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TRPA1: A Gatekeeper for Inflammation

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Abstract

Tissue damage evokes an inflammatory response that promotes the removal of harmful stimuli, tissue repair, and protective behaviors to prevent further damage and encourage healing. However, inflammation may outlive its usefulness and become chronic. Chronic inflammation can lead to a host of diseases, including asthma, itch, rheumatoid arthritis, and colitis. Primary afferent sensory neurons that innervate target organs release inflammatory neuropeptides in the local area of tissue damage to promote vascular leakage, the recruitment of immune cells, and hypersensitivity to mechanical and thermal stimuli. TRPA1 channels are required for neuronal excitation, the release of inflammatory neuropeptides, and subsequent pain hypersensitivity. TRPA1 is also activated by the release of inflammatory agents from nonneuronal cells in the area of tissue injury or disease. This dual function of TRPA1 as a detector and instigator of inflammatory agents makes TRPA1 a gatekeeper of chronic inflammatory disorders of the skin, airways, and gastrointestinal tract.

Keywords

sensory transduction; inflammatory pain; somatosensation; transient receptor potential ion channel

INTRODUCTION

Acute inflammation is a normal biological response to tissue injury that activates neuronal, immune, and epithelial cells that mediate protective responses and behaviors. For example, a burn injury causes hypersensitivity to thermal, mechanical, and chemical stimuli that encourages guarding behaviors to promote healing. In contrast, inflammatory responses that persist in the absence of injury no longer serve a biological purpose and can cause severe tissue damage and unnecessary pain.

Tissue injury, caused by trauma or disease, leads to the release of inflammatory agents that activate both neuronal and nonneuronal cells at the site of injury. Nonexcitable cells, such as keratinocytes, epithelial cells, and fibroblasts that reside within the damaged tissue, and immune cells that infiltrate the damaged area release inflammatory mediators. Such

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mediators include ATP, adenosine, bradykinin (BK), prostaglandins (PGs), leukotrienes, histamine, tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), proteases, and glutamate (1–3). Several components of this inflammatory soup activate a subset of primary afferent sensory neurons that release inflammatory neuropeptides such as substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP). These neuropeptides promote extravasation of plasma proteins; vasodilation; neutrophil accumulation; and hypersensitivity to thermal, chemical, and mechanical stimuli. Thus, sensory neurons play important roles in mounting an inflammatory response, sensing sites of inflammation, and promoting protective behaviors.

In the past decade, the transient receptor potential ankyrin-repeat 1 (TRPA1) channel has emerged as a key regulator of neuropeptide release and neurogenic inflammation (Figure 1). In mammals, TRPA1 is expressed in a subset of C-fibers that express the nerve growth factor receptor TrkA and the heat- and capsaicin-sensitive ion channel TRPV1 (4, 5). These afferents have cell bodies in nodose, dorsal root, and trigeminal ganglia (NG, DRG, and TG, respectively) and project to a variety of peripheral targets, including the skin and viscera (Figure 1). C-fibers are polymodal, in that they are activated by noxious thermal, mechanical, and chemical stimuli. Upon activation, depolarization causes action potential firing to signal pain or itch to the central nervous system. Depolarization also leads to the release of SP, NKA, and CGRP in target tissue, and subsequent sensitization of the peripheral terminals occurs in the area of insult (3).

The role of mammalian TRPA1 as a direct detector of mechanical and thermal stimuli in these polymodal nociceptors remains somewhat controversial, as some studies show that attenuation of TRPA1 leads to small changes in baseline thermal or mechanical responsiveness (6). These issues have been extensively discussed in a number of reviews and are not covered in detail here (7–10). Instead, we focus on the well-established role of TRPA1 both as a target for inflammatory mediators and as a gatekeeper for the release of inflammatory neuropeptides by C-fibers. In this review we (*a*) examine the unique properties of TRPA1 that allow it to serve as a detector of many endogenous and exogenous inflammatory agents, (*b*) describe its role in inflammatory pain, and (*c*) introduce recent research on TRPA1 function in inflammation of visceral organs.

TRPA1 IS ACTIVATED BY INFLAMMATORY MEDIATORS

TRPA1 is one member of the large TRP family of ion channels that is found in diverse species (11, 12). TRP channels contain six transmembrane domains, are selective for cations, and form tetramers (13–15). They play diverse signaling roles in mammalian physiology and are gated by a wide variety of endogenous ligands, physical stimuli, and environmental irritants. TRP channels are divided into seven subgroups on the basis of primary sequence. TRPA1 is the sole member of the TRPA subgroup that is defined by a large number of ankyrin repeats (16 in humans) in theN-terminal domain (Figure 2). Ankyrin repeats are 33-amino-acid motifs that are found within many proteins and mediate protein-protein interactions, although it is not known whether ankyrin repeats in TRPA1 also serve this function.

Mammalian TRPA1 is robustly activated by a wide variety of exogenous irritants that cause pain and inflammation. Environmental chemicals that target TRPA1 include allyl isothiocyanate (AITC), cinnamaldehyde, and allicin, which are the pungent compounds found in mustard, cinnamon, and garlic extracts, respectively. A large number of airborne irritants have also been found to be TRPA1 activators (Table 1). Many of these irritants, including isocyanates and heavy metals, are produced during the manufacturing of polymers, fertilizers, pesticides, and other products. Another TRPA1 agonist, acrolein, acts as an irritant in tear gas, vehicle exhaust, and burning vegetation (16). Similarly, some anesthetics, such as isoflurane or lidocaine, also activate TRPA1 (17, 18).

