

Role of the transient receptor potential vanilloid 1 in inflammation and sepsis

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Abstract: The transient receptor potential vanilloid 1 (TRPV1) is a thermoreceptor that responds to noxious temperatures, as well as to chemical agonists, such as vanilloids and protons. In addition, its channel activity is notably potentiated by proinflammatory mediators released upon tissue damage. The TRPV1 contribution to sensory neuron sensitization by proalgesic agents has signaled this receptor as a prime target for analgesic and anti-inflammatory drug intervention. However, TRPV1 antagonists have notably failed in clinical and preclinical studies because of their unwanted side effects. Recent reports have unveiled previously unrecognized anti-inflammatory and protective functions of TRPV1 in several diseases. For instance, this channel has been suggested to play an anti-inflammatory role in sepsis. Therefore, the use of potent TRPV1 antagonists as a general strategy to treat inflammation must be cautiously considered, given the deleterious effects that may arise from inhibiting the population of channels that have a protective function. The use of TRPV1 antagonists may be limited to treating those pathologies where enhanced receptor activity contributes to the inflamed state. Alternatively, therapeutic paradigms, such as reduction of inflammatory-mediated increase of receptor expression in the cell surface, may be a better strategy to prevent abrogation of the TRPV1 subpopulation involved in anti-inflammatory and protective processes.

Keywords: transient receptor potential, nociceptor, capsaicin, pain, ion channel, analgesia

TRPV1 receptor

Transient receptor potential vanilloid 1 (TRPV1), also known as the capsaicin receptor, was first cloned from rat dorsal root ganglion neurons using an expression-cloning screening strategy.¹ This newly cloned cDNA was first named VR1, for vanilloid receptor subtype 1. Because this receptor is a member of the transient receptor potential family of cation channels, it was given the name TRPV1 because it represented the first known member of the transient receptor potential vanilloid subfamily of transient receptor potential channels. To date, TRPV1 orthologs have been identified in eukaryotes, including human, rat, guinea pig, rabbit, mouse, dog, and porcine tissues, but not in prokaryotes. The ability of TRPV1 to respond to noxious stimuli and to be functionally sensitized by proinflammatory mediators has signaled it as a “pathological” receptor, having a significant role in the pain transduction pathway, and in the maintenance of inflammatory conditions in a variety of diseases and injury states.

TRPV1 structure and expression

TRPV1 is an 838-amino acid protein with a molecular weight of 95 kDa, consisting of six transmembrane segments, with an amphipathic pore-forming region between

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the fifth and sixth transmembrane segments, a large N-terminus intracellular domain, and a C-terminal cytosolic region (Figure 1). Functional TRPV1 channels exist as homomultimers,² although functional heteroligomers may be formed between TRPV1 and TRPV3³ or between TRPV1 and TRPV2,^{4,5} which may be responsible, at least in part, for the variable responses to agonists and antagonists. The 432-amino acid N-terminus contains at least six ankyrin repeats,^{6,7} which are essential for channel function^{8,9} and for orchestrating a plethora of protein–protein interactions that govern the assembly of TRPV1-containing signalplexes.^{10,11} The 145-amino acid C-terminal contains subdomains involved in distinct channel functions. For instance, adjacent to the channel gate,¹² a highly conserved region known as the transient receptor potential domain, is involved in the functional coupling of stimuli sensing and gate opening.^{13,14} Furthermore, the C-terminus contains the molecular determinants for subunit tetramerization,^{15,16} two nucleotide-binding Walker-type sites,¹⁷ as well as consensus sequences for modulation by phosphoinositides and protein kinases.^{18,19} More notably, this region has been suggested to hold the temperature sensor of the receptor.²⁰

TRPV1 shows a wide tissue distribution. High levels of expression are observed in dorsal root ganglia, trigeminal ganglia, and nodose ganglia.¹ TRPV1 is predominantly expressed in small and medium diameter neurons, mainly in the peptidergic ones, that are important in the development of neurogenic pain and inflammation,²¹ and to a lesser extent in the nonpeptidergic neurons that play a critical role in mediating chronic²² and mechanical pain.²³ Although there is still a controversy about the central nervous system distribution of TRPV1,²⁴ several studies have demonstrated the expression of this channel in a wider diversity of brain regions, including

the hypothalamus, cerebellum, cerebral cortex, striatum, midbrain, olfactory bulb, medulla, hippocampus, thalamus, and substantia nigra.²⁵ In non-neuronal tissues, TRPV1 expression is detected in keratinocytes²⁶ and melanocytes of the epidermis,²⁷ bladder urothelium,²⁸ smooth muscles,²⁹ glial cells, liver, polymorphonuclear granulocytes,³⁰ mast cells,³¹ dendritic cells, and macrophages.³²

