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The role of TRPA1 in visceral inflammation and pain

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Abbreviations: 4-HNE, 4-hydroxynonenal; B_2R, B_2 bradykinin receptor; CGRP, calcitonin gene-related peptide; DAG, diacylglycerol; DRG, dorsal root ganglia; GM-CSF, granulocyte macrophage colony stimulating factor; IL, interleukin; MIP-1α, macrophage inflammatory protein 1; MCP-1, macrophage chemotactic protein 1; PAR-2, protease-activated receptor-2; PKA, protein kinase A; PKC, protein kinase C; PIP_2, phosphatidylinositide biphosphate; PLC, phospholipase C; TNBS, trinitrobenzene-sulphonic acid; TRP, transient receptor potential; TRPA, ankyrin TRP; TRPM, melastatin TRP; TRPV, vanilloid TRP

Despite significant progress in our understanding of the cellular and molecular mechanisms underlying sensory transduction and nociception, clinical pain management remains a considerable challenge in health care and basic research. The identification of the superfamily of transient receptor potential (TRP) cation channels, particularly TRPV1 and TRPA1, has shed light on the molecular basis of pain signaling during inflammatory conditions. TRPV1 and TRPA1 are considered as potential targets in the treatment of inflammatory pain because of their ability to be activated by nociceptive signals and sensitized by pro-inflammatory mediators. Notably, TRPA1 is expressed in visceral afferent neurons and is known to participate in inflammatory responses and the establishment of hypersensitivity. This review summarizes the current knowledge of the role of TRPA1 in sensory transduction, particularly in the context of visceral inflammation and pain in the gastrointestinal and urinary tracts.

According to the World Health Organization, over 20% of the world population has experienced some degree of chronic pain.[1] Pain is the most important symptom in terms of prevalence and potential personal/economic consequences; in the USA only, the cost of chronic pain exceeds US$210 billion annually.[2] Despite significant advances in our understanding of the mechanisms underlying sensory transduction and nociception, the efficacy of therapeutic approaches remains variable and clinical improvements are modest. The discovery and characterization of ion channels expressed in primary afferent neurons and their involvement in nociception has provided new potential targets for the management of clinical pain syndromes.

Nicolas Jancsó was the first to report that the vanilloid capsaicin, the chemical responsible for the piquancy of hot pepper, acted on nociceptive afferent neurons (nociceptors) to induce pain.[3] Almost 40 years after these preliminary observations, the ion channel transient receptor potential (TRP) vanilloid 1 was identified as the molecular sensor for capsaicin.[4] TRPV1 is highly expressed in nociceptors and can be activated by a wide range of noxious stimuli; while protons (H^+), heat, pressure or lipids directly activate TRPV1,[5,6] pro-inflammatory mediators such as serotonin, bradykinin, histamine, proteases, chemokines or nerve growth factors indirectly sensitize the channel by lowering its activation threshold.[7,8] Since the discovery of TRPV1, 28 different TRP subunit genes have been identified, and their products classified into three TRP subfamilies: vanilloid TRPs (TRPVs), melastatin TRPs (TRPMs) and ankyrin TRPs (TRPAs) (reviewed in ref. 9). Over the last decade, a growing body of evidence has suggested that TRP channels, particularly TRPV1, could play a role in the establishment of inflammation and pain. This is supported by the observation that TRPV1 knockout mice show impaired response to heat and reduced thermal hyperalgesia during inflammation.[10,11] More recently, another member of the TRP channel family, TRPA1, has also emerged as an important player in these neurological processes. The focus of this review is to provide a better understanding of the role of TRPA1 in sensory transduction, particularly in the context of visceral inflammation and pain.

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TRPA1: Structure, Distribution and Regulation

TRPA1, formerly referred to as ANKTM1, was originally identified and cloned by Jaquemar and colleagues in 1999.[12] In their study, the authors described a transformation-sensitive mRNA present in fibroblasts, which encoded a transmembranous TRP-like protein supporting several ankyrin-like domains.[12] It was later established that the mammalian TRPA1 gene is orthologous to the nociception gene *painless* in *Drosophila melanogaster*, thus suggesting a conserved role for TRPA1 in sensory functions in humans.[13,14]

TRPA1, is composed of six putative transmembrane regions (S1–S6), flanked by cytosolic C- and N-terminal tails with several amino-terminal ankyrin repeats (**Fig. 1**). In its functional

