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ROLE OF TRP CHANNELS IN PAIN: AN OVERVIEW

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2.1 INTRODUCTION

Despite the investment of significant resources by the pharmaceutical industry to identify novel analgesic drugs, chronic pain, which is most commonly defined as pain lasting longer than 3 months (i.e., outlasting the usual healing process), still represents a difficult treatment challenge in a large sector of the population, consisting of an estimated 50 million Americans (<http://www.painfoundation.org>). Patients suffering from disabling painful conditions often need complex and aggressive treatment that combines medical and surgical approaches (Campbell et al., 2006; Gidal and Billington, 2006; Katz and Berkin, 2008). The mainstay of medical pain therapy remains drugs that have been around for decades, like nonsteroidal anti-inflammatory drugs (NSAIDs), or drugs that have been around even for centuries, such as opiates (Katz and Berkin, 2008). Many patients, however, find that over-the-counter NSAID medications are ineffective for pain relief. Opiates are very powerful painkillers, but their clinical use is limited by adverse effects (Gallagher and Rosenthal, 2008). Also, many clinicians are concerned about the abuse of opiates (<http://www.opiates.com/prescription-painkillers-addiction.html>).

Of the newer agents, the COX-2 inhibitor rofecoxib (sold by Merck under the brand name Vioxx) was withdrawn from the market over concerns of its cardiovascular side effects (Brophy, 2007), casting a large cloud over the

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future of this class of drugs (Scanzello et al., 2008). Adverse effects also appear to plague the use of other recent additions to the market. For example, pregabalin (marketed as Lyrica), which is an $\alpha 2\delta$ calcium channel blocker, is poorly tolerated by some patients due to its central nervous system (CNS) adverse effects, especially somnolence and dizziness (Owen, 2007). The clinical use of ziconotide (brand named Prialt), which is a conopeptide N-type calcium channel blocker, is restricted to intractable (opiate-refractory) pain due to a combination of side effects and the need for intrathecal delivery (Wallace, 2006). Consequently, chronic pain is often undertreated and remains a significant unmet medical need (http://www.aarp.org/health/brain/diseases/chronic_pain.html) (Dray, 2008; Katz and Berkin, 2008).

In late 2000, the U.S. Congress declared the 10-year period that began January 1, 2001 as the Decade of Pain Control and Research (<http://www.ampainsoc.org/decadeofpain>). Furthermore, the Joint Commission of Accreditation of Healthcare Organizations (JCAHO) has mandated pain as the “fifth vital sign” (the other four being blood pressure, respiration, pulse, and temperature). Over the past few years, significant scientific progress has been made in our understanding of the mechanisms that underlie inflammatory and neuropathic pain. Preclinical research has identified new factors and mechanisms that are involved in the development and maintenance of chronic pain, many of which represent potential therapeutic targets (Stucky et al., 2001; Cortright et al., 2007; Cheng and Ji, 2008; Oertel and Lötsch, 2008; Zhuo, 2008). A key discovery was the molecular cloning of the vanilloid (capsaicin) receptor transient receptor potential vanilloid subfamily member 1 (TRPV1), a polymodal nociceptor on primary sensory neurons (Caterina et al., 1997). Targeting TRPV1 represents a new strategy in pain relief (Malmberg and Bley, 2005; Roberts and Connor, 2006; Szallasi et al., 2007; Knotkova et al., 2008). In contrast to traditional analgesic agents that either suppress inflammation (e.g., NSAIDs) or inhibit pain transmission (e.g., opiates), TRPV1 antagonists aim to prevent pain by blocking a receptor where pain is generated (Fig. 2.1). As discussed in subsequent chapters, small-molecule TRPV1 antagonists are being evaluated in proof-of-concept pain clinical trials. Other transient receptor potential (TRP) channels on sensory neurons represent emerging therapeutic targets (Cortright et al., 2007; Dray, 2008; Eid and Cortright, 2009; Cortright and Szallasi, 2009b; Patapoutian et al., 2009). The clinical value of TRPV1 antagonists might be the litmus test for the feasibility of this novel approach.

THE CENTRAL ROLE OF TRP CHANNELS IN NOCICEPTION AND INFLAMMATORY PAIN

Nociceptors were first described by Charles Scott Sherrington more than a century ago. A nociceptor (from the Latin *nocere* or “to hurt”) is defined as a “pain cell” that is capable of sensing noxious stimuli and transmitting the

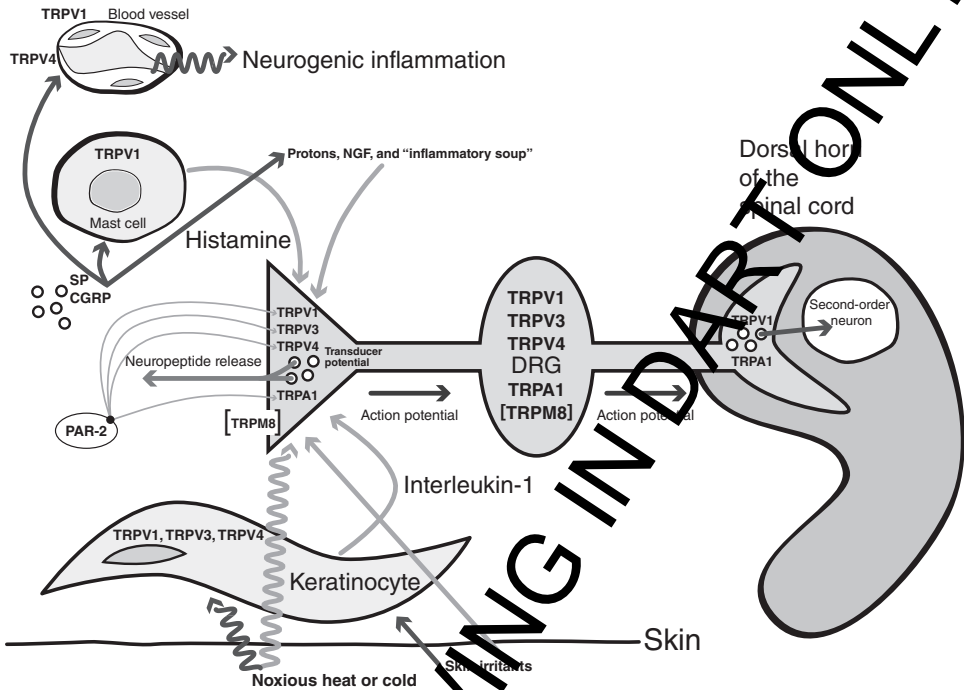


Figure 2.1 Simplified, schematic representation of the complex participation of neuronal and non-neuronal TRP channels in nociception, neurogenic inflammation, and inflammatory pain. Temperature (heat- and cold)-sensitive TRP channels, so-called “thermoTRPs,” are expressed both in nociceptive neurons and in cells that are in contact with these neurons (e.g., keratinocytes and immune cells in the skin). When nociceptive neurons are activated by noxious environmental stimuli, an action potential is generated (afferent function), which is transmitted to the central nervous system where it is perceived as painful, and, at the same time, proinflammatory neuropeptides (e.g., SP and CGRP) are released in the periphery, initiating the biochemical cascade collectively known as neurogenic inflammation. Epithelial cells (e.g., keratinocytes) are believed to generate interleukins when their TRP channels are stimulated by skin irritants; these cytokines, in turn, sensitize sensory nerve endings. Agents in “inflammatory soup” sensitize or activate nociceptive neurons via both direct and indirect effects on TRP channels (e.g., receptor protein phosphorylation). A third route of nociceptive sensitization is by protease-activated receptor-2 (PAR-2). Vascular endothelial cells also express TRPV1 and TRPV4; these channels may enhance or block the neurogenic inflammatory response. TRP channels, in particular TRPV1, expressed on central terminals of primary sensory neurons, are believed to play a role in the process of central sensitization, also known as the “wind-up” phenomenon. Of note, following injury, DRG neurons undergo a “phenotypic change” (also known as “injury-induced messenger plasticity”) when the expression of some TRP channels is increased, whereas others are downregulated. SP, substance P; CGRP, calcitonin gene-related peptide; NGF, nerve growth factor; PAR-2, protease-activated receptor 2; DRG, dorsal root ganglion.