TRPV1 is a nonselective cation channel with near equal selectivity for Na⁺, K⁺, Li⁺, Cs⁺, and Rb⁺ ions,¹ but moderate selectivity for divalent cations. When activated by capsaicin, the permeability of Mg²⁺ and Ca²⁺ relative to Na⁺ (Px/PNa) is roughly 5 and 10, respectively.^{1,33,34} Lower Px/PNa values of 3–4 are reported when the channel is activated by heat.³⁵ TRPV1 is also highly permeable to protons and large polyvalent cations, suggesting the existence of a large pore. Several amino acids in the putative pore-forming region between the fifth and sixth transmembrane segment domains are implicated in cation selectivity. Mutation of Glu-648 (E648A) reduces Mg²⁺ permeability and increases Ca²⁺ permeability. Mutation of Asp-646 (D646N) reduces Mg²⁺ permeability and blockade by the cationic dye, ruthenium red.³⁶

The single-channel conductance of capsaicin-activated channels is approximately 90–100 pS at positive potentials. At negative potentials (–60 mV), the conductance is significantly lower, with values of approximately 50 pS.¹ TRPV1 currents exhibit significant outward rectification due to a combined effect of voltage on both channel conductance and open probability.³⁷

TRPV1 has different modes of activation

TRPV1 is a polymodal channel, activated by physical and chemical stimuli, including heat, vanilloids, lipids, spider

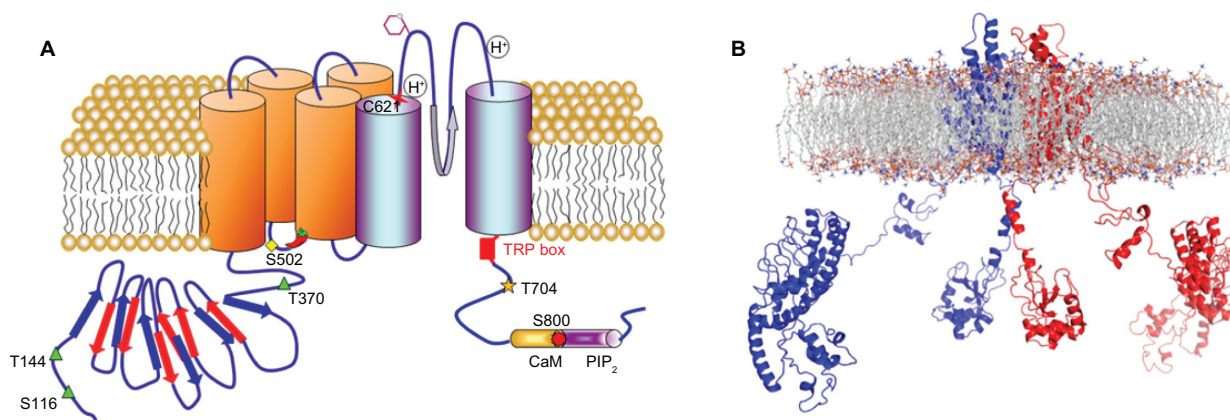


Figure 1 **A)** Putative membrane topology of a transient receptor potential vanilloid I subunit displaying the location of residues involved in ligand-binding, proton activation, and post-translational modifications. The transient receptor potential vanilloid I domain, and calmodulin- and phosphatidylinositol-4,5-bisphosphate-binding domains are also depicted. **B)** Side view of the ribbon structural model of two opposite monomers of the transient receptor potential vanilloid I channel inserted into the lipid bilayer, after molecular dynamic simulation. The other two monomers are not shown for clarity.

toxins, protons, cations, and voltage.^{35,38,39} The channel is activated by noxious temperatures with a threshold of approximately 43°C,¹ and a temperature-dependent gating characterized by a $Q_{10} \geq 20$ (Q_{10} is used to estimate the temperature dependence of channel gating).⁴⁰ The temperature threshold is highly influenced by other ligands that act allosterically and by the receptor phosphorylation state. Thus, when simultaneously activated by other ligands, the threshold may decrease down to 20°C. It has been proposed that temperature regulates TRPV1 by changing the intrinsic voltage sensitivity of the channel.³⁷ The temperature sensitivity of this channel is allosterically linked to chemical and voltage activation.²⁰ Although the mechanisms underlying heat activation remain unclear, a role of the C-terminus and the outer pore region has been proposed.^{14,41}

TRPV1 is activated by capsaicin, the pungent component of hot chili peppers. Capsaicin and related compounds, including resiniferatoxin and olvanil, are highly lipophilic and share a structural similarity to several endogenous fatty acid derivatives that have also been identified as TRPV1 agonists.^{42,43} These include anandamide (an endocannabinoid), N-arachidonoyl dopamine, oleoyldopamine, 12-hydroperoxyeicosatetraenoic acid (a lipoxygenase product), and 18–20 carbon N-acylethanolamines.⁴⁴ Vanilloids interact at intracellular regions of TRPV1, as implied by a membrane-impermeable charged capsaicin analog that is only effective when applied cytosolically.⁴⁵ Consistent with this observation, several intracellular molecular determinants of capsaicin binding have been identified. The amino acid residues, Arg-114 in the N-terminus and Glu-761 in the C-terminal domain, play a key role in ligand binding.⁴⁶ In addition, Tyr-511 and Ser-512 located between the second and third transmembrane segments are also critical for vanilloid binding and channel activation,⁴⁷ and Thr-550 has also been pointed towards as involved in structuring the vanilloid binding site in rat and human TRPV1 channels.⁴⁸