TRPA1 is also a target of endogenous inflammatory agents. Reactive oxygen species (ROS) are released by cells in response to tissue damage and can cause lipid peroxidation, which results in the formation of reactive carbonyl species like 4-hydroxynonenal (4-HNE) and 4-oxononenal (4-ONE), which act directly on TRPA1 (19, 20). Nitrative stress, another hallmark of inflammation, is caused by reactive nitrogen species (RNS) that can produce nitrated fatty acids like nitrooleic acid (21). Although nitrooleic acid directly activates TRPA1, nitrated fatty acids also have anti-inflammatory properties (21, 22). Further in vivo studies will be necessary todetermine the functional significance of the interaction between TRPA1 and nitrated fatty acids. PGs, another class of fatty acid derivatives, are produced at sites of inflammation and mediate inflammatory responses and sensitization by a variety of mechanisms. One PG derivative, 15d-PGJ_2, specifically activates TRPA1 (19, 20, 23, 24).

What molecular characteristics of TRPA1 make it such a promiscuous sensor of structurally disparate chemicals? Part of the answer lies in the extensive N-terminal ankyrin repeat domain. Thiosulfinates (allicin), isothiocyanates (AITC), reactive carbonyl compounds (acrolein), and 15d-PGJ_2 activate TRPA1 channels directly by covalent modification of specific cysteine residues located in the ankyrin repeat domains of the N terminus (Figure 2) (25–27). Several other TRPA1 agonists, such as isocyanates, nitrooleic acid, lidocaine, hydrogen peroxide, and hypochlorite, may also target this site because the N-terminal cysteine residues are required for activation (18, 21, 28). The overall sequence of the N-terminal domain and the number of ankyrin repeats vary among species; this structural variation in the N-terminal domain determines the repertoire of stimuli that activate or modulate the channel. For example, human TRPA1 is activated by AITC, but not by heat, whereas rattlesnake TRPA1 is activated by heat with a Q_{10} of ~14 and displays little AITC sensitivity. Human TRPA1 that contains ankyrin repeats 10–15 of rattlesnake TRPA1 displays considerable heat sensitivity with a Q_{10} of ~10 (29). Likewise, the N-terminal domain of *Drosophila* TRPA1 is required for temperature detection (30, 31). These studies indicate that the N-terminal domain is a critical site for the chemical and thermal sensitivity of TRPA1.

Another mechanism of TRPA1 activation, common among TRP channels, is modulation by G protein–coupled receptors (GPCRs) through second-messenger signaling cascades (Figure 2). For example, injury-evoked BK production activates TRPA1-expressing nociceptors through the G_q- and phospholipase C (PLC)-coupled BK_2 receptor (BK_2R); PLC signaling modulates TRPA1 to promote sensitization to thermal, mechanical, and chemical stimuli (16, 32–36). The signaling molecules that activate TRPA1 downstream of PLC are

unknown, but both phosphatidylinositol 4,5-bisphosphate (PIP_2) and calcium can modulate TRPA1 activity and are thus good candidates (5, 37, 38). In addition to nociceptive sensitization through BK_2R, the pruritogen receptors Mas-related G protein–coupled receptors (Mrgprs) A3 and C11 are functionally coupled to TRPA1 via $G\beta\gamma$ and PLC, respectively (39). GPCR coupling allows TRPA1 to increase its repertoire of exogenous and endogenous ligands.

TRPA1-positive C-fibers densely innervate the skin, airways, and gastrointestinal (GI) tract. This broad expression, combined with the robust activation of TRPA1 by inflammatory mediators and the ability of TRPA1 to promote in flammation, makes this ion channel a prime suspect ininflammatory disorders such as chronic itch and pain, asthma, cough, and colitis. We highlight new insights into the role of TRPA1 in these diverse diseases.

INFLAMMATORY PAIN AND ITCH

The link between inflammatory pain and TRPA1 was first shown by studying natural plant products that elicit neurogenic inflammation, including AITC, an irritant found in wasabi and other *Brassica* plants (5). Topical application of AITC was widely used in pain studies to trigger the release of SP and CGRP and to promote thermal and mechanical hypersensitivity, but the site of action was unknown for many years. Studies now show that AITC directly activates the TRPA1 channel and that pharmacological blockage or genetic knockout of TRPA1 significantly attenuates hypersensitivity to thermal and mechanical stimuli induced by AITC and the other environmental irritants described above (6, 16, 40).

TRPA1 is required for the hypersensitivity that occurs in inflammatory pain models. Injection of complete Freund's adjuvant or carrageenan into the rodent hind paw leads to a robust and persistent reduction in the response threshold to mechanical and thermal stimuli such that previously nonnoxious stimuli are painful (a condition termed allodynia). In addition, the intensity of the response to previously noxious stimuli is enhanced (a condition termed hyperalgesia) (2). Pharmacological inhibition of TRPA1 significantly reduces allodynia and hyperalgesia, and TRPA1-deficient animals do not display sensitization (16, 32, 40). Similarly, TRPA1 mediates sensitization in a rodent model of osteoarthritis wherein injection of monosodium iodoacetate into the rodent knee causes movement-evoked and spontaneous pain. TRPA1 antagonists attenuate evoked mechanical hypersensitivity, but not the ongoing, spontaneous pain associated with this disease model (41, 42).