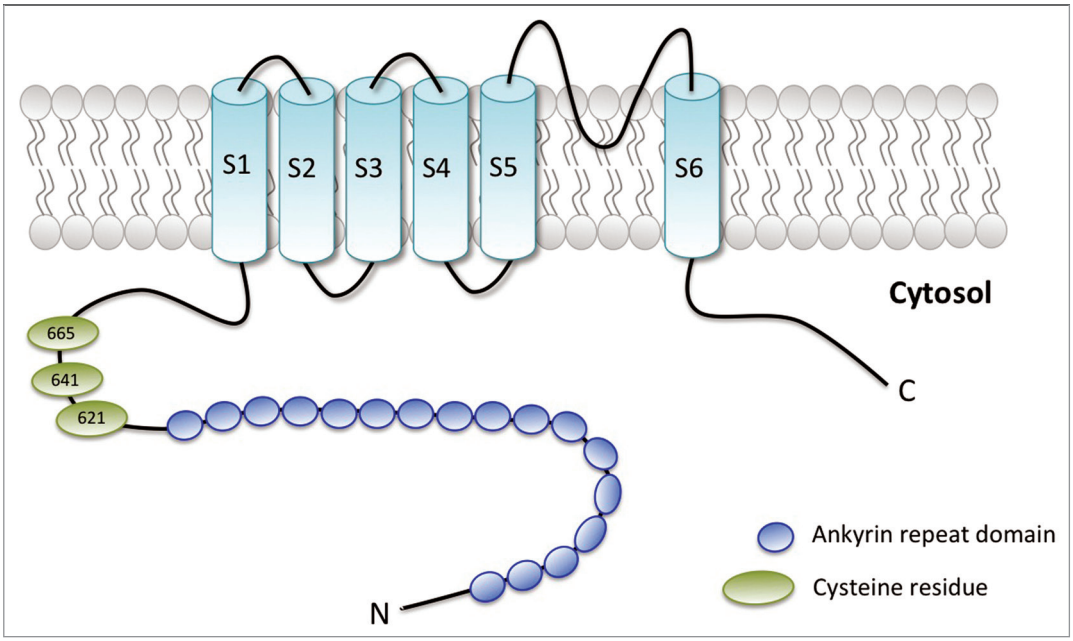

Figure 1. Schematic representation of human TRPA1. Each subunit is composed of six membrane-spanning domains (S1–S6) flanked by cytosolic C- and N-terminal domains. The amino-terminal tail supports several ankyrin repeat domains (blue circles). The pore region is located between the fifth and sixth transmembrane domains of each channel subunit. Green ovals represent cysteine residues identified as essential for covalent activation of TRPA1.

configuration, TRPA1 forms tetramers via the interaction of the cation-permeable pore regions located between the fifth and sixth transmembrane domains of the channel subunits.

TRPA1 is mainly expressed in small-diameter peptidergic nociceptors of the dorsal root (DRG), nodose and trigeminal ganglia, along with TRPV1.[15,16] Recently, TRPA1 expression was also observed in colonic myenteric neurons, where it is believed to modulate spontaneous colonic functions.[17] Although TRPA1 has been characterized and studied mainly in the nervous system, its expression was also reported in non-neuronal tissues such as skeletal muscle, lung, small intestine, colon and pancreas.[18]

TRPA1 is activated by a wide spectrum of chemical and mechanical stimuli; TRPA1 is known to respond to dietary irritants such as isothyocyanates (mustard oil, wasabi, horseradish) and allycin (garlic), to name only a few.[19-22] Several endogenous pro-inflammatory mediators, including cyclopentane prostaglandins and byproducts of oxidative stress (4-hydroxynonenal [4-HNE], 4-oxononenal), have been shown to directly activate TRPA1 by covalent modification of cysteine residues on the channel.[23-27] Subsequent to TRPA1 activation, increases in intracellular Ca^{2+} induce the peripheral release of neuropeptides (substance P and calcitonin gene-related peptide (CGRP)), purines, and other transmitters from sensitized nerve fiber endings, which ultimately results in neurogenic inflammation and hypersensitivity.[28-31] It is interesting to note that Ca^{2+} does not only represent an intermediate player in TRPA1-mediated events, but also acts as a direct modulator of TRPA1 activity. Indeed, electrophysiological recordings have demonstrated an increase in TRPA1 activity during Ca^{2+} perfusion in vitro.[21,32-34] Furthermore, extracellular Ca^{2+} is also known to induce TRPA1 desensitization, either by direct binding to the extracellular portion of the channel, or by mediating increases in intracellular Ca^{2+}, also recognized to desensitize other TRP channels.[21,32,34,35]