A pH lower than 5.0 at the extracellular side of the channel activates TRPV1 ion channels. Actually, ligand-, voltage-, and temperature-evoked gating are potentiated by mildly acidic extracellular pH.⁴⁹ Two glutamate residues located near the extracellular pore-forming region appear critical for proton regulation, ie, Glu-648, at the loop between the fifth and sixth transmembrane segments, is involved in direct activation of the channel by strong pH (pH 4), while Glu-600 located at the end of the fifth transmembrane segment is important for the response of the channel to mildly acidic external conditions (pH 6.5).⁴⁹ Nevertheless, neutralization of Glu-600 gives rise to a constitutively active channel at 37°C.⁴⁹

In addition to protons, positively charged compounds are also able to activate TRPV1, suggesting a generalized activation mechanism based primarily on neutralization of Glu-600. External cations tend to enhance agonist-evoked currents, and divalent cations at high (>10 mM)³⁴ or even at physiological concentrations⁵⁰ gate the channel directly. Polyvalent cations are even more potent channel regulators. For instance, Gd^{3+} and the polyamine, spermine,^{51,52} sensitize and activate TRPV1 at micromolar concentrations. These actions may involve interactions at multiple acidic residues, ie, Glu-600, Glu-648, and Asp-646.

TRPV1 also has a voltage-dependent gating. The channel is activated, at least partially, at strong positive potentials and is deactivated at negative potentials. The sensitivity of voltage-dependent activation and deactivation depends on the recording temperature and on the presence of agonists. In the absence of TRPV1 activators, strong membrane depolarization is required to activate the channel ($V_{0.5}$ of +150 mV at 21°C), whereas in the presence of agonists, much smaller depolarization suffices to gate the channel, namely $V_{0.5}$ of 0 mV at 37°C, and +10.6 mV at 21°C in the presence of 50 nM capsaicin.³⁷ Thus, the heat or ligand sensitivity of TRPV1 may reflect a shift in its intrinsic voltage dependence. Consequently, the temperature threshold for TRPV1 activation is not constant, but fluctuates depending on the membrane potential. The voltage sensor remains unknown, although the fourth transmembrane segment has been signaled as a putative candidate to hold it. However, unlike voltage-gated channels, TRPV1 and other transient receptor potential channels lack an array of charged residues in their transmembrane segment domains.

From the aforementioned observations, it appears obvious that various activators of TRPV1 potentiate the effect evoked by others, leading to enhanced activity, suggesting a coupling of their receptor sites. This gating cooperativity of various ligands seems synergistic rather than additive²⁰ and, given the polymodal and synergistic modes of activation, implies that the TRPV1 ion channel act as an “integrator” of exogenous stimuli.³⁵ In fact, TRPV1 acts similarly in relation to endogenous agents, which makes it of particular relevance in the context of inflammation, given the wide variety of inflammatory agents generated in inflamed conditions.

In the continuous presence of an activating stimulus, TRPV1 undergoes desensitization. This phenomenon can occur rapidly after a prolonged single application of an agonist, or slowly following repeated agonist applications (also known as tachyphylaxia). Receptor desensitization is believed to occur predominantly via a Ca^{2+} -dependent

process because it is largely abolished in the absence of Ca^{2+} . However, it should be noted, that some Ca^{2+} -independent desensitization also occurs, especially with heat activation.⁵³ The Ca^{2+} -dependent mechanism arises because of the high TRPV1 Ca^{2+} permeability, allowing Ca^{2+} influx to activate an inhibitory process. Indeed, fast desensitization was significantly reduced in a TRPV1 mutant that possesses markedly reduced Ca^{2+} permeability.³³ Furthermore, desensitization is attenuated by inhibitors of calcineurin, a Ca^{2+} -activated phosphatase, thus linking desensitization to a dephosphorylation event.⁵⁴ In addition, Ca^{2+} may signal via calmodulin, which interacts with TRPV1 at the N-terminal and C-terminal regions (positions 189–222 and 767–801). Indeed, disruption of the calmodulin C-terminal region partially inhibits fast desensitization.⁵⁵

Regulation of TRPV1 channel activity

There is increasing evidence that TRPV1 is subjected to complex regulation manifested at several levels, from gene expression to post-translational modification and formation of receptor heteromers, as well as from subcellular compartmentalization and association with regulatory proteins to many second messengers.¹¹