Disease models of diabetes strongly implicate TRPA1 in the inflammatory pain states that accompany this metabolic disorder. Diabetic neuropathy affects more than 80% of all diabetes patients and can cause severe pain, tingling and numbing sensations, and disability (43). Chronic diabetic neuropathy is associated with peripheral demyelination and the degeneration of nerve fibers, both of which significantly alter the properties of primary afferent sensory neurons that innervate the affected limb and contribute to diabetic neuropathic pain. Several lines of evidence support a role for TRPA1 in painful diabetic neuropathy. First, TRPA1 expression is significantly increased in the DRG of neuropathic rodents (44). Second, neuropathic tissues produce ROS, which activate TRPA1 and lead to

nociceptor sensitization (45, 46). Third, acute treatment with TRPA1 antagonists decreases mechanical hypersensitivity in rodents with diabetic peripheral neuropathy (47).

TRPA1 may also be involved in the onset of diabetic neuropathy, as pharmacological blockage of TRPA1 in the initial phases of streptozotocin-evoked diabetes attenuates the development of mechanical hypersensitivity (48). Studies also suggest that TRPV1-positive sensory fibers that innervate the pancreas regulate β-cell activation and islet inflammation by promoting the release of inflammatory peptides (49). However, the exact role of TRPA1 in these pancreatic fibers has yet to be discerned in diabetic models. In contrast, TRPA1 function is required for tissue inflammation and pain-like behaviors in experimental models of acute pancreatitis (50, 51).

A number of studies suggest that migraine pain may result from neurogenic inflammation. Migraine is a complex episodic disorder associated with throbbing head pain, nausea, and sensitivity to light and sound. TG neurons that innervate the cranial meninges play an important role in the pathogenesis of migraine (52). These sensory neurons have dual functions: an afferent role in transmitting pain and an efferent role in releasing inflammatory neuropeptides. The ability of TG neurons to regulate blood flow in the meninges is particularly relevant, as meningeal bloodflow has been clinically shown to correlate with migraine headache (53). In particular, CGRP, through its ability to robustly increase blood flow, is thought to be a key neuropeptide involved in the induction of migraine headache. The activation of TG neurons through nasal application of TRPA1 or TRPV1 activators causes a CGRP-dependent increase in meningeal blood flow (54). The particular importance of TRPA1 in inducing headache is highlighted by the fact that umbellulone—the major active compound found in the headache-inducing scent from *Umbellaria californica* (also known as the headache tree)—is a specific activator of TRPA1, promotes CGRP release, and increases meningeal blood flow in a TRPA1-dependent manner (55). Although the role of TRPA1 in migraine has not been fully elucidated, TRPA1 activation may be sufficient to cause acute headache.

Pruritus, or itch, is associated with many inflammatory conditions, including insect bites, atopic dermatitis, and psoriasis. Acute itch serves an important protective function by warning against harmful environmental agents such as insects, toxic plants, and other irritants. In contrast, pruritus can also be a debilitating condition that accompanies numerous skin, systemic, and nervous system disorders. Approximately 15% of primary afferent C-fibers are activated by endogenous itch-producing compounds released by nonneuronal cells in the skin (56, 57). Histamine-dependent itch is mediated by a subset of C-fiber afferents that express TRPV1 and the histamine receptor (58). Although many itch pathways involve histamine signaling, there are other key neural pathways, as most pathophysiological itch conditions are insensitive to antihistamine treatment, and novel therapeutic targets have yet to be identified (56, 57). Recent studies have implicated TRPA1 in histamine-independent acute and chronic itch.

Some histamine-independent itch is mediated by MrgprA3 and MrgprC11, which are members of a newly identified, sensory neuron–specific Mrgpr family of GPCRs (59). MrgprC11 is targeted by mast cell pruritogens released during allergic inflammation,

whereas MrgprA3 is activated by the antimalaria drug chloroquine, which causes acute itch in rodents and intolerable itch in some patients (59). However, it was not known how Mrgpr receptor activity was coupled to sensory neuron activation. Recently, TRPA1 was shown to be required for itch-evoked, Mrg-dependent signaling in sensory neurons and for itch-evoked scratching induced by mast cell enkephalin peptide pruritogens and chloroquine (39). Thus, TRPA1 may define a new signaling pathway that mediates histamine-independent itch.

TRPA1 IN AIRWAY INFLAMMATION

The respiratory tract is continuously exposed to airborne irritants, noxious chemicals, and particulates. Primary afferent sensory neurons innervate the airways and act as sentinels for potentially damaging agents (60–65). The upper respiratory tract (nasal cavity, pharynx, and larynx) and lower respiratory tract (trachea, bronchi, and lungs) are heavily innervated by primary afferent C-fibers and Aδ-fibers (62, 66, 67) from the jugular ganglion, NG, DRG, and TG. Stimulation of these fibers in the airways leads to the release of inflammatory neuropeptides, such as SP, CGRP, and NKA (60), which induce bronchoconstriction, vasodilation, recruitment of immune cells, and modulation of the inflammatory response (68). Such processes promote behaviors, such as cough, increased mucus secretion, and shallow breathing, aimed at expelling the irritant and limiting exposure. Prolonged inflammation due to repetitive irritant exposure, or diseases such as cystic fibrosis, can ultimately lead to chronic cough, chronic obstructive pulmonary disease (COPD), asthma, and reactive airway dysfunction syndrome.

TRPA1 was initially proposed to mediate inflammatory responses in the airways because of its robust expression in vagal neurons (69, 70) and because a variety of TRPA1 agonists trigger action potential firing in sensory fibers that directly innervate the airways (20, 69). TRPA1 mayalso play a role in nonneuronal cells, such as lung epithelia and smooth muscle, but such a role has not been directly tested. As discussed below, TRPA1 is now linked to both acute and chronic inflammatory disorders of the respiratory tract (Figure 3).

