder to demonstrate. Nonetheless, a coherent body of work with channel agonists and antagonists, applied centrally or peripherally, suggests a role for TRPV1 in descending modulation. TRPV1 mRNA occurs on cell bodies and synapses in brainstem structures involved in pain, namely the PAG and the RVM. Binding sites for the TRPV1 radioligand [3H]RTX occur in these locations as well as in the cortex, thalamus, hypothalamus, cerebellar cortex, locus ceruleus and spinal cord (Roberts et al. 2004) and the somatosensory cortex, anterior cingulate and amygdala (Steenland et al. 2006). Radioligand affinity for its target varies between structures (Szabo et al. 2002), which implies that accessory factors may be required for receptor availability. LTP in the amygdala is reported to be TRPV1 dependent (Zschenderlein et al. 2011). On the other hand, a recent publication on a TRPV1 reporter mouse claims expression restricted to the hippocampus, PAG, hypothalamus and midbrain only (Cavanaugh et al. 2011).

Accumulating data also indicate a role for TRPC channels in synaptic plasticity. LTP elicited at hippocampal interneuron synapses can be blocked by a nonspecific TRP channel inhibitor, and accompanying evidence on the calcium dependence of these channels implicates the TRPC family (Topolnik et al. 2006). RNAi experiments in hippocampal slice culture have shown that TRPC3 is required for dendritic spine formation in the presence of brain-derived neurotrophic factor (BDNF) (Amaral and Pozzo-Miller 2007). The influx of sodium and calcium ions through TRPC3 is proposed to stand upstream of NMDA receptor activation, leading to enhanced synaptic transmission in the form of LTP (Minichiello 2009). In hippocampal neuron culture, TRPC5 and TRPC6 activity mediates the phosphorylation of Akt by BDNF; this may have consequences for synaptic plasticity, since both Akt phosphorylation and LTP induction protocols can lead to the transient insertion of calcium-permeable AMPA receptors in the neuronal membrane (Fortin et al. 2012). Finally, the TRPC5 knockout mouse, which resists pilocarpine induction of seizures, is defective in LTP induction (Phelan

et al. 2013), suggesting that plasticity and regulated excitability might be coupled outputs of TRP-mediated calcium homeostasis.

TRPM, the melastatin family of TRP channels, currently includes eight members. TRPM3 is highly expressed in the kidney, brain, spinal cord and testis and in some experimental preparations works as an osmosensor (Grimm et al. 2003). This function would be consistent with a role in kidney physiology. TPRM3 in beta cells is moreover activated by pregnenolone sulphate (Wagner et al. 2008), a cholesterol derivative synthesised in the adrenal and the brain, and standing upstream of the glucocorticoids, mineralocorticoids and sex steroids. Pregnenolone sulphate (PS) was proposed as a pain mediator in the same year that TRPM3 was cloned, on quite independent grounds related to expression of enzymes in the spinal cord (Patte-Mensah et al. 2003). The association of the channel and the steroid motivated a study that showed heat activation of TRPM3 expressed in HEK cells and the potentiation of this effect by low doses of PS. In the tail immersion test, TRPM3 -/- mice tolerated temperatures up to 57 °C to a greater extent than wild-type mice. A different behavioural response to PS was not reported by this study (Vriens et al. 2011), and so the relevance of the steroid as an endogenous ligand for TRPM3-mediated nociception remains to be demonstrated.

The PAG is connected monosynaptically to the RVM, in which the activity of a population of pain modulatory OFF cells is correlated with analgesia. Injection of TRPV1 agonists into the PAG enhances the excitability of the OFF cells and suppresses thermoception in the plantar test (Maione et al. 2006). This is discrepant with the effects of capsaicin in the periphery. Consistent with this report, infusions of a TRPV1 antagonist into the PAG enhance the response of rats to thermal stimulation of the paw (Starowicz et al. 2007). The activation of TRP channels in the PAG plausibly modulates pain responses, since RVM neurons project to the dorsal horn, synapsing with the primary nociceptive afferents as well as with the relay and interneurons. The antinociceptive projections are GABAergic and glycinergic, but it is unclear that they originate from the OFF cells (Ossipov et al. 2010). The effect of capsaicin on excitation in the ventrolateral PAG depends on glutamate receptors (Palazzo et al. 2002). McGaraughty et al. (2003) recorded neuronal responses to infused capsaicin simultaneously with tail-flick latencies at 52 °C. They reported that the OFF neurons in dorsal PAG are active during analgesia only after some two hours of ON neuronal activity and pain-avoiding behaviour and suggested that pain reduction occurred only after desensitisation of TRPV1 by capsaicin.

Capsaicin microinjected into the ACC increases the activity of selected neurons, while repressing others (Steenland et al. 2006). The correlation of this TRPV1-mediated neuronal activity with behaviourally relevant stimuli is unknown, but since ACC is connected to the PAG, a descending effect on nociception is presumed.

Systemic injection of capsaicin increases excitability within the locus ceruleus, a structure that responds to noxious stimuli (Hajós et al. 1987), is reciprocally connected with the RVM and sends a noradrenergic descending projection to the dorsal horn (Ossipov et al. 2010). The noradrenergic output can be suspended after

peripheral nerve injury (Rahman et al. 2008), and this presumably facilitates pain sensation, but the involvement of TRP channels in this process is not known.

6 Analgesics

The roles of TRP channels in mediating sensitivity to noxious stimuli make them attractive targets for analgesics. Most drug development studies have focussed on TRPV1 and TRPA1, which are clearly linked to aspects of peripheral nociceptor function. For example, Honore et al. (2000) found repeated dosing of two distinct TRPV1 antagonists was able to abolish spontaneous pain and thermal and mechanical behaviour responses in animal models of inflammatory and neuropathic pain. Capsaicin causes sensitisation of TRPV1; however, application of high-dose patches of ~8 % to the skin can be used to cause desensitisation and is used as a treatment for patients suffering with neuropathic pain. A review of six studies involving 2,073 participants with post-herpetic neuralgia or HIV neuropathy found these high-concentration capsaicin patches were effective at inducing pain relief (Derry et al. 2013). Pain ratings of sufferers of chronic lower back pain, a common and notoriously difficult to treat condition, are reduced by application of a capsicum plaster (Frerick et al. 2003). The minimal side effects resulting from this topically applied TRPV1-mediated analgesic provide further support for the potential role of TRP channels in the development of improved analgesics. Low doses of icilin and menthol, both TRPM8 agonists, are able to reduce mechanical and thermal hypersensitivity caused by peripheral nerve injury (Proudfoot et al. 2006). Antagonism of TRPV1 and TRPA1 during the acute phase of pancreatitis reduced pain behaviour and inflammation as well as preventing progression of the pathological changes seen in chronic pancreatitis though these treatments were unable to reverse pain behaviours in models of established chronic pancreatitis (Schwartz et al. 2013). TRPA1 has been shown to play a role in hyperalgesia, and the antagonist HC-030031 attenuates inflammatory- and neuropathy-induced mechanical hypersensitivity (Eid et al. 2008).

In spite of the evidence that TRP channels are involved in sensing noxious stimuli, their potential as analgesic drug targets has not been fulfilled in a substantial way. The widespread expression of TRP channels, together with their ability to heteromultimerise increases the likelihood that such drugs may also induce a number of off-target effects.

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