Limited information is available about what controls TRPV1 transcription in nociceptors. Two functional TRPV1 promoter regions and transcription initiation sites have been identified in the rat, ie, a distal promoter region, P1, and a second more proximal promoter region, P2.⁵⁶ The P1 region containing a classic TATA box and a downstream transcription initiation site directs the strongest promoter activity within the 233-bp core fragment. The proximal promoter region, P2, which lacks a TATA box, contains an associated transcription initiation site that corresponds to the consensus sequence known as the “initiator” element. Alternate use of dual promoters may represent an important aspect of how TRPV1 gene expression can be dynamically regulated. Nerve growth factor induces activation of the GTPase Ras, which is coupled to the activation of both transcription and translation of TRPV1.⁵⁷ Nerve growth factor positively regulates transcriptional activity of both rat TRPV1 promoters.

A large body of evidence indicates that post-translational modifications of TRPV1, such as phosphorylation mediated by protein kinase A, protein kinase C, and calmodulin-dependent protein kinase, increase its activity. Phosphorylation at Ser-116 in the N-terminus of TRPV1 is pivotal in protein kinase A-mediated downregulation of TRPV1 desensitization.⁵⁸ In addition, Thr-144, Thr-370, and Ser-502

are important in protein kinase A-mediated phosphorylation/sensitization of the channel. Moreover, protein kinase C-mediated phosphorylation of TRPV1 not only potentiates capsaicin-evoked or proton-evoked responses, but also reduces its temperature threshold, such that receptors are active under physiological conditions (37°C).⁵⁹ Two serine residues on TRPV1, Ser-502 and Ser-800, have been recognized to be important in protein kinase C-mediated effects. In addition to this direct effect, protein kinase C can also produce phosphatidylinositol 4,5-bisphosphate (PIP_2) hydrolysis increasing TRPV1 activity, although PIP_2 has been proposed to be involved in sensitization of these channels by proinflammatory agents.⁵⁹ Calmodulin-dependent protein kinase-mediated phosphorylation of TRPV1 at Ser-502 and Thr-704 plays an important role in channel activation in response to capsaicin application.⁶⁰ In addition, calcineurin-mediated dephosphorylation at the same sites can produce TRPV1 desensitization.⁶¹ Similarly, the nonreceptor cellular tyrosine, c-Src kinase, positively regulates TRPV1 channel activity by tyrosine phosphorylation.⁶¹

In addition to phosphorylation, the activity of TRPV1 may be regulated by N-glycosylation,⁶² given that extracellular Asn-604 has been identified as a glycosylation site.⁶³ Similarly, adenosine 5' triphosphate may allosterically modulate TRPV1 by direct interaction with the nucleotide-binding Walker-type domains and increasing vanilloid-induced channel activity.⁹ Modulation of the redox state also impacts the physiological activity of TRPV1, possibly involving the Cys-621 amino acid residue located on the extracellular surface.⁶⁴

Another essential pathway that influences TRPV1 activity is the formation of signalplexes, or the physical assembly of signaling molecules into discrete macromolecular entities.¹¹ Several signaling proteins have been described as TRPV1-interacting proteins, that could be part of a “TRPV1 receptome” modulating nociceptor activity. As mentioned, TRPV1 associates with intracellular signaling enzymes, including protein kinase A, protein kinase C, Src, inositol 1,4,5-trisphosphate, and calmodulin-dependent protein kinases, and also with calcineurin 2B phosphatase.⁶⁵ It may also interact with the purinergic P_2X_3 receptor,⁶⁶ calmodulin,⁶⁷ the membrane protein, Pirt,⁶⁸ the scaffolding protein, AKAP79/150,⁶⁹ and with cytoskeleton proteins like tubulin.⁷⁰ Protein kinases modulate channel gating by post-translational modification involving the phosphorylation/dephosphorylation of specific residues that, in turn, lead to a decrease in the temperature threshold of channel activation and a potentiation of its activity, by either destabilizing the closed and

desensitized states and/or stabilizing the open state. Other proteins that bind to TRPV1 are snapin and synaptotagmin IX, two components of the SNARE complex that mediates Ca^{2+} -dependent exocytosis.⁷¹ Although the precise role of snapin and synaptotagmin IX binding to TRPV1 remains elusive, it could be involved in sorting the receptor into vesicles that will be exocytosed through regulated exocytosis or in promoting channel recruitment to the plasma membrane under inflammatory conditions.