pain signal (Belmonte and Cervero, 1996). In mammals, primary sensory (nociceptive) neurons form an anatomic connection between potentially harmful external and internal agents and the CNS (Fig. 2.1) (Mollnes, 2002). Many non-neuronal cells, for example, urothelial cells and keratinocytes, also express nociceptor TRP channels (Fig. 2.1), in particular TRPV1 (Denda et al., 2001; Birder et al., 2002; Southall et al., 2003; Wilder-Smith et al., 2007), TRPV3 (Facer et al., 2007), and TRPV4 (Chung et al., 2005; Gevaert et al., 2007), and it has been suggested that these cells may also function as pain sensors (Southall et al., 2003; Birder 2005, 2006).

Generally speaking, primary sensory neurons are bipolar cells with somata in the dorsal root ganglion (DRG) and in the trigeminal ganglion (TG). The central axons of these neurons enter the CNS where they form synapses with second-order neurons in the dorsal horn of the spinal cord (DRG neurons) or in the spinal nucleus of the trigeminal tract (TG neurons) (Fig. 2.1). Many neurons innervating the viscera are located in the nodose ganglia. Their peripheral fibers travel with the vagus nerve, whereas their central axons project to the area postrema (Holzer, 1991). Most primary sensory neurons possess unmyelinated axons (C-fibers) and are capsaicin sensitive (Holzer, 1991). A small subset of neurons with thin myelinated axons (A δ -fibers) also expresses TRPV1 receptors. Interestingly, it has been shown that A δ -fibers that do not normally express TRPV1 do so under inflammatory conditions or following injury (Ma, 2002; Rashid et al., 2003). This abnormal, TRPV1-positive A δ -fiber population has been suggested to contribute to neuropathic pain in patients with diabetic polyneuropathy (Rashid et al., 2003). Indeed, desensitization by TRPV1 agonists (e.g., capsaicin and its ultrapotent natural analogue, resiniferatoxin) relieves chronic pain in these patients (Knotkova et al., 2008) despite the degeneration of C-fibers (Lauria et al., 2006; Facer et al., 2007).

A unifying feature of TRP channels relevant to pain is their sensitivity to temperature, hence the term “thermoTRPs” (Dhaka et al., 2006; Bandell et al., 2007; Talavera et al., 2008). Of the currently known 28 TRP channels, seven sense hot and warm temperatures (TRPV1 to TRPV4, TRPM2, TRPM4, and TRPM5), whereas two (TRPA1 and TRPM8) are activated by cold (Levine and Alessandri-Haber, 2007). Combined, these channels cover a wide temperature range, with extremes falling between 10°C (TRPA1) and 53°C (TRPV2). Another shared feature of these channels is their sensitivity to a variety of natural products (Table 2.1) (Appendino et al., 2008). In fact, the TRPV1 channel was originally termed the capsaicin receptor (capsaicin is responsible for the piquancy of hot chili peppers) or the vanilloid receptor TR1, based on the vanillyl fragment present in capsaicin and resiniferatoxin, a diterpene ester isolated from the latex of the perennial *Euphorbia resinifera* (Szallasi and Blumberg, 1999). In addition to capsaicin, TRPV1 is also a receptor for pungent compounds in jellyfish (Cuypers et al., 2006) and for some spider toxins (Siemens et al., 2006). TRPA1 is activated by both cinnamaldehyde (from cinnamon) (Bandell et al., 2004; Namer et al., 2005) and

allicin (an active ingredient in garlic) (Macpherson et al., 2005). TRPM8 is also referred to as the menthol receptor (Peier et al., 2002a), and TRPV3 represents a target for camphor (Moqrich et al., 2005). TRPV4 is thought to mediate the actions of bisandrographolide, the bioactive ingredient in the Chinese medicinal plant *Andrographis paniculata* (Smith et al., 2006).

While some natural products from plants show selectivity for particular TRP channels (such as resiniferatoxin for TRPV1), others are not as “picky.” For example, citral, a bioactive component in lemongrass, which is used both as a taste enhancer and as an insect repellent, functions as a partial agonist for all TRPs in sensory neurons (TRPV1, TRPV3, TRPA1, and TRPM8), with a lasting blockage of TRPV1, TRPV3, and TRPM8 and a transient inhibition of TRPV4 and TRPA1 (Stotz et al., 2008). Menthol is an even more interesting compound in that it activates TRPM8 (hence its well-known cooling effect), but, paradoxically, it also stimulates TRPV3, causing a warm sensation, and blocks TRPA1 (Macpherson et al., 2006). Furthermore, there is significant “cross talk” between the TRP channels that modifies the bioactivity of natural TRP channel agonists. An interesting example of this phenomenon is camphor, which acts as a direct agonist for TRPV3 and then strongly desensitizes both TRPA1 and TRPV1 (Xu et al., 2005). Cannabinoids constitute another example since they desensitize capsaicin responses, not via cannabinoid CB1 or CB2 receptors, but rather via TRPA1 activation (Akopian et al., 2008). Apparently, the antinociceptive and antihyperalgesic actions of cannabinoids are mediated by distinct biological targets, consistent with the observation that these cannabinoid effects occur at different concentrations (Johanek et al., 2001).

TRP channels play a central role in thermal nociception and also in detecting noxious chemicals (Fig. 2.1) (Liedtke and Heller, 2007; Nilius et al., 2007). This is interesting biology, but, per se, it would not make these channels potential targets for analgesic drugs. Importantly, TRPV1 is also activated and/or sensitized by agents in “inflammatory soup,” ranging from tissue acidosis (protons) through cytokines (e.g., nerve growth factor [NGF], bradykinin, 12- and 15-hydroxyperoxyeicosatetraenoic acid [HPETE], and other arachidonic acid metabolites [Table 2.1]) (Caterina and Julius, 2001; Pingle et al., 2007; Szallasi et al., 2007). These agents act in concert to lower the heat activation threshold of TRPV1 (Di Marzo et al., 2002; Szallasi et al., 2007). These findings have identified TRPV1 as a promising target to relieve inflammatory pain (Fig. 2.1). Indeed, both genetic deletion (Caterina et al., 2006; Davis et al., 2000) and pharmacological blockade of TRPV1 ameliorate heat hyperalgesia in rodent models of inflammatory pain (Malmberg and Bley, 2005; Szallasi et al., 2007; Gunthorpe and Szallasi, 2008). Of relevance is the finding that TRPV1 expression is increased in reflux esophagitis (where “heartburn” is due to exposure to acidic gastric contents) and in inflammatory bowel disease (IBD) (Yiangou et al., 2001; Matthews et al., 2004; Bhat and Bielefeldt, 2006). TRPV1 is also elevated in irritable bowel syndrome (also known as colon irritable), a fairly common condition of unknown etiology