During inflammatory conditions, TRPA1 activity is regulated by several different mechanisms, including the modulation of its trafficking to the membrane (**Fig. 2**). Indeed, in vitro experiments on HEK293T cells and mouse DRGs have demonstrated that mustard oil induces TRPA1 activation and translocation to the cell membrane, in a protein kinase A (PKA) and phospholipase C (PLC)-dependent manner.[36] This increase in TRPA1 trafficking to the cell surface is believed to be mediated by induction of vesicle fusion with the plasma membrane.[37-40]

Finally, TRP channels can also be regulated downstream of G protein-coupled receptor activation. TRPV1 activation has been reported following stimulation of sensory neurons with the pro-inflammatory mediator bradykinin, which results in thermal hyperalgesia and acute pain.[41] Interestingly, this effect was maintained in TRPV1-deficient mice, suggesting the involvement of another channel in the cellular events evoked by bradykinin.[41] Using TRPA1-deficient animals, independent studies have demonstrated that TRPA1 is required for bradykinin-evoked sensory neuron excitation ex vivo and hyperalgesia in vivo.[19,42] These observations indicate that TRPV1 and TRPA1 are interdependently regulated downstream of B_2 bradykinin receptor (B_2R) activation, and act in concert to induce hyperalgesia. Further research is warranted in order to determine if this crosslink requires physical association of the two channels, or is dependent on a regulatory partnership. In addition to its effect on TRPA1/TRPV1 interaction, bradykinin has also been shown to sensitize TRPA1 via activation of PLC (**Fig. 2**).[43] PIP_2 has been suggested as an endogenous inhibitor of TRPA1;[44] by breaking down