Several proteins that regulate folding (chaperones), protein biosynthesis, surface expression, and channel function have been described to associate with thermotransient receptor potentials. Recently, the γ -aminobutyric A receptor-associated protein, a small cytosolic protein initially described by its ability to interact with the γ subunit of the GABA_A receptor,⁷² was pointed towards as a TRPV1 interacting partner with the cytosolic N-terminal domain of the channel.⁷³ Noteworthy, in heterologous systems, γ -aminobutyric A receptor-associated protein expression significantly augmented the levels of TRPV1 and its targeting to the plasma membrane, where it appears to favor the formation of receptor clusters. Functionally, γ -aminobutyric A receptor-associated protein appears to induce a decrease in channel activity.⁷³

TRPV1 in inflammation

Inflammation is the physiological response to tissue injury caused by pathogens or harmful agents, and is clinically characterized by swelling, redness, heat, pain, and loss of function of the affected tissue or organ. This response is a complex process perfectly orchestrated by several cell types and chemical mediators, which initiate and regulate the necessary mechanisms to remove injurious agents and repair the affected area. The cellular components include circulating monocytes, macrophages, neutrophils, lymphocytes, and dendritic cells, while the humoral components include cytokines and other chemical substances that destroy pathogens or act as mediators for other cells. When tissue damage occurs, resident immune cells, such as macrophages or dendritic cells, are activated and release mediators in order to initiate the inflammatory response. Usually, during acute inflammation, the magnitude of the inflammatory response is locally adjusted to the injurious condition and finally resolved, maintaining homeostasis. However, an imbalance of the regulatory mechanisms is the cause of inflammation as a pathological process and leads to chronic inflammatory states. Regulatory mechanisms of inflammation include mediators of immune, vascular, or neural origin that maintain the inflammatory process within the physiological range. The role of TRPV1,

as a major player in the process of neurogenic inflammation, has been traditionally considered to be neuronal. However, the expression of the channel in immune cells also suggests a contribution to the immune response.^{30–32,74}

Inflammatory mediators are released at the site of injury from immune cells, such as chemokines, cytokines, prostaglandins, bradykinin, or growth factors, as well as from sensory neurons that secrete the neuropeptides, substance P and calcitonin gene-related peptide.⁷⁵ Some of these mediators are able to activate directly local sensory neurons responsible for transducing the painful sensation that, paradoxically, is necessary to react and to avoid or minimize further damage.^{76–80} In addition, inflammatory agents are responsible for nociceptor sensitization changing the perception of stimuli, which leads to hyperalgesia (exaggerated response to a mild noxious stimulus) and/or to allodynia (response to a non-noxious stimulus), further minimizing additional damage and facilitating tissue repair. In chronic conditions, this process is exacerbated by synaptic changes at the spinal cord, a process known as central sensitization.⁸¹ Neuronal sensitization is believed to play a pivotal role in the development and maintenance of chronic pathological pain conditions.⁸²

Inflammatory regulation of TRPV1

Peripheral sensitization of TRPV1 by proinflammatory agents is mediated by different molecular mechanisms, which include long-term upregulation of TRPV1 expression, but also acute functional modification of the channel (Figure 2). Indeed, increased expression of the channel has been shown in several chronic inflammatory diseases.^{83–85} This process is also mediated by fast mobilization from a subcellular vesicular reservoir located near the plasma membrane that is recruited by SNARE-dependent exocytosis.^{11,86}

TRPV1 sensitization by nerve growth factor has been well documented, and is a good example of all the inflammatory potentiation strategies described earlier for the modulation of TRPV1 function and expression. Nerve growth factor increases TRPV1 transcription and transport to the peripheral nociceptor terminal, a process mediated by the p38/mitogen-activated protein kinase signaling pathway.^{87,88} Acute regulation of TRPV1 by nerve growth factor leads to phospholipase C activation and PIP_2 hydrolysis. In parallel, nerve growth factor activates phosphatidylinositol 3-kinase-protein kinase C epsilon and calmodulin-dependent protein kinase signaling cascades, increasing TRPV1 opening probability and its translocation to the cell surface from the vesicular pool.^{89–91} Similar to nerve growth factor, insulin growth