TABLE 2.1 ThermoTRP Channels: Selected Activators and Relevance to Pain

| | Selected Activators | Relevance to Pain |
|-------|---|---|
| TRPV1 | Heat (>43°C) Protons Capsaicin, resiniferatoxin, piperine Anandamide, NADA, 12-HPETE Jellyfish and spider venoms | Noxious heat detection Thermal hyperalgesia during inflammation |
| TRPV3 | Warm temperature (>33°C) Camphor, thymol, eugenol Incense acetate | Candidate sensor for noxious stimuli in keratinocytes Proposed role in neuropathic pain (upregulated after nerve injury) |
| TRPV4 | Warm temperature (>25°C) Change in osmolality Candidate mechanosensor | Key role in mechanical hyperalgesia under inflammatory conditions Important role in colic pain Major player in chemotherapy-induced neuropathy |
| TRPA1 | Cold (<17°C) Hypertonicity Mustard oil, allicin Reactive oxidants (cigarette smoke, exhaust fumes, tear gases, etc.) | Major chemosensor in airways Candidate mechanosensor: mechanical hyperalgesia in colitis and overactive bladder Mediator of cold hyperalgesia (pathological cold pain) Target for paradoxical pain by anesthetic drugs |
| TRPM8 | Cold (<23°C) Menthol, icilin | Role in cold allodynia Possible contribution to genitourinary hyperalgesia and pain Possible role in colic pain |

NADA: N-arachidonyldopamine.

characterized by frequent bowel movements and tenesmus (painful straining at stool) (Chan et al., 2003). Because there is no effective medical therapy, irritable bowel syndrome is frustrating for both patients and their physicians. Therefore, it is an exciting possibility that per os TRPV1 antagonists may provide symptomatic relief. Indeed, there is anecdotal evidence that eating hot, spicy food exacerbates symptoms in patients with irritable bowel syndrome. Moreover, TRPV1 is emerging as an indirect, downstream target for various endogenous agents, such as endothelin-1, that evoke pain (Plant et al., 2007).

A shared (and controversial) feature of thermoTRP channels, in particular TRPV1 (Prescott and Julius, 2003) and TRPM8 (Liu and Qin, 2005), is their regulation by phosphatidylinositol 4,5-bisphosphate (PIP2) (Brauchi et al.,

2007; Qin, 2007). TRPV1 possesses PIP2 recognition sites (Lishko et al., 2007; Kim et al., 2008). It was postulated that TRPV1 is under the inhibitory control of PIP2 (Prescott and Julius, 2003), implying a pivotal role for phospholipase C, the enzyme that cleaves PIP2, in TRPV1 activation. However, PIP2 may be either inhibitory or activating, depending on the context (Lukacs et al., 2007). Of note, recently it was suggested that ethanol potentiates TRPV1-mediated responses via the PIP2-TRPV1 interaction (Vetter et al., 2008).

2.3 THE EMERGING ROLE OF TRP CHANNELS IN VISCERAL PAIN

As reviewed elsewhere, the majority of sensory fibers that project into the viscera possess TRPV1 (Holzer, 2004). TRPV1-positive nerves appear to mediate visceral pain in response to noxious rectal distension (Spencer et al., 2008). This is somewhat surprising since TRPV1 is not supposed to have mechanosensitive properties. Although surprising, it is not unprecedented, since TRPV1(-/-) mice exhibit decreased mechanical hyperreactivity of the bladder during cystitis (Wang et al., 2008). Moreover, silencing by RNA interference of TRPV1 has been reported to ameliorate visceral pain in rats (Christoph et al., 2006), implying a role for TRPV1 in visceral pain during colitis. Indeed, the first generation TRPV1 antagonist capsazepine diminishes discomfort to colorectal distension in mice (Sugiura et al., 2007), similar to the decrease seen in TRPV1 (-/-) animals (Jones et al., 2005). Increased TRPV1 immunoreactivity was observed in colonic sensory afferents in patients with IBD (both Crohn's disease and ulcerative colitis [Yiangou et al., 2001]) and in rectal sensory fibers with rectal hypersensitivity and fecal urgency (Chan et al., 2003). Currently, it is unclear whether these changes in TRPV1 expression are pathogenic or adaptive. In a rat model of irritable bowel syndrome, TRPV1 antagonists prevent the development of visceral hypersensitivity initiated by acetic acid treatment during the neonatal period (Winston et al., 2007). These findings imply a pathogenic role for the dysfunction of TRPV1-positive colonic fibers in irritable bowel syndrome. In accord, a correlation has been described between the number of TRPV1-immunoreactive fibers in the rectosigmoid colon and the abdominal pain score in patients with irritable bowel syndrome (Akbar et al., 2008). Taken together, these observations suggest that TRPV1 is a relevant therapeutic target for the treatment of visceral pain.

In a rat model of IBD, topical capsaicin treatment reduces bowel ulceration in response to trinitrobenzene sulfonic acid (TNBS) (Goso et al., 1993). In this model, the small-molecule TRPV1 antagonist JYL1421 suppresses microscopic colitis and significantly reduces (but does not completely abolish) visceromotor response to colorectal distension (Miranda et al., 2007). TRPV1 also appears to be involved in the post-inflammatory hyperalgesia that occurs

after resolution of dextran sodium sulfate (DSS)-induced experimental colitis (Eijkelkamp et al., 2007). Nonetheless, it may be a premature conclusion that TRPV1 is exclusively responsible for the beneficial effect of capsaicin in pre-clinical models of colitis. In a murine model of visceral pain, TRPV1 (-/-) mice show a 60% reduction in pain response magnitude compared to wild-type controls (Jones et al., 2005). So, what is responsible for the remaining 40% of the pain behavior? The amiloride-sensitive acid-sensing ion channels (ASICs) may be a major contributor (Sugiura et al., 2007). Indeed, ASIC (-/-) mice display a reduction in pain behavior, which is similar in magnitude to that observed in the TRPV1 knockouts (Jones et al., 2005). Furthermore, new evidence shows that TRPA1 (presumably present on TRPV1-positive fibers, Fig. 2.1) is markedly upregulated during TNBS-evoked colitis (Yang et al., 2008). Consistent with a pathogenic role of the increased TRPA1, intrathecal administration of TRPA1 antisense oligodeoxynucleotide reverses hyperalgesia to colonic distension (Yang et al., 2008). It has been known for decades that capsaicin desensitization prevents neurogenic inflammation by cigarette smoke (Lundberg and Sarria, 1983; Lundberg et al., 1983), although it is now known that these responses are initiated by TRPA1 rather than TRPV1 (André et al., 2008; Simon and Liedtke, 2008). One cannot help but wonder if a similar phenomenon may also play at least a partial role in the beneficial effect of capsaicin desensitization in the TNBS colitis model (Goso et al., 1993).