Airway Irritants that Activate TRPA1

There is a growing list of airborne chemicals that induce airway irritation and elicit behavioral responses by activating TRPA1. Such chemicals include industrial pollutants (isocyanates, heavy metals, and oxidizing agents) and general anesthetics (Table 1). Many of these airway irritants have been shown to activate pulmonary sensory neurons and airway afferent fibers in a TRPA1-dependent manner. However, the precise mechanisms by which TRPA1 is activated are mostly unknown. Whereas isocyanates and the topical anesthetic lidocaine require, at least in part, the reactive N-terminal cysteines of TRPA1 to exert their effects, zinc activates the channel through interaction with different cysteine and histidine residues (Cys1021 and His983) (Figure 2) (18, 71, 72). Thus, many airway irritants may act directly on TRPA1 to induce neurogenic inflammation.

TRPA1 Regulates Bronchial Contraction

Signs of airway inflammation include bronchial contraction and plasma extravasation. Bronchial contraction is induced by acetylcholine release from the vagus nerve endings; such release stimulates airway smooth muscles. Inflammatory mediators like histamine, some PGs, and leukotrienes also induce bronchoconstriction (73). In addition, sensory neurons contribute to airway inflammation, as SP and capsaicin are potent bronchoconstrictors (74), whereas CGRP is a bronchodilator (75).

Some lines of evidence suggest that TRPA1 activates airway smooth muscles through neu ropeptide release. Direct activation of TRPA1 by two common components of smoke, acrolein and crotonaldehyde, can stimulate vagal neurons, promote CGRP and SP release from the airways, and induce plasma extravasation (76–78). TRPA1 inhibition prevents both the activation of sensory neurons and plasma extravasation (14, 77). In addition, TRPA1 agonists such as 4-ONE and the general anesthetics isoflurane and desflurane induce TRPA1-dependent bronchial contraction (20, 79, 80).

TRPA1-Induced Cough

Cough is a reflex that helps clear the respiratory tract of environmental irritants, foreign particles, and mucus and is often associated with inflammatory diseases such as bronchitis and COPD. The vagus nerve innervates both the upper and lower respiratory tracts via neurons residing in the NG and jugular ganglion. The vagus nerve has a fundamental role in the cough reflex: Activation of afferent vagal fibers induces coughing in both guinea pigs and humans. The cough reflex can be elicited by both mechanical and chemical cues, which stimulate multiple afferent sensory fiber subtypes innervating the airways (reviewed in References 81 and 82). Several pieces of evidence implicate TRPA1 in the generation of irritant-induced cough reflexes. First, the TRPA1 agonists cinnamaldehyde and acrolein depolarize isolated vagus nerves. Second, vagus nerve activation is attenuated by pharmacological inhibition or genetic knockout of TRPA1 (83). Finally, TRPA1 agonists evoke cough that can be attenuated by TRPA1 inhibitors (83, 84).

The genetic contribution of TRPA1 to cough is not known, because experiments in more genetically tractable species like *Mus musculus* are hindered by the fact that mice do not have a cough reflex. However, mice do show alterations in breathing patterns in response to airway irritants. Animals exposed to airborne TRPA1 agonists, including AITC, toluene diisocyanate, zinc, H_2O_2, and hypochlorite, show a decrease in breathing frequency and lengthening of the pauses at the beginning or end of the respiratory cycle. These signs of airway irritation are absent in TRPA1 knockout animals (28, 85, 86). Thus, TRPA1 triggers breathing-pattern changes that reduce airway exposure to harmful agents.

TRPA1 and Asthma

Asthma, an inflammatory condition of the lungs, is characterized by bronchoconstriction and airway hyperreactivity, leading to shortness of breath, wheezing, and coughing. This inflammatory response is often associated with exposure to environmental allergens, with subsequent infiltration in the lungs of eosinophils and mast cell degranulation (87). Asthma-like responses can be recapitulated in rodent animal models through the use of ovalbumin

(OVA) exposure to induce an allergic reaction. In animals sensitized with OVA, infiltration of immune cells, bronchoconstriction, and wheezing can be monitored after exposure to aerosolized OVA.

In addition to immune cells, TRPV1- and TRPA1-positive primary afferent C-fibers also play key roles in asthma (88–93). OVA-sensitized rodents injected with a TRPA1 antagonist show adecrease in asthmatic responses (93). More dramatically, OVA-challenged Trpa1 knockout mice show little sign of lung inflammation, near-normal airway resistance, reduced eosinophil infiltration in the bronchi, and decreased production of proinflammatory cytokines and neuropeptide release in the airways (94).

What is the exact role of TRPA1 in asthma? The most likely scenario is that TRPA1 exerts its effects by mediating sensory neuron activity. The mode of TRPA1 activation in allergen-induced asthma is also unclear. Although a direct interaction with the allergen itself has not been ruled out, the inflammatory events following the response of the immune system likely sensitize or activate TRPA1 by generating endogenous mediators of inflammation, such as ROS, RNS, and PGs. Another possibility is that TRPA1 functions in one or more subtypes of immune cells. However, immune cells isolated from spleen express very low levels of TRPA1, and the expression of TRPA1 in immune cell lines is not consistently observed (94, 95). Thus, using the OVA model of asthma in tissue-specific TRPA1-deficient animals may help distinguish between these possible modes of action. Regardless of the mode of action, TRPA1 is an exciting and promising target for the development of drugs aimed at treating the asthmatic response.