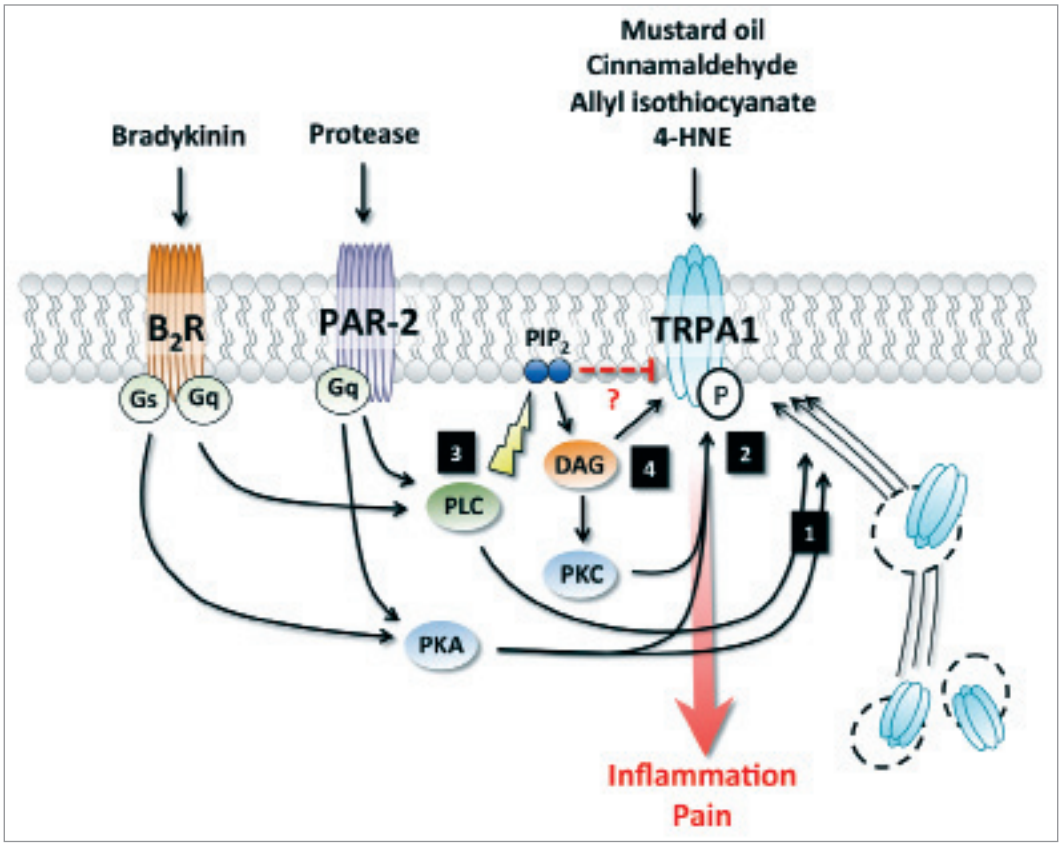

Figure 2. Modulation of TRPA1 activity and trafficking. (1) Activation of PKA and PLC by PAR-2 or B_2R induces trafficking of TRPA1 to the plasma membrane. (2) PKA and PKC-dependent phosphorylation potentiate TRPA1 activation. (3) Activation of PLC downstream of PAR-2 or B_2R enhances TRPA1 activity by releasing the channel from PIP_2-mediated inhibition. (4) DAG modulates TRPA1 activity either directly, by activation of the channel itself, or in a PKC-dependent manner. 4-hydroxynonenal, 4-HNE; B_2 Bradykine receptor, B_2R; Diacylglycerol, DAG; protease-activated receptor-2, PAR-2; protein kinase A, PKA; protein kinase C, PKC; phosphatidylinositide, PIP_2; phospholipase C, PLC.

phosphatidylinositides (PIP_2), PLC would block its inhibitory effect on TRPA1, and thus sensitize the channel.[43] Diacylglycerol (DAG), a byproduct of PIP_2 hydrolysis by PLC, could also be involved in this process, either by directly activating TRPA1 or by mediating PKC-dependent phosphorylation of TRPA1.[19,45] Finally, PKA has also been suggested as a signaling intermediate molecule in bradykinin-mediated TRPA1 sensitization, by directly phosphorylating the channel (**Fig. 2**).[43,45]

TRPA1 and Visceral Pain

Gastrointestinal tract. Abdominal pain is a hallmark of several inflammatory diseases of the gastrointestinal (GI) tract, including irritable bowel syndrome, inflammatory bowel disease and functional dyspepsia.[46,47] The GI tract is certainly the most studied among the internal organs with regards to the role of TRPA1 in visceral inflammation and nociception. Indeed, several experimental models of colitis have demonstrated the efficacy of mustard oil in inducing colitis.[28-31] Mustard oil-induced colitis is characterized by the upregulation of several pro inflammatory mediators including interleukin (IL)-1β, IL-6, granulocyte macrophage colony stimulating factor (GM-CSF), macrophage chemotactic protein 1 (MCP-1) and macrophage inflammatory protein 1 (MIP-1α), all of which are implicated in leukocyte recruitment and activation.[28] This inflammatory response, along with the release of substance P and CGRP from sensitized nerve fiber endings, contributes to the development of visceral hypersensitivity.[28-31]

A few years ago, Yang et al. demonstrated that reduction of TRPA1 expression by antisense oligodeoxynucleotide significantly reduced colonic hypersensitivity induced by trinitrobenzene-sulphonic acid (TNBS)-mediated colitis in mice.[48] These results were further supported and expanded by a recent study showing that TRPA1 agonists allyl isothiocyanate and trans-cinnamaldehyde induced mechanosensory responses in vagal and pelvic serosal afferents of $TRPA1^{+/+}$ mice, but not in TRPA1-deficient animals.[49] These observations were corroborated by in vivo recording of visceromotor responses to colorectal distention, which showed a significant reduction in mechanical hyperalgesia in $TRPA^{-/-}$ mice, therefore directly implicating TRPA1 in colonic pain.[49] Similar results were obtained in the rat stomach using intrathecal injection of TRPA1 antisense.[50] In the colon, it is interesting to note that mechanical hypersensitivity evoked by TRPA1 agonists was further amplified in afferents from mice with chemically induced colitis, suggesting a role for TRPA1 in mechanosensory function and sensitization during inflammatory conditions.[49]

Activation of the G protein-coupled receptor protease-activated receptor-2 (PAR-2) can induce colitis and visceral hypersensitivity. Interestingly, PAR-2 is also involved in the modulation of TRPA1 activity (**Fig. 2**). TRPA1 and PAR-2 have been observed in a co-localization pattern in rat DRG neurons.[43] The same study also demonstrated TRPA1 sensitization downstream of PAR-2 activation. Similar to what has been observed upon bradykinin treatment, this mechanism appears to be dependent on the cleavage of PIP_2 by PLC, which releases the inhibition of TRPA1.[43] PAR-2 has also been shown to modulate TRPA1 in a PKA-dependent manner, either via TRPA1 phosphorylation or induction of its trafficking to the membrane (**Fig. 2**).[36,45] The interaction between PAR-2 and TRPA1 is suggested to play a role in different experimental models of GI disorders. Notably, PAR-2-mediated sensitization of TRPA1 represent a key mechanism in mast cell-mediated mechanical hyperalgesia in the guinea pig esophagus.[45,51] Furthermore, Cattaruza and colleagues have reported that TRPA1 deletion significantly reduced mechanical colonic hyperalgesia induced by PAR-2 activating peptide.[52]