In man, capsaicin exerts a protective effect against gastric mucosal damage by ethanol (Mózsik et al., 2007), suggesting that functional TRPV1 is protective in the gastrointestinal tract during inflammation or chemical damage (Eysselein et al., 1991). If this hypothesis holds true, a potential side effect for TRPV1 antagonists given *per os* could be exacerbation of gastric ulcer formation. Confusingly, genetic deletion of TRPV1 has a protective action against gastric ulcers (P. Reeh, pers. comm.). Clearly, more research is needed in this area.

In summary, the exact contribution of TRPV1 to visceral pain is still being debated (Hicks, 2006). As discussed above, ASIC and other acid-sensitive ion channels may also be involved in visceral pain (Holzer, 2003). Recently, TRPA1 (Miticic and Holzer, 2008; Yang et al., 2008) and TRPV4 (Brierley et al., 2008) have emerged as molecular mechanotransducers on visceral afferents, suggesting these TRP channels may also play an important role in visceral pain. TRPV4 appears to be preferentially expressed in high levels in colonic sensory neurons (Brierley et al., 2008). Behavioral responses to painful colonic distension are significantly reduced in TRPV4 (-/-) mice (Brierley et al., 2008), as is the mechanical hyperalgesia that occurs in response to protease-activated receptor 2, (PAR-2) (Grant et al., 2007). Of note, PAR-2 also sensitizes TRPV1 (Amadesi et al., 2004). Thus, PAR-2 appears to function as a regulator of TRP channels (Surprenant, 2007). Since gut bacteria produce high amounts of PAR-2, TRPV4 is an attractive pharmacological target to relieve visceral pain. Unfortunately, as discussed below, pharmacological blockade of TRPV4 may have severe adverse effects.

2.4 CONTRIBUTION OF TRP CHANNELS TO NEUROPATHIC PAIN, CANCER PAIN, AND MIGRAINE

There is good experimental evidence that sensory neurons expressing TRP channels, in particular TRPV1, are important mediators of pathological pain (Fig. 2.1). For instance, rats desensitized to resiniferatoxin are devoid of the thermal hyperalgesia and guarding behavior that develops following mechanical damage of the sciatic nerve (Bennett model) (A. Szallasi, M. Tal, and G. Bennett, unpublished data). Strikingly, resiniferatoxin also abolishes pain behavior when given to rats in a “therapeutic fashion” that is, to animals already in discomfort following the operation.

As detailed in the chapter by Jimenes-Andrade and Mantyh in this volume, cancer pain is a promising indication for TRPV1 blockade. Here it suffices to mention that TRPV1 expression is enhanced in DRG neurons ipsilateral to bone cancer (osteosarcoma) in the mouse (Nishida et al., 2007). In mice and dogs, treatment with resiniferatoxin to desensitize TRPV1-containing neurons ameliorates bone cancer pain (Brown et al., 2005; Menendez et al., 2006). In mice, this effect was mimicked by both genetic disruption of the TRPV1 gene and pharmacological TRPV1 blockade by the selective antagonist JNJ-17203212 (Ghilardi et al., 2005).

In man, capsaicin-containing topical patches (e.g., NGX-4010 by NeurogesX) and injectable capsaicin preparations (e.g., Adlea by Anesiva) were reported to provide relief from pain associated with diabetic neuropathy, AIDS-related neuropathy, and post-herpetic neuralgia (Knotkova et al., 2008). Other indications for topical capsaicin treatment include migraine, cluster headache, osteoarthritis, lateral epicondylitis (e.g., “tennis elbow”), Morton’s neuroma, and postsurgical pain (e.g., bursectomy and hernia repair) (Knotkova et al., 2008). The therapeutic value of capsaicin and other TRPV1 agonists is discussed in the chapter by Bley in this volume.

The rationale for using potent, selective small-molecule TRPV1 antagonists to relieve inflammatory pain is the recognition that TRPV1 is directly activated by agents in the “inflammatory soup,” including the so-called “endovanilloids” (Fig. 2.1 and Table 2.1) (Di Marzo et al., 2002; Szallasi et al., 2007; see also the chapter by Bhattacharya et al. in this volume). In other words, TRPV1 antagonists prevent the binding of endovanilloids to TRPV1. No such straightforward explanation exists for the mechanism of capsaicin desensitization. It is well established that capsaicin “silences” TRPV1-expressing neurons via ill-defined molecular processes (Szallasi and Blumberg, 1999). Indeed, neurons desensitized to capsaicin are also unresponsive to mustard oil (Jancsó et al., 1985; Patacchini et al., 1990), although this chemical agent acts on TRPA1 rather than TRPV1 (Jordt et al., 2004). Since TRPV1 agonists like capsaicin and resiniferatoxin block neuropathic pain whereas TRPV1 antagonists apparently do not, it is a reasonable assumption that other receptors present on capsaicin-sensitive neurons besides TRPV1 are directly involved in neuropathic pain. In accord, evidence was presented at the 2008 World

Pharmaceutical Congress by investigators at Glenmark that the TRPV3 antagonist GRC15133 is capable of inhibiting neuropathic pain (Gullapalli et al., 2008). A second mechanism of capsaicin desensitization was described as “vanilloid-induced messenger plasticity” (Szallasi and Blumberg, 1999). This reversible and long-lasting process was suggested to involve downregulation of TRPV1 and of neuropeptides that are proalgesic (e.g., substance P [SP] and calcitonin gene-related peptide [CGRP]) as well as upregulation of peptides (e.g., galanin), enzymes (e.g., nitric oxide synthase [NOS]) and receptors (e.g., cholecystokinin [CCK-1] receptors) that are analgesic (Szallasi and Blumberg, 1999).

TRPV1 is now well established as a major mediator of thermal hyperalgesia. The link between TRPV1 and mechanical hyperalgesia is much weaker. In the skin, the expression of TRPV1 appears to be restricted to mechanically insensitive nerve fibers (Lawson et al., 2008). In accord, perineural resiniferatoxin administration blocks thermal, but not mechanical, hyperalgesia during inflammation (Neubert et al., 2008). Resiniferatoxin was previously reported to cause some decrease in mechanical hyperalgesia, presumably mediated by a spinal site, but this effect was very transient compared to the lasting blockade of thermal hyperalgesia (Xu et al., 1997). This is a problem for TRPV1 antagonists because many pain clinicians consider mechanical allodynia and hyperalgesia more significant than thermal hyperalgesia. Recently, a specific small-molecule TRPA1 antagonist was reported to reverse complete Freund’s adjuvant (CFA)-induced mechanical hyperalgesia in wild-type, but not in TRPA1-deficient, mice (Petras et al., 2007).

As discussed in the chapter by Holland and Goadsby in this volume, the relationship between migraine and TRPV1 remains controversial. There is anecdotal evidence that capsaicin applied to the nasal mucosa is beneficial in patients with cluster headache (Sicuteri et al., 1989). Moreover, ethanol is known to worsen migraine symptoms (Szallasi et al., 2006), and it has been suggested that ethanol sensitizes TRPV1 via PIP2 (Vetter et al., 2008). CGRP released from sensory neurons has been postulated to play an important role in migraine (Geppetti et al., 2005). Indeed, CGRP antagonists prevent migraine attacks, although these compounds are much less effective when given during the attacks (Goadsby, 2005, 2008). These findings imply a therapeutic value for TRPV1 antagonists in migraine patients (Szallasi et al., 2006). The clinical trials, however, have proved very disappointing. In fact, GSK terminated its migraine clinical trials with TRPV1 antagonists due to lack of clinical efficacy (Gunthorpe and Szallasi, 2008). With the benefit of hindsight, the negative clinical trial is not unexpected. It is unclear what endovanilloid could be generated during migraine. Moreover, in the trigeminal system, the colocalization of TRPV1 and CGRP is limited. In contrast, CGRP is highly coexpressed with TRPV4. Based on this observation, some neurologists advocate the local injection of TRPV4 antagonists directly into TG for migraine refractory to conventional medical therapy (Liedtke, 2008).