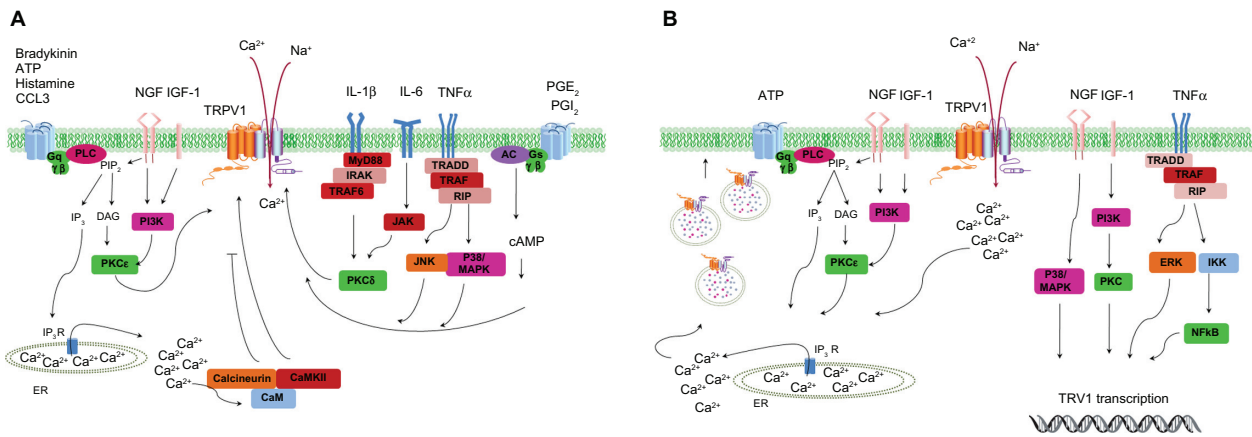


Figure 2 Regulation of transient receptor potential vanilloid 1 function and expression by proinflammatory mediators. **A)** Acute post-translational modification of transient receptor potential vanilloid 1 function. Activation of phospholipase C/protein kinase C, protein kinase A, calmodulin-dependent protein kinase, and other intracellular signaling cascades increase transient receptor potential vanilloid 1 activity and cytosolic Ca²⁺ levels. **B)** Increase of transient receptor potential vanilloid 1 expression by proinflammatory agents. Rapid receptor translocation to the cell surface from the vesicular reservoir (left side). Long-term upregulation of protein levels by transcription/translation process (right side).

factor-1 also enhances TRPV1 membrane currents through phosphatidylinositol 3-kinase and protein kinase C pathways, increasing channel activity and receptor translocation to the cell surface,⁹² inducing long-term overexpression of TRPV1.⁹³ Both nerve growth factor and insulin growth factor-1 provoke TRPV1 plasma membrane translocation by SNARE-dependent neurosecretion, as was demonstrated by the blockade of Ca²⁺-dependent neuronal exocytosis with a botulinomimetic peptide which abolished TRPV1 potentiation in dorsal root ganglion neurons.⁹⁴

Cytokines, such as tumor necrosis factor alpha, interleukin-1β, and interleukin-6, can also regulate TRPV1 function, increasing neuronal excitability.^{76,95} For instance, the receptors for tumor necrosis factors alpha (ie, TNFR1 and TNFR2) are coexpressed with TRPV1 in sensory neurons, where they can also produce rapid and long-term modification of TRPV1 function. This cytokine increases TRPV1 expression on dorsal root ganglion and trigeminal ganglion neurons via the extracellular signal-regulated kinase pathway.^{96,97} Additionally, tumor necrosis factor alpha rapidly sensitizes TRPV1 activity and enhances the Ca²⁺ influx induced by capsaicin. This rapid mechanism seems to be mediated by p38/mitogen-activated protein kinase and the c-jun N-terminal kinase pathway, but not by extracellular signal-regulated kinase.^{97–99} Although protein kinase C phosphorylation seems also to be implicated, the exact mechanism remains unknown.^{76,100–102} Tumor necrosis factor alpha can also activate the TRPA1 receptor, which has been implicated in maintaining inflammation-related pain.¹⁰³ TRPA1 is coexpressed in a subset of TRPV1-expressing nociceptors in trigeminal and dorsal root ganglion neurons¹⁰⁴ and functions to detect products of tissue

injury, inflammation, and oxidative stress that cause pain and neurogenic inflammation.¹⁰⁵ Under conditions of inflammation or nerve injury, expression of TRPA1 is persistently increased, concurrent with TRPV1.¹⁰⁶

Rapid sensitization of TRPV1 currents by interleukin-1β has also been shown to be mediated by protein kinase C activity,¹⁰⁷ via a mechanism independent of TRPV1 surface translocation by SNARE-dependent exocytosis.⁹⁴ Although little is known about the ability of interleukin-6 to sensitize TRPV1,^{78,108} exposure of dorsal root ganglion cultures to interleukin-6 increases TRPV1 response to heat by a mechanism that involves Janus kinase and protein kinase C.¹⁰⁹

Other inflammatory mediators, such as bradykinin, prostaglandin E₂, adenosine 5' triphosphate, and histamine, also sensitize TRPV1. Bradykinin induces excitation and sensitization of TRPV1 to heat via the protein kinase C pathway.^{110–112} In the same way, TRPV1 potentiation by adenosine 5' triphosphate¹¹³ or by histamine¹¹⁴ is mediated via the phospholipase C/protein kinase C pathway. However, only adenosine 5' triphosphate has been shown to mobilize TRPV1 to the plasma membrane mediated by the SNARE complex.⁹⁴ Mechanisms involved in TRPV1 sensitization by prostaglandin E₂ and prostaglandin I₂ are through phosphorylation by protein kinase A,⁵⁵ the receptor anchoring for which seems to be mediated by the protein, AKAP150,¹¹⁵ and also by protein kinase C.⁵⁵