TRPA1 IN GASTROINTESTINAL INFLAMMATION AND PAIN

The GI tract is exposed to numerous and diverse commensal microflora that play critical roles in proper digestion of food and development of the immune system (96). However, an imbalance in the interactions between the innate immune system and the adaptive immune system, tissue barrier functions of the GI mucosal lining, and the commensal microflora may cause inflammatory bowel diseases (IBDs) such as ulcerative colitis (UC) and Crohn's disease (CD), which are chronic disorders of the lower GI tract (96, 97). The important role of enteric innervations in colic health is highlighted by (*a*) clinical observations that patients suffering from chronic IBD show elevated levels of neuropeptides such as SP and CGRP in plasma and colic tissue samples (98, 99) and by (*b*) experimental models of IBD that implicate a critical role for sensory nerve fibers, neuropeptides, and neuropeptide receptors in pathogenesis (100, 101). In addition, patients with IBD often suffer from abdominal pain, which is likely to arise from the sensitization of visceral nociceptors innervating the GI tract (102). The importance of TRPA1 in GI inflammation and pain is demonstrated by its expression in sensory fibers that innervate the GI tract, by its critical role in mediating GI hypersensitivity to mechanical stimuli, and by its role in regulating neuropeptide release (Figure 4).

TRPA1 Expression in the Gastrointestinal Tract

The enteric nervous system consists of intrinsic nerve fibers that control autonomous GI functions, such as peristalsis and ion/water secretion, and extrinsic nerve fibers that originate

from the DRG and NG and convey visceral input to the central nervous system (101). Retrograde labeling of nerve fibers innervating the intestine shows enriched Trpa1 mRNA specifically in DRG and NG neurons that innervate the GI tract (103, 104). In addition, Trpa1 is functionally expressed in DRG neurons that innervate the GI tract (105, 106). TRPA1 protein expression is also detected in sensory fibers innervating the stomach and colon (103, 104). Thus, TRPA1 is ideally situated to detect inflammatory agents in the intestine and to mediate both afferent and efferent roles of extrinsic sensory fibers.

TRPA1 expression has also been detected in whole intestinal tissue samples, suggesting that it is expressed in cells intrinsic to the gut (107, 108). Indeed, functional expression of TRPA1 was detected in intrinsic neurons of the intestine, as well as in nonneuronal enterochromaffin cells,which are mucosal endocrine cells that line the intestine (109, 110). Therefore, TRPA1 may have functions in intestinal physiology distinct from its role in sensory neurons.

TRPA1 Mediates Inflammatory Hypersensitivity to Mechanical Stimuli in the Intestine

In experimental models of IBD, inflammation is induced by exposing the intestine to reactive chemicals that render larger molecules antigenic, such as 2,4,6-trinitrobenzene sulfonic acid (TNBS) and oxazolone, or by damaging the mucosal lining (111). Visceral pain is measured by electromyography recordings of the visceromotor response (VMR) of the GI tract following mechanical distention (105). TNBS-induced colic inflammation causes a TRPA1-dependentincrease in the VMR to colorectal distention (112, 113). In addition, TNBS-treated animals have a TRPA1-dependent increase in the level of c-fos staining, a marker of neuronal activity, in the spinal cord (112). Hypersensitivity is accompanied by a TNBS-induced increase in Trpa1 mRNA expression in DRG neurons that innervate the colon (106, 113). Interestingly, TRPA1 is not required for the VMR response or for spinal c-fos staining in noninflamed control animals. These results suggest that TRPA1 is specifically required for inducing or maintaining hypersensitization during colitis. However, at the highest stimulus range, TRPA1 may also be required for normal responses in noninflamed animals (103).

TRPA1 is also important in inducing mechanical hypersensitivity in the colon through direct activation of sensory fibers. As in the skin (16), BK applied to sensory afferents in the colon causes TRPA1-dependent mechanical hypersensitivity in those fibers (103). Intracolonic application of mustard oil in neonatal animals increases functional expression of TRPA1 in DRG neurons innervating the colon and induces hypersensitivity to mechanical stimuli in adult animals (105). However, there are no detectable signs of inflammation in the adult. Thus, TRPA1 activity early in development may produce long-lasting mechanical hypersensitivity that is independent of tissue damage.

TRPA1-Dependent Gastrointestinal Secretion of Neuropeptides in Response to Inflammatory Agents

In addition to their sensory role, extrinsic nerve fibers also contain neuropeptides, such as SP and CGRP, that are released upon stimulation. Both intrinsic neurons and extrinsic neurons contribute to the total neuropeptide content of the GI tract, but SP is found mostly in

intrinsic neurons, and CGRP is found mostly in extrinsic neurons (100, 101, 114, 115). As in other peripheral fibers, Trpa1 is coexpressed extensively with SP- and CGRP-expressing fibers in the GI tract (103, 104). In the isolated vagus nerve, AITC application induces TRPA1-dependent release of CGRP (116). In isolated colon tissue, acrolein, 4-HNE, and 4-ONE cause TRPA1-dependent release of CGRP and SP (117). These results suggest that TRPA1 in the GI tract serves as an important mediator of neuropeptide release triggered by the presence of inflammatory agents.

Interestingly, the colitis-inducing agent TNBS promotes the secretion of CGRP and SP from isolated colon (117). TNBS causes calcium influx in cultured DRG neurons from wild-type animals, but not in neurons from Trpa1 knockout animals. In addition, TNBS activates TRPA1-dependent currents in both DRG neurons and heterologous cells (117). TNBS is likely to activate TRPA1 directly because TNBS-induced currents require the reactive cysteine and lysine residues implicated in activation by covalent modification (26). Thus, in this model of colitis, direct activation of TRPA1 by TNBS leads to neuropeptide release from extrinsic sensory fibers.