2.5 DIFFERENTIAL TRP CHANNEL EXPRESSION DEFINES FUNCTIONAL SENSORY NEURON SUBTYPES: IMPLICATIONS FOR DRUG DEVELOPMENT

Primary sensory neurons are heterogenous in several aspects, including their anatomy, neurochemistry, and function. For example, these neurons differ in the myelin sheet that protects their axons (myelinated A β -fibers, thin myelinated A δ -fibers, and unmyelinated C-fibers); they use different mediators (e.g., peptidergic and non-peptidergic); and they convey different somatosensory information to the CNS (e.g., touch, pain, itch, and temperature). One way to subclassify primary sensory neurons is by the TRP channels that they express. A major population of neurons with C-fibers, as well as a minor subset of A δ neurons, coexpresses TRPV1 with the related channels TRPV3 and TRPV4 and also with TRPA1 (Kobayashi et al., 2005). TRPV1, TRPV3, and TRPV4 are heat-activated channels so their presence on the same neurons is not unexpected. It is more difficult to explain why these heat receptors are coexpressed with the cold receptor TRPA1. Adding to the complexity, TRPA1 seems to be present on both peptidergic and non-peptidergic neurons (Hjerling-Leffler et al., 2007).

A second major subset of primary sensory neurons, encompassing both A- and C-fiber neurons, is characterized by their TRPM8 expression (Kobayashi et al., 2005). The minimal overlap between TRPV1 and TRPM8 expression suggests that TRPV1-positive neurons and TRPM8-expressing neurons are fundamentally different, although TRPA1 appears to be present on both TRPV1- and TRPM8-expressing populations (Kobayashi et al., 2005). In keeping with this concept, TRPV1-like immunoreactivity is elevated, whereas TRPM8 is, by contrast, reduced in injured human brachial plexus nerves (Facer et al., 2007). Based on these findings, it has been postulated that TRPV1 may be a more relevant therapeutic target than other thermoTRPs for pain related to posttraumatic neuropathy (Facer et al., 2007). Intriguingly and in contrast to expression in DRG, TRPM8 is coexpressed with TRPV1 in vagal sensory neurons innervating the mouse lung (Nassenstein et al., 2008).

It has been suggested that TRPV1 forms heteromultimers with other TRP channels (Lisopi and Wood, 2005; Szallasi et al., 2007). If this hypothesis holds true, antagonists that do not distinguish between thermoTRPs may have a therapeutic value by targeting TRP heteromultimers. The shared TRP domain in these channels may represent a target for such inhibitors (Garcia-Sanz et al., 2007). Of note, N-(4-tertiarybutylphenyl)-4-(3-chloropyridin-2-yl)tetrahydroquinazolin-1(2H)-carboxamide (BCTC), originally described as a TRPV1 antagonist, also functions as a potent inhibitor of TRPM8 (Weil et al., 2005).

Of note, thermoTRP channels are also colocalized with other receptors involved in pain transmission. In an innovative study, capsaicin has been used to deliver sodium channel blockers into neurons expressing TRPV1. QX-314 is a quaternary derivative of lidocaine that is ineffective when administered alone because it is not capable of crossing the membrane. However, when

coadministered with capsaicin, QX-314 enters the sensory neuron through the open TRPV1 pore and gains access to its binding site on the sodium channel (Binshtok et al., 2007). This elegant approach affords selective targeting of TRPV1-expressing sensory neurons (Binshtok et al., 2007).

The peripheral terminals of TRPV1-expressing primary sensory neurons are sites of release for a variety of proinflammatory neuropeptides (e.g., SP and CGRP) that initiate the biochemical cascade collectively known as neurogenic inflammation (Fig. 2.1) (Geppetti and Holzer, 1996). Neurogenic inflammation is thought to play a central role in the pathogenesis of various disease states that range from migraine (chapter by Holland and Goadsby in this volume) through asthma (chapter by Materazzi et al. in this volume) to IBD and cystitis (chapter by Avelino and Cruz in this volume). Obviously, diseases with a prominent neurogenic inflammatory component are potential therapeutic indications for TRP channel blockers.

2.6 TAKING A SHORT TR(i)P BEYOND PAIN

Neuropeptides released from sensory neurons have been linked to various conditions encompassing pruritus, cough, emesis, neuroimmune regulation (e.g., type-1 diabetes), glucose control (metabolic syndrome and type-2 diabetes), obesity, and sepsis. The participation of TRP channels in these disorders has been exhaustively reviewed elsewhere (Birder, 2007; Jordt and Ehrlich, 2007; Kim and Baraniuk, 2007; Nilius, 2007; Nilius et al., 2007; Venkatachalam and Montecchino, 2007; Cortright and Szallasi, 2009a; see also the chapter by Nilius and Vennekens and chapter by Tsui et al. in this volume). Clearly, these topics go beyond the scope of this chapter, namely, pain, but a brief recapitulation of these observations might be useful to the degree the findings imply novel innovative uses for drugs targeting TRP channels. For example, the TRPV1 agonist resiniferatoxin is a powerful antiemetic agent in ferrets (Andrews and Bhandari, 1993), implying a potential for this class of compounds to inhibit intractable nausea and vomiting secondary to radiation and/or chemotherapy (Sharkey et al., 2007). Inhaled capsaicin is a standard agent to evoke cough response in human studies, and potent small-molecule TRPV1 antagonists are being tested in the clinics as promising antitussive drugs (McLeod et al., 2008; see also the chapter by Mazeratti et al. in this volume). TRP channels other than TRPV1, in particular TRPA1, are also potential targets for antitussive drugs (Kim and Baraniuk, 2007; Brooks, 2008).

Pruritus is another promising indication for drugs acting on TRP channels (Paus et al., 2006; Bíró et al., 2007). On an empirical basis, both capsaicin and menthol have been in clinical use to relieve itch for decades, identifying TRPV1 and TRPM8 as relevant pharmacological targets for novel antipruritic agents (reviewed in Bíró et al. [2007]). The “supercooling” agent icilin, which is several hundredfold more potent than menthol, reduces the degree of excoriations by scratching at least 50% in rats on a Mg^{2+} -deficient diet (Bíró et al., 2007). It can

be also argued that TRPV3 and TRPV4 in keratinocytes participate in the pathomechanism of pruritus. In fact, TRPV3 is a known target for skin sensitizers, and activation of TRPV3 in murine keratinocytes by eugenol was reported to release the proinflammatory substance interleukin-1 (IL-1) (Xu et al., 2006).