The cellular mechanisms underlying chemokine-induced excitation of sensory neurons include potentiation of TRPV1, in addition to inhibition of K⁺ conductance.⁹⁵ CCL3 via the CCR1 receptor enhanced the response of dorsal root ganglion neurons to capsaicin, and decreased the response to

hot-plate latency in mice. CCL3-mediated TRPV1 sensitization was reduced by phospholipase C and protein kinase C inhibitors.¹¹⁶ Activation of other chemokine receptors, such as CCR2, also expressed in the dorsal root ganglia, produced sensitization of TRPV1 by phospholipase C/protein kinase C phosphorylation.¹¹⁷

TRPV1 in inflammatory conditions

Besides the direct effect of inflammatory mediators on TRPV1, activation of nociceptors also induces the release of neuropeptides which act both autocrinally on the terminals and paracrinally on target cells, such as mast, immune, and vascular smooth muscle cells.^{118,119} These peptides contribute to the destruction of the harmful agent and to the repair of damaged tissue. For instance, when the neuropeptides calcitonin gene-related peptide and substance P are released from sensory neurons, their vasodilatory effects facilitate the arrival of more immune cells and proinflammatory mediators at the site of injury, which contributes to plasma extravasation and swelling. In fact, direct activation of sensory nerves is enough to induce an inflammatory response without the presence of pathogens or tissue injury, a process known as neurogenic inflammation or sterile inflammation.¹²⁰

TRPV1 is expressed in sensory neurons, mainly in peptidergic neurons, found in many tissues close to blood vessels, epithelia, and vascular smooth muscle.^{121,122} Release of calcitonin gene-related peptide and substance P from sensory neurons is induced by TRPV1 activation via a wide variety of physical and chemical stimuli.¹²³ Sensitization of TRPV1 by inflammatory mediators increases the release of these neuropeptides from a vesicle reservoir.^{97,124} Due to the proinflammatory effects of these neuropeptides, TRPV1 activation has been long considered as a proinflammatory receptor. However, other neuropeptides with anti-inflammatory properties, such as somatostatin, can also be released as a consequence of Ca²⁺ influx through the TRPV1 channel.^{125,126}

TRPV1 acts as a transducer of noxious thermal and chemical stimuli in nociceptive sensory neurons, and is vital in mediating enhanced heat sensitivity during inflammation. Preclinical and clinical studies suggest that the TRPV1 receptor is an important component of several disease states, such as pain (inflammatory, visceral, cancer, and neuropathic), airways disease (including chronic cough), inflammatory bowel disease, interstitial cystitis, urinary incontinence, pancreatitis, and migraine.¹²⁷

Acute and chronic arthritis is characterized by debilitating pain, and by an increment in the levels of neuropeptides in synovial fluid. Due to the role of TRPV1 as an integrator of

multiple noxious stimuli as well as its presence in neuropeptide-containing fibers that are present in the knee joint synovium and adjacent bone, this channel has been implicated in the pathological symptoms of acute and chronic arthritis, although the precise mechanism is unclear.¹²⁸ Keeble et al studied the vascular and hyperalgesic components of joint inflammation in wild-type and TRPV1 knockout mice after intra-articular injection of Freund's complete adjuvant, and demonstrated that knee swelling and vascular hyperpermeability were significantly lowered in the joints treated with Freund's complete adjuvant in TRPV1 null mice. Furthermore, intra-articular injection of tumor necrosis factor alpha in these mice produced decreased thermal hyperalgesia and joint swelling, indicating a critical role of tumor necrosis factor alpha and TRPV1 in the pathophysiology of rheumatoid arthritis.¹²⁹

Cancer pain is a significant clinical problem because it is the first symptom of the disease in approximately 20%–50% of all cancer patients. Bone is the most common site of origin of chronic pain in patients with metastatic lung, prostate, and breast cancers or myeloma.¹³⁰ There are at least three mechanisms in bone cancer that may contribute to the activation and sensitization of TRPV1 expressed by sensory fibers that innervate the tumor-bearing bone.¹³¹ The first is acidosis produced by osteoclasts, the principal bone-resorbing cells, and by lysis of tumor cells that have a lower intracellular pH than normal cells.¹³² The second is mediated by products released from cancerous tissue, like bradykinin, adenosine 5' triphosphate, and nerve growth factor, which can modulate TRPV1 function indirectly via activation of second-messenger signaling pathways.¹³⁰ Because the bone receives a rich sensory innervation by fibers that express TRPV1,¹³³ production of these proalgesic agents may also sensitize TRPV1 channels, thereby generating a state of hyperalgesia and/or allodynia. Finally, the third mechanism is mediated directly by tumor-induced injury to primary afferent neurons.¹³⁴ In a recent study, it has been shown that activation of TRPV1 was involved in bone cancer pain.¹³⁵ The investigators found increases in TRPV1 protein levels and in the number of TRPV1-positive neurons in the dorsal root ganglia from a murine model of bone cancer. In support of a role of TRPV1 in bone cancer pain, it has been demonstrated that a receptor antagonist significantly attenuates painful symptoms.¹³⁰