The role of TRPA1 in the pathogenesis of IBD is less clear. Knocking out Trpa1 either prevents the development of experimental colitis or has no effect compared with control groups (112, 117). Many factors, including differences in the strain genetic backgrounds, may account for these disparate results. Indeed, distinct genetic loci affect susceptibility to experimental colitis (118, 119). In addition, SP and CGRP, which are the main downstream targets of TRPA1 signaling, play opposite roles in the pathogenesis of IBD. CGRP has a protective role in all forms of experimental colitis, whereas SP is required for pathogenesis (100, 117, 120–122). Genetic analysis suggests that CGRP acts by antagonizing the effect of SP (117). Therefore, slight differences in strain background may lead to dramatically different outcomes, and it will be necessary to decouple the effects of TRPA1 disruption on CGRP and SP secretion to determine the relative contribution of each pathway to colitis.

CONCLUSIONS AND FUTURE PROSPECTS

Research over the past decade shows the critical role of TRPA1 as a sensor of inflammation throughout the body. In addition to the inflammatory conditions described in this review, there are other inflammatory diseases in which TRPA1 may play a role. In cancer research, there is an increasing appreciation of the role that chronic inflammation plays in tumorigenesis and of the presence of inflammation in the tumor microenvironment (123). For example, chronic IBD increases a patient’s risk of developing colorectal cancer. Recent work has also suggested that neurogenic components of inflammation may contribute to pain and other debilitating consequences of cancer (124). It will be interesting to know if and how TRPA1 may contribute to the pathogenesis of cancer and other inflammatory diseases.

TRPV1 and TRPA1 are coexpressed in many DRG, TG, and NG neurons that innervate the skin and viscera. What are the relative contributions of TRPA1 and TRPV1 in mediating neurogenic inflammation? Activation of either channel causes similar downstream effects, such as neuropeptide release and hyperalgesia. For example, TRPA1 and TRPV1 are

required both for hypersensitivity to mechanical stimuli and for pathogenesis during TNBS-induced colitis (117, 125–127). In the airways, activation of TRPA1 or TRPV1 triggers the cough reflex, and both channels contribute to airway hyperresponsiveness (83, 90, 128–131). However, in some cases TRPA1 and TRPV1 have significantly distinct effects on inflammatory outcomes. In skin inflammatory pain models, TRPA1 contributes to both thermal hypersensitivity and mechanical hypersensitivity, whereas TRPV1 contributes only to thermal sensitization (16, 132). In the airways, TRPA1, but not TRPV1, is required for part of the asthmatic response in OVA-sensitized animals (93, 94). Although TRPV1 is found in most TRPA1-expressing neurons, these two TRP channels respond to different sensory cues and couple to distinct downstream signaling pathways. How such signals translate to distinct pathophysiological conditions is an open question.

Several properties of TRPA1 make it an attractive drug target to treat inflammatory disorders. First, in most instances genetic ablation or pharmacological blockade of TRPA1 does not significantly alter basal tactile and pain detection, which serves an important protective function. This property of TRPA1 is an advantage over many other pain therapies that alter pain hypersensitivity, as well as normal sensitivity to thermal and mechanical stimuli. Second, the peripheral expression of TRPA1 allows for selective targeting of drugs by inhalation, ingestion, or topical application. Selective drug delivery to peripheral targets may reduce many side effects compared with drugs that are administered systemically.

In addition to selective antagonists of TRPA1, endogenous inhibitory pathways may offer a fruitful approach to selectively targeting TRPA1. The ω-3 polyunsaturated fatty acid–derived resolvins are potent anti-inflammatory agents found at sites of inflammation (133). Resolvin D1 selectively inhibits TRPA1 activity, whereas resolvin E1 selectively inhibits TRPV1 activity (134). Resolvins attenuate inflammatory hypersensitivity to thermal and mechanical stimuli without affecting basal pain processing. Although G_i-coupled GPCRs are implicated in resolvin signaling, the molecular mechanisms underlying TRP channel specificity remain to be determined. Nevertheless, molecules that target specific resolvin-mediated GPCR signaling pathways may allow selective treatment of TRPA1-mediated inflammation and pain.

Although TRPA1 has advantageous properties as a drug target, its potential disadvantages also need to be considered. Because of the widespread presence of TRPA1 in many tissue types, targeting TRPA1 comes with a distinct possibility of unwanted side effects. Although not as well characterized, TRPA1 expression has been detected in nonneuronal tissues and cell types; this distribution may further complicate treatment with antagonists. A better understanding of thespecific site of TRPA1 action by using conditional knockouts may offer ways to mitigate the risks associated with off-target effects of TRPA1 inhibitors.

In summary, the ability of TRPA1 to be activated by a large variety of endogenous and exogenous inflammatory compounds makes TRPA1 an ideal detector of inflammatory cues. Recently, a gain-of-function mutation in *TRPA1* was linked to a rare pain disorder, familial episodic pain syndrome, which is characterized by episodes of debilitating upper-body pain (135). Future genome-wide studies will reveal whether TRPA1 mediates other pathologies in patients suffering from chronic inflammatory pain conditions.