The emerging role of TRPV1 in neuroimmune regulation in general (Cortright and Szallasi, 2009a) and in type-1 diabetes in particular (Suri and Szallasi, 2008) was recently reviewed elsewhere and is also the subject of the chapter by Tsui et al. in this volume. Of note, TRPV1 has also been linked to obesity, metabolic syndrome, and type-2 diabetes (Gram, 2003; Suri and Szallasi, 2008). TRPV1 ($-/-$) mice on high fat diet are protected from visceral obesity, the type of “pear-shaped” obesity that has been linked to metabolic syndrome in man (Motter and Ahern, 2008). Type-2 diabetes has been suggested to have a significant low-grade inflammatory component mediated by capsaicin-sensitive nerves (Gram, 2003). Indeed, the small-molecule TRPV1 antagonist BCTC has been reported to improve glucose tolerance in a mouse model of type-2 diabetes (Gram and Hansen, 2007).

2.7 DISEASE-RELATED CHANGES IN TRP CHANNEL EXPRESSION: A NEW SPIN COMPENSATING DRUG DEVELOPMENT

TRP channels not only show bidirectional changes during disease states (up- or downregulation) but can be also expressed in cells that do not normally express such channels (Szallasi et al., 2007). Representative examples are discussed below. These observations have important practical implications for drug development. For example, animal experiments suggest that TRPM8 may be a relevant target to ameliorate cold hyperalgesia that develops following nerve injury (Katsura et al., 2006; Ji et al., 2007; Xing et al., 2007). In support of this hypothesis, mRNA encoding TRPM8 is increased in the rat DRG following chronic constriction injury (Frederick et al., 2007). However, in man, TRPM8 appears to be downregulated after nerve injury (Facer et al., 2007) and in painful dental pulp (Alvarado et al., 2007). Indeed, no evidence for the involvement of TRPM8 in cold allodynia has been found in neuropathic pain patients (Namer et al., 2008). This is a worrisome example of the species-related differences in TRP channel biology that hinder extrapolation of animal experiments to patients. In contrast, TRPA1 appears to be upregulated in human DRG after nerve injury (Anand et al., 2008). In rats, antisense knockdown of TRPA1 alleviates cold hyperalgesia after spinal nerve ligation (Katsura et al., 2006). However, the relevance of these observations is unclear, since cold allodynia appears to be independent of TRPA1 in neuropathic pain patients (Namer et al., 2008).

In rodents, the expression of TRPV4 is increased at both the mRNA and protein levels following mechanical nerve injury, induced by CCD (chronic compression of dorsal root ganglia [DRG]) (Zhang et al., 2008). TRPV4 has

also been linked to chemotherapy (e.g., taxol- or vincristine)-induced neuropathy (Alessandri-Haber et al., 2004, 2008). When given intrathecally, TRPV4 oligodeoxynucleotide antisense reverses mechanical allodynia induced by CCD (Zhang et al., 2008) and ameliorates mechanical hyperalgesia in animal models of neuropathy of various etiologies, such as diabetes, alcoholism, and chemotherapy (Alessandri-Haber et al., 2008). TRPV4 appears to be also involved in inflammatory pain, as implied by the reduced response to “inflammatory soup” in TRPV4 (-/-) mice (Chen et al., 2007). This finding is consistent with the role of TRPV4 as an osmosensor and with the hypotonic nature of the inflammatory soup.

TRPV1 shows bidirectional expression changes in various disease states. During inflammation and in bone cancer, TRPV1 levels increase substantially (Niiyama et al., 2007). Conversely, TRPV1 expression is downregulated in neuropathic pain secondary to injury (Lauria et al., 2006). It has been hypothesized that the downregulation of TRPV1 expression in diabetic skin is related to the diminished NGF levels (Facer et al., 2007). As reviewed elsewhere (Knotkova et al., 2008), a traditional indication for capsaicin-containing topical preparations is diabetic neuropathy. However, the clinical experience with capsaicin is conflicting, with some studies reporting significant pain relief, whereas others have been unable to replicate these results. In the skin of patients with diabetic neuropathy, TRPV1-expressing epidermal nerve fibers are markedly reduced, accompanied by decreased TRPV3 expression in keratinocytes (Facer et al., 2007).

Although strictly speaking not a disease, it should be mentioned that chronic morphine administration upregulates TRPV1 expression in the spinal cord in a MAP kinase-dependent manner (Chen et al., 2008). This is intriguing because morphine tolerance is often associated with the development of thermal hyperalgesia. In fact, intrathecal pretreatment with the TRPV1 antagonist SB366791 (N-[3-methoxyphenyl]-4-chlorocinnamide) has been shown to attenuate morphine tolerance and to prevent thermal hyperalgesia (Chen et al., 2008). It is hoped that TRPV1 antagonists will reduce the need for opioids and, as an added benefit, will also prevent tolerance to opioids. Interestingly, acute morphine administration has the opposite effect since it negatively modulates TRPV1 via inhibition of adenylate cyclase (Vetter et al., 2006).

2.8 TRPVs ON NOCICEPTIVE NEURONS AS TARGETS FOR NOVEL ANALGESIC DRUGS: ATTRACTIVE BUT NOT SO INNOCENT

2.8.1 The Capsaicin Receptor TRPV1

As discussed above, the role of TRPV1 in inflammatory pain was confirmed by genetic deletion (Caterina et al., 2000; Davis et al., 2000) and pharmacological blockade experiments (Gunthorpe and Szallasi, 2008). The initial enthusi-

asm for TRPV1 antagonists was generated by two basic tenets. First, the expression of TRPV1 was believed to be fairly selective for primary sensory neurons (Holzer, 1991). And second, TRPV1 was thought to be “silent” under physiological conditions (Holzer, 1991). Sadly, neither postulate turned out to be true. Now it is clear that the tissue expression of TRPV1 is extremely wide, ranging from CNS neurons through epithelial cells (e.g., keratinocytes and urothelial cells), vascular endothelium, and immune cells (mast cells and lymphocytes) to hepatocytes and fibroblasts (Nilius, 2007; Cortright and Szallasi, 2009a; Gunthorpe and Szallasi, 2008). Compared to DRG neurons, the expression of TRPV1 is fairly low in these other cell types. Nevertheless, TRPV1 appears to be functional in a variety of tissues. Hypotheses are abundant regarding the role of TRPV1 in these other cell types, but experimental evidence is scarce. Notable suggestions include a role for brain TRPV1 in memory formation and in mood disorders (Gibson et al., 2008) and a contribution of TRPV1 on keratinocytes to hair growth and dermatologic disorders (Bodó et al., 2005). It was speculated that TRPV1-expressing brain neurons may play a role in various neurological and psychiatric disorders including schizophrenia (Chahl, 2007), Parkinson’s disease (Szallasi et al., 2007), Huntington chorea, and Alzheimer’s disease (Yamanaka et al., 2007). Of note, other than some spotty incontinence (Birder et al., 2002), the phenotype of TRPV1 knockout mice is fairly unremarkable. Knockout animals, however, often compensate for the missing protein. Therefore, conditional TRPV1 knock-downs would be better models to evaluate the potential role of non-DRG TRPV1 receptors.