The expression of TRPA1 has also been demonstrated in DRG neurons innervating the pancreas, and is believed to participate in inflammation and pain related to acute pancreatitis in mice.[53,54] TRPA1 agonists have been shown to induce pancreatic inflammation and hyperexcitability of spinal nociceptors.[53] Furthermore, cerulein-evoked pancreatic inflammation induced a significant increase in the expression and activation of both TRPA1 and TRPV1, as well as overall excitability of pancreatic sensory neurons.[54] Interestingly, while the inhibition of both TRPA1 and TRPV1 individually reduced the severity of pancreatitis, the combined treatment appeared to be more effective. Importantly, these observations were corroborated in pain-related behavior experiments; combined treatment with TRPA1 and TRPV1 antagonists prevented the reduction of exploratory behaviors observed in mice treated with cerulean alone.[54] These observations, similar to what was found in thermal hyperalgesia-induced by bradykinin, suggest a functional crosstalk between TRPA1 and TRPV1 in the modulation of pain signaling during pancreatitis.

Urinary tract. Alteration in afferent activity is believed to be a key factor in urinary tract dysfunction; hyperexcitablity of afferent neurons innervating the urinary tract has been proposed as a possible mechanism behind idiopathic detrusor over activity and painful bladder symptoms (reviewed in ref. 55 and 56).

In mice, TRPA1 expression has been reported in small afferent fibers innervating the trigone of the bladder,[16] where it appears to modulate bladder contraction under physiological conditions.[33] Subsequent studies also demonstrated that the majority of DRG neurons innervating the mouse bladder expressed TRPA1, often in a co-localization pattern with TRPV1.[57]

The urothelium, the epithelial layer lining the bladder, interacts closely with underlying afferent nerve fibers and is believed to play an important role in sensory transduction in the urinary tract.[58] TRPA1 expression has been reported in the human and rat urothelium, and is believed to modulate bladder function in pathological conditions.[59,60] Notably, TRPA1 upregulation has been observed in the urothelium of patients with bladder outlet obstruction, when compared to healthy controls.[59] Furthermore, activation of TRPA1 by intravesical administration of trans-cinnamaldehyde has been shown to induce hyperreflexia through C-fiber-mediated afferent pathway in rats.[60] These results are supported by another study demonstrating altered urodynamic functions, including increase micturition frequency and reduced voiding volume, in response to other TRPA1 agonists such as allyl isothiocyanate and hydrogen sulfide.[61] Taken together, these observations suggest that TRPA1 is involved in the regulation of bladder sensory function and micturition reflex.

TRPA1 is also implicated in the pathology of overactive bladder, a chronic condition often linked to spinal cord injury and associated with spontaneous and involuntary bladder contractions.[62] Andrade and colleagues reported an upregulation of TRPA1 channels in the bladder and bladder-innervating DRG neurons of rats subjected to spinal cord injury.[62] Importantly, the inhibition of TRPA1 by either selective antagonists or targeted gene deletion was shown to normalize bladder contractions in this model, thus identifying TRPA1 as an important player in overactive bladder syndrome.[62]

Conclusion

Although we have gained significant insights into the mechanisms underlying sensory transduction and nociception, efficient pain management remains a considerable challenge in health care and basic research. One of the most important breakthroughs with regards to inflammatory pain has been the discovery of the sensory and nociceptive role of TRP channels. After TRPV1, TRPA1 has recently emerged as another potential therapeutic target in the treatment of chronic visceral pain. Indeed, the role of TRPA1 in GI inflammatory disorders is becoming increasingly clear and, although causal implication remains to be established, TRPA1 upregulation has been observed in several disease model systems. In-depth research is warranted to determine the exact role of TRPA1 in visceral pain and neurogenic inflammation, but our new understanding of its homeostatic and pathophysiological functions certainly offers bright perspectives for the development of novel therapeutic approaches in the treatment of chronic pain associated with visceral inflammation.

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