Glossary

Bradykinin (BK)	a potent inflammatory peptide that induces vasodilation and increased sensitivity to pain (hyperalgesia)
Prostaglandin (PG)	a family of inflammatory molecules generated by cyclooxygenase metabolism of fatty acids
Substance P (SP)	a member of the tachykinin family of neuropeptides and a potent inducer of extravasation, vasodilation, immune cell recruitment, and inflammatory pain
Calcitonin gene-related peptide (CGRP)	a neuropeptide stored in and released by a subset of sensory fiber terminals; a potent vasodilator and regulator of inflammatory pain
Transient receptor potential (TRP) channels	a conserved family of ion channels comprising more than 100 members; involved in the detection of visual, gustatory, thermal, chemical, and mechanical stimuli
Neurogenic inflammation	inflammation initiated by the activation of sensory neurons and the subsequent release of proinflammatory neuropeptides
C-fibers	a type of afferent sensory fibers characterized by slow conduction velocity; can be activated by thermal, mechanical, and chemical stimuli
TRPV1	a TRP family member activated by capsaicin and heat; a subset of TRPV1-positive neurons also express TRPA1
Nodose ganglion (NG)	a ganglion of the vagus nerve (cranial nerve X) that innervates the respiratory tracts, heart, and digestive tract
Dorsal root ganglion (DRG)	a ganglion located along the dorsal root of the spinal cord; sends out processes that innervate the viscera and the skin
Trigeminal ganglion (TG)	a ganglion of the trigeminal nerve (cranial nerve V); sends out processes that innervate the upper respiratory tract, face, and meninges
Peripheral sensitization	the process that causes peripheral terminals of sensory neurons to decrease their response threshold after repetitive stimulation
Nociceptors	sensory neurons that are activated by noxious stimuli and usually produce the sensation of pain
Covalent modification of cysteine residues	such covalent modification at the N terminus of TRPA1 by electrophilic compounds causes activation of the channel
Pruritogen	any compound that causes itch
Visceromotor response (VMR)	muscle contraction of the viscera in response to a given stimulus

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SUMMARY POINTS

1. Inflammation is a biological response to tissue injury that activates neuronal, immune, and epithelial cells that mediate protective responses to promote healing. Chronic inflammation persists in the absence of injury/disease and can cause severe tissue damage and unnecessary pain. TRPA1 is required for acute and chronic inflammation.
2. TRPA1-expressing sensory neurons that innervate the skin, airways, and GI tract detect irritants and release neuropeptides, such as neurokinin A, substance P, and calcitonin gene-related peptide, that promote and modulate inflammatory responses.
3. TRPA1 is robustly activated by a wide variety of exogenous irritants and endogenous mediators that cause pain hypersensitivity and inflammation.
4. Genetic evidence and pharmacological evidence make TRPA1 a prime target for the development of anti-inflammatory drugs to be used in acute and chronic conditions.

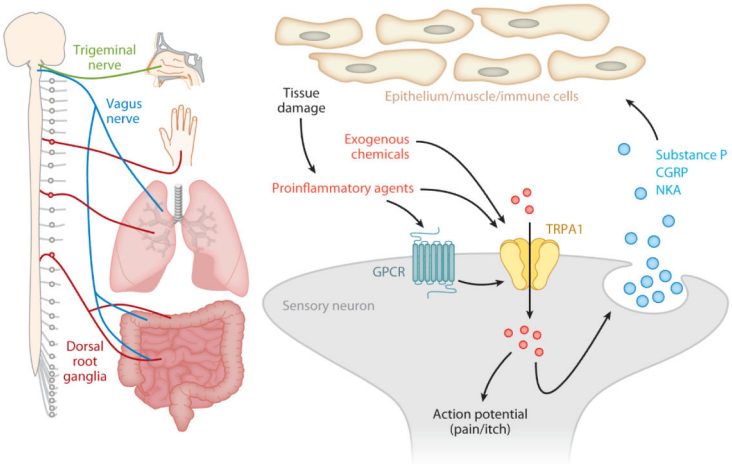

Figure 1.

Mechanisms of neurogenic inflammation. (*Left*) TRPA1 is expressed by sensory afferents that have cell bodies in the vagus nerve (*blue*), trigeminal ganglia (*green*), and dorsal root ganglia (*red*). These afferents innervate peripheral targets, including the skin, the airways, and the GI tract. (*Right*) TRPA1 activation is required for the release of neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), and neurokinin A (NKA), which promote and modulate inflammatory responses.

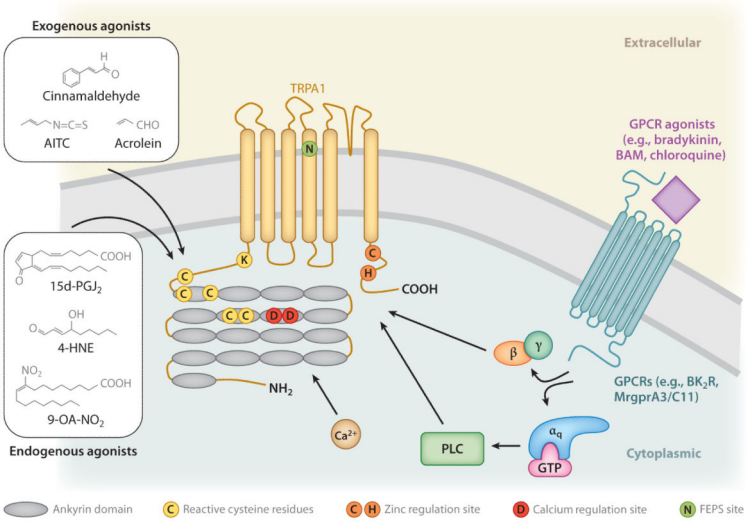

Figure 2.