TRPV1 involvement in body temperature regulation seems to have an endogenous tone, as implied by the hyperthermic action of TRPV1 antagonists (Gavva, 2008; see also the chapter by Garami et al. in this volume). It has been known for over a century that capsaicin evokes the opposite effect, that is, hypothermia (Holzer, 1991; Szallasi and Blumberg, 1999). Currently, this concept is still controversial. Several classes of structurally unrelated TRPV1 antagonists evoke hyperthermia (Gavva, 2008; Gunthorpe and Szallasi, 2008). In fact, this adverse effect can be so severe that Amgen decided to discontinue the clinical trials with its lead compound after body temperature had reached 40°C in one patient (Gavva, 2008; Gunthorpe and Szallasi, 2008). Other potent TRPV1 antagonists (e.g., GRC6211 by Glenmark/Lilly) have no effect on body temperature (S. Narayanan, pers. comm.) or, conversely, cause hypothermia following a very mild and transient initial hyperthermic response (e.g., A-425619). Clearly, more research is needed to resolve these conflicting findings.

2.2 TRPV3, a Close Relative of TRPV1

TRPV3 is a warm-sensitive (>33°C) channel that, in contrast to TRPV1, is insensitive to acid or capsaicin (Peier et al., 2002b; Smith et al., 2002; Xu et al., 2002; Chung et al., 2004). The preclinical proof of concept for the role of TRPV3 in thermal nociception and hyperalgesia was furnished by knockout

experiments (Moqrich et al., 2005). Indeed, GRC15133, which is a selective TRPV3 antagonist developed at Glenmark, was shown to relieve both inflammatory and neuropathic pain in animal models (Gullapalli et al., 2008). Similar to TRPV1, TRPV3 is expressed in keratinocytes (Peier et al., 2002b; Chung et al., 2004) where it has been suggested to mediate the release of IL-1, a proinflammatory agent that, in turn, may sensitize nociceptive neurons (Xu et al., 2006). In the human skin, TRPV3 shows interesting disease-related changes in expression. For example, TRPV3 is downregulated in the skin of patients with diabetes (Facer et al., 2007), whereas TRPV3-like immunoreactivity is increased in skin biopsies obtained from the breasts of women with mastalgia secondary to macromastia or other conditions that cause breast tenderness (Gopinath et al., 2005). While the existence of warm-activated TRPV3 in keratinocytes is well established (Peier et al., 2002b; Chung et al., 2004), the presence of TRPV3 in nerve fibers innervating the skin is controversial. In human skin samples, no TRPV3-like immunoreactivity was detected in the epidermal nerve endings (Gopinath et al., 2005). However, strong TRPV3-like immunoreactivity was found in the brachial nerve plexus following nerve injury (Facer et al., 2007).

In rodents, TRPV3 is not only highly colocalized with TRPV1 but may also compensate for TRPV1. Indeed, increased TRPV3 expression was observed in mice when TRPV1 was genetically inactivated by “knockdown” via RNA interference (transgenic short hairpin RNA, shRNA_{tg}, animals), although TRPV3 expression was not increased in TRPV1 “knockout” mice (Christoph et al., 2008).

TRPV3 knockout mice have a fairly unremarkable phenotype with only mild alterations in hair texture (G. Story, pers. comm.). This is in sharp contrast to animals with constitutively active, gain-of-function TRPV3 mutations that suffer from severe alopecia (Asakawa et al., 2006) and a skin condition that mimics human atopic dermatitis (Imura et al., 2007; Xiao et al., 2008). Most recently, incense acetate, an incense ingredient, was shown to exert potent anxiolytic-like and antidepressant-like behavioral activity in wild-type, but not in TRPV3 knockout, mice (Moussaieff et al., 2008). These findings were interpreted to imply a role for brain TRPV3 in emotional life (at least in the mouse). It remains to be seen if this observation has relevance for humans. However, some caution is no doubt appropriate, especially since brain TRPV1 has been implicated in rimonabant-induced mood disorders (Gibson et al., 2008). An attractive clinical indication for TRPV3 antagonists that block brain TRPV3 is neuroprotection via hypothermic effects (Guatteo et al., 2005; Lipski et al., 2006).

2.8.3 TRPV4, a Mechanosensor TRP with Multiple Functions

TRPV4 was originally defined as an osmosensor, hence the alternative name VR-OAC (osmotically activated channel) (Table 2.1). Indeed, TRPV4 is essential for the normal response to changes in osmotic pressure (Liedtke and Friedman, 2003) and in mechanical pressure (Suzuki et al., 2003).

Subsequently, TRPV4 has been shown to be warm-sensitive (25–34°C) and is therefore a thermoTRP channel (Güler et al., 2002). Experiments with TRPV4 (–/–) mice suggest that TRPV4 plays a role in normal warm sensation (Lee et al., 2005) and also participates in thermal hyperalgesia following inflammation (Todaka et al., 2004). Warm temperatures have been shown to activate TRPV4 in keratinocytes (Chung et al., 2003, 2004). Consistent with the role of TRPV4 as a mechanosensor (Suzuki et al., 2003), TRPV4 knockout mice show reduced mechanical hyperalgesia (Chen et al., 2007). Arterial response to shear is mediated by TRPV4 expressed on vascular endothelial cells (Hartmannsgruber et al., 2007). In the kidney, TRPV4 serves a double role, both as a flow sensor (mechanosensation) and as an osmosensor (Wu et al., 2007).

TRPV4 has been proposed to play a pivotal role in visceral hypersensitivity (Cenac et al., 2008). Of relevance, TRPV4 is sensitized by PAR-2 to cause mechanical hyperalgesia in mice (Grant et al., 2007; Sipe et al., 2008). This is significant since gut bacteria produce large quantities of PAR-2. Consequently, it has been postulated that TRPV4 is an important mediator of colic pain in patients with inflammatory bowel conditions (Brierley et al., 2008).

Many pain experts believe that mechanical hyperalgesia is a more important player than thermal hyperalgesia in chronic human pain. Unfortunately, TRPV4 knockout mice have a severe phenotype (incontinent [Gevaert et al., 2007] and deaf [Tabuchi et al., 2005]) that casts a big dark cloud over the clinical utility of TRPV4 antagonists. Even worse, TRPV4 (–/–) animals have impaired osmoregulation due to abnormal antidiuretic hormone (ADH) secretion, and pharmacological TRPV4 blockade has been suggested to cause a sicca syndrome-like condition (Liedtke, 2008). Given the essential role of TRPV4 in osmotransduction and in mechanosensation (Liedtke, 2007), the deleterious adverse effects of TRPV4 blockade are hardly unexpected. Consequently, drug discovery activity directed toward TRPV4 has been marginalized.

New findings, however, have rekindled interest in drugs targeting TRPV4 that do not get absorbed into the systemic circulation. It has been suggested that inhaled TRPV4 agonists may be beneficial in cystic fibrosis patients and that TRPV4-containing eye drops may protect the cornea of patients with sicca syndrome (Sjogren's) (Liedtke, 2008). In theory, enemas containing TRPV4 antagonists may relieve colic pain, and TRPV4 antagonists injected directly into the TG via the foramen ovale are expected to ameliorate migraine pain (Liedtke, 2008). Parenthetically, TRPV4 is essential for the structural integrity of the broncho-alveolar unit (Alvarez et al., 2006; Reiter et al., 2006). TRPV4 is negatively regulated by cGMP. Since activation of TRPV4 was shown to cause endothelial failure and circulatory collapse (Willette et al., 2008), TRPV4 blockade is predicted to exert a protective action in pulmonary circulation.

Last, TRPV4 deficiency suppresses bone loss in animal experiments (Mizoguchi et al., 2008). This finding implies that TRPV4 inhibitors may be of clinical value to prevent osteoporosis in postmenopausal women.

2.8.4 TRPA1, a Sensor of Reactive Oxidants and a Potential Target to Block Pathological Cold Pain

Of thermoTRPs, TRPA1 is unique in that it is activated by reversible covalent modification of the sulfhydryl (SH) groups of cysteine residues rather than by conventional ligand–receptor interaction (Macpherson et al., 2007a). In fact, TRPA1 has emerged as a major chemosensor for reactive oxidants (e.g., unsaturated dialdehydes) in airways (Andersson et al., 2008; Bessac et al., 2008) where, among other noxious stimuli, it is activated by cigarette smoke (André et al., 2008), exhaust fumes, and tear gases (McLahon and Wood, 2006). Similar to TRPV4, TRPA1 is a candidate mechanosensor with postulated roles in mechanonociception (Andrade et al., 2008), colitis (Penuelas et al., 2007; Yang et al., 2008), and overactive bladder (Du et al., 2007, 2008). Indeed, TRPA1 knockout mice have impaired bradykinin-induced mechanical hyperalgesia (but no hearing deficits). TRPA1 is also a cold thermosensor that is active when temperature drops below 17°C (Story et al., 2003; Bandell et al., 2004). Antisense knockdown of TRPA1 results in reduced cold hyperalgesia but has no influence on normal cold sensing (Katsura et al., 2006).

TRPA1 is upregulated during inflammation, an effect most likely mediated by NGF (Diogenes et al., 2007), and after nerve injury (Frederick et al., 2007; Ji et al., 2008). It has been postulated that TRPA1 antagonists (Petrus et al., 2007) may reduce inflammatory pain caused by prostaglandins and by other fatty acid metabolites (Trevisan et al., 2007; Taylor-Clark et al., 2008). Interestingly, TRPA1 is a target for irritation by the commonly used antifungal agent clotrimazol (Mesequet et al., 2008) and may be also responsible for the paradoxical postoperative pain caused by anesthetics (Matta et al., 2008). TRPA1 antagonists, however, may prove a double-edged sword. They may be beneficial by relieving pain and neurogenic inflammation, but, at the same time, they may be potentially dangerous by blocking a major sensor for noxious environmental chemicals (Macpherson et al., 2007b; Tai et al., 2008). In fact, mice whose TRPA1 channel has been deleted by genetic manipulation show deficiencies in respiratory behavior to oxidants (Bessac et al., 2008).

2.8.5 TRPM8, a Cool Receptor

Although TRPM8 is best known as the menthol receptor (Bautista et al., 2007; Patel et al., 2007), the “M” stands not for the menthol but for melastatin, a protein identified by comparing benign nevi to malignant melanoma (Nilius et al., 2007). In fact, TRPM8 activation suppresses the viability of human melanoma (Yamamura et al., 2008). Parenthetically, TRPM8 also plays a role in the differentiation of prostatic epithelium (Bidaux et al., 2007), and it has been suggested that TRPM8 ligands may be of clinical value in controlling the growth of prostatic carcinoma (Prevarskaya et al., 2007).

TRPM8 was the first cold receptor to be cloned (McKemy et al., 2002; Dhaka et al., 2007). TRPM8 is upregulated following mechanical nerve injury

(Frederick et al., 2007), and it has been postulated to play a role in cold allodynia (Xing et al., 2007). TRPM8 agonists have been suggested to induce analgesia to mechanical and thermal allodynia (Proudfoot et al., 2002) and to relieve pruritus (Biró et al., 2007); in fact, menthol is a traditional treatment for itch. Mouse genetics has shown that TRPM8 is required for cold hypersensitivity after nerve injury and inflammation (Colburn et al., 2007).

New functions of TRPM8 seem to include cold sensation in airways in response to inhaled air (Sabnis et al., 2008; Xing et al., 2008) and control of bladder activity (Du et al., 2008; Lashinger et al., 2008).

2.9 CONCLUDING REMARKS

Heat- and cold-sensitive TRP channels, so-called thermoTRPs, are in the focus of attention as potential targets for novel analgesic drugs (Fleetwood-Walker et al., 2007; Levine and Alessandri-Haber, 2007; Cortright and Szallasi, 2009b; Patapoutian et al., 2009;). These channels are expressed on nociceptive neurons where they play a pivotal role in sensing and integrating noxious stimuli (Fig. 2.1). Some of these channels, exemplified by TRPV1, are not only polymodal (i.e., they react to a variety of seemingly unrelated stimuli) (Table 2.1), but they also have a dynamic threshold of activation. For example, agents in “inflammatory soup” act in concert to sensitize TRPV1 in order to reduce its activation threshold to heat (Fig. 2.1) (Szallasi et al., 2007). TRPV1 is also a downstream target for bradykinin, NGF, and other endogenous proalgesic substances. Therefore, TRPV1 functions as a “molecular gateway to the pain pathway” (Caterina and Julius, 2001).

Targeting TRP channels on nociceptors is an attractive new and logical strategy in drug development. TRP channel antagonists aim to prevent pain by blocking a receptor where pain is generated (Fig. 2.1). TRPV1, arguably the most important signal integrator in nociceptive neurons, has many “firsts” in this field. TRPV1 was the first thermoTRP to be discovered on sensory neurons (Caterina et al., 1997). Genetic deletion (Caterina et al., 2000; Davis et al., 2000) and pharmacological blockade of TRPV1 (Gunthorpe and Szallasi, 2008) furnished the first proof of concept that TRP inhibitors may relieve hyperalgesia and pain. Most important, potent and selective small-molecule TRPV1 antagonists were the first to move into clinical trials as potential analgesic drugs (Szallasi et al., 2007).

TRPV1 also turned out to be a receptor with many unsuspected assets. There is emerging evidence that TRPV1 may play an important role in various disease states, ranging from type-1 diabetes (Suri and Szallasi, 2008) through neurologic and psychiatric disorders (Chahl, 2007) to obesity and cancer (Prevarskaya et al., 2007). These observations have opened up new avenues for drug development but also serve as warning signals for unforeseen adverse effects.

TRPA1 and TRPV3 are now emerging as intriguing new targets for drug development. TRPA1 is believed to function as a sensor of tissue damage by

noxious chemicals, including reactive oxidants in inhaled air (Bessac et al., 2008; Simon and Liedtke, 2008). TRPA1 is a target for both algescic and analgesic prostaglandin metabolites (Trevisani et al., 2007), and it has been linked to both mechanical and cold hyperalgesia. TRPV3 is upregulated following neuronal injury (Frederick et al., 2007). Indeed, small-molecule TRPV3 antagonists relieve neuropathic pain in preclinical models (Gullapalli et al., 2008).

In summary, TRP channel antagonists are predicted to inhibit various pain modalities from post-inflammatory heat or cold hyperalgesia to spontaneous (ongoing) pain. Since these channels are preferentially (though not exclusively) expressed on nociceptors, TRP channel inhibitors are hoped to block pain without the mechanistic limitations that plague the use of existing analgesic compounds. Preclinical experiments and clinical trials are ongoing, and it remains to be seen if TRP channel antagonists will live up to these expectations.

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