Diverse mechanisms of TRPA1 activation. Endogenous and exogenous agonists covalently modify cysteines (*yellow*; C) in the TRPA1 N terminus to promote channel activity. In addition, signaling molecules downstream of G protein–coupled receptors (GPCRs) regulate TRPA1 channel activity. Other putative binding/modulatory sites that regulate channel activity include ankyrin domains (*gray*), calcium-binding domains (*red*; D), the familial episodic pain syndrome (FEPS) mutation (*green*; N), and zinc-binding sites (*orange*; C, H). Additional TRPA1 domains for activation by phospholipase C (PLC) and Gβγ are not known.

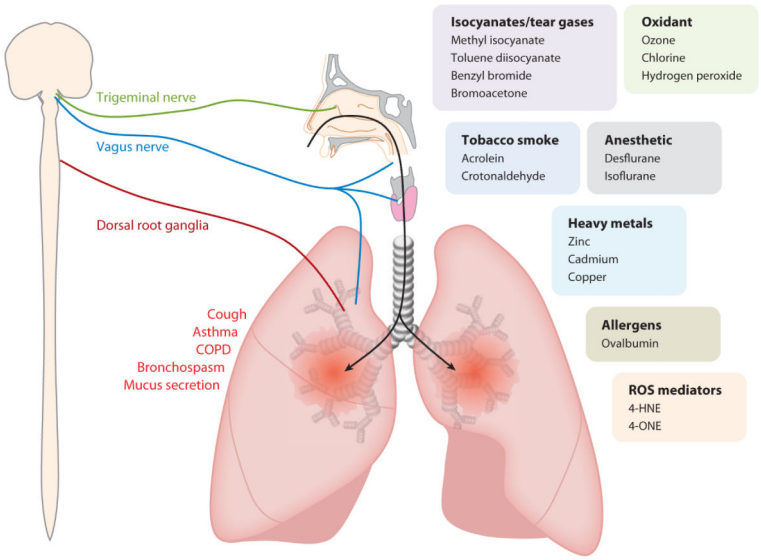

Figure 3.

TRPA1 in airway inflammation. The respiratory system is densely innervated by TRPA1-expressing primary afferent fibers from the trigeminal nerve, vagus nerve, and dorsal root ganglia. TRPA1 is activated by numerous exogenous irritants and endogenous mediators of airway inflammation. TRPA1 activation in the airways has been linked to cough, asthma, chronic obstructive pulmonary disease (COPD), bronchospasm, and mucus secretion.

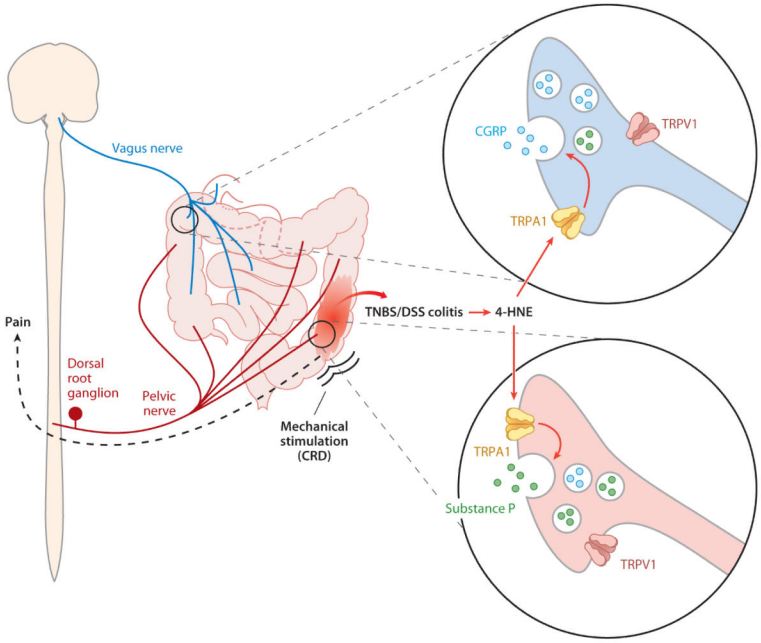

Figure 4.

TRPA1-expressing sensory nerves innervate the colon and mediate neuropeptide release in response to TRPA1 activators such as 4-hydroxynonenal (4-HNE). Experimental colitis models induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) or dextran sodium sulfate (DSS) lead to hypersensitivity to colorectal distension (CRD) and pain.

Table 1

Airborne irritants that activate TRPA1

Irritant class	Chemical name	Source	Mechanism of TRPA1 activation	TRPA1-dependent effects	Reference(s)
Isocyanates	Toluene diisocyanate	Industrial manufacturing	N-terminal Cys	Decreased respiratory rate Increased pause after inhalation	21
	Allyl isothiocyanate	Mustard oil	N-terminal Cys	Decreased respiratory rate Increased pause after inhalation Cough	84
Cigarette smoke α,β-Aldehydes	Mixture of chemicals	Cigarette smoke extract	–	Bronchial contraction Plasma extravasation	78
	Acrolein	Smoke	N-terminal Cys	Vagus nerve activation Bronchial contraction Cough	16, 26, 78, 83
	Crotonaldehyde	Smoke	–	Bronchial contraction Cough	16, 78
Heavy metals General anesthetics	Zinc	Industrial manufacturing	His983/Cys1021	Reduced breathing rate	71
	Desflurane	Surgery	–	Bronchial contraction	80
	Isoflurane	Surgery	–	Bronchial contraction	79
Oxidizing agents	Hypochlorite	Industrial manufacturing	N-terminal Cys	Reduced breathing rate Increased pause after exhalation	28
	H_2O_2	Industrial manufacturing	N-terminal Cys	Reduced breathing rate Increased pause after exhalation	28