Itch, a principal symptom in skin diseases, is an important skin manifestation of systemic diseases, and one of the most debilitating symptoms in allergic and atopic dermatitis.¹³⁶ It can be triggered by localized, systemic, peripheral,

or central stimuli, and there are numerous pruritogenic substances, including neuropeptides, cytokines, proteases, and histamine.¹³⁷ Less is known about pathophysiological specificity among the different diseases, but cross-talk between neuron terminals and dermal mast cells is being recognized as an important mechanism involved in pathogenesis. TRPV1-expressing primary afferents generate responses to pruritogenics via multiple mechanisms, like PLC β 3 activation.¹³⁸ In addition, keratinocytes express a wide range of mediators and receptors involved in itch, and TRPV1 activation by them results in the release of pruritogenic mediators, as well as cellular proliferation, differentiation, and apoptosis.¹³⁹ Histamine, the best known pruritogenic agent, induces itch by activating PLA₂, lipoxygenase and the TRPV1 signaling pathway, as is shown by the decrease in histamine-induced scratching in TRPV1-deficient mice.¹⁴⁰

Protective role of TRPV1 against inflammation

Cumulative evidence suggests that TRPV1 may have an anti-inflammatory action in some pathological conditions. Indeed, the number of diseases in which TRPV1 plays a protective role is expanding. For instance, TRPV1 has been shown to have a protective role against inflammatory conditions in the cardiovascular system, and it has been implicated in protecting against ischemia/reperfusion-induced inflammation of the heart.¹⁴¹ A similar action has been reported for liver¹⁴² and kidney¹⁴³ pathologies, thus emphasizing a new emerging anti-inflammatory role for TRPV1.

The TRPV1 receptor also plays a critical modulatory role in contact dermatitis, a chronic allergic condition typified by skin inflammation and itching.¹⁴⁴ The genetic disruption of TRPV1 channels or blockade of the TRPV1-dependent sensory neurogenic component by resiniferatoxin increased the inflammatory response in an ear murine model of contact dermatitis. This enhancement suggests that capsaicin-sensitive neurons expressing the TRPV1 channel may act to downregulate the hypersensitivity, possibly by influencing the immune state of the skin.

Another protective function of TRPV1 against inflammatory conditions has been reported in the pathological condition of colitis,¹⁴⁵ one of the disorders under the collective heading of gastrointestinal disturbances referred to as chronic inflammatory bowel diseases. Immunoreactive TRPV1 fibers have been detected on nerve terminals within the myenteric ganglia and the interganglionic fibers throughout the gastrointestinal tract.¹⁴⁶ Using a murine model produced by the infusion of 2,4-dinitrobenzene sulfonic acid through

the rectum of mice,¹⁴⁷ it was reported that the TRPV1 null mice exhibited higher levels of inflammation than wild-type animals, indicating a protective role of TRPV1 channels in the initiation of this inflammatory condition.

Although this protective action of TRPV1 may be surprising, given the widely known proinflammatory activity of this channel, it should be considered that the main mechanisms involved in the development of chronic inflammation can be drastically different in each inflammatory disease. For instance, TRPV1 may mediate the release of both proinflammatory neuropeptides (substance P and calcitonin gene-related peptide) in some conditions, and of anti-inflammatory (somatostatin) peptides in others, depending on which subpopulation of nociceptors is more abundant in the affected tissue. Likewise, the immune cells and inflammatory mediators involved will depend on the specific inflammatory process and the affected tissue. Moreover, this balance usually changes during the development of pathology according to the time course or state of the disease. Therefore, the contribution of TRPV1 should be analyzed in detail for each inflammatory condition along with the mechanism involved in the specific inflammatory process. This evaluation will become essential because abrogation of the anti-inflammatory role of TRPV1 by potent antagonists may lead to aggravation of the disease or to the appearance of side effects.

Inflammatory process of sepsis

Sepsis is defined as the systemic inflammatory response elicited by an infection. The clinical manifestations of sepsis are abnormality in at least two of the following: body temperature (hyperthermia or hypothermia), heart rate (tachycardia), respiratory rate (tachypnea), and white blood cell count (leukocytopenia, leukocytosis or presence of immature forms greater than 10%). Increasingly grave stages of the systemic inflammatory response to an infection are severe sepsis and septic shock. Sepsis is considered when signs of organ dysfunction are present, while septic shock is defined by the presence of hypotension or hypoperfusion which finally leads to multiple organ failure.^{148,149} Despite the advances in antibiotics and critical care, severe sepsis remains the leading cause of death in intensive care units, in part because antibiotics cannot control systemic inflammation. In fact, the clinical symptoms of severe sepsis are not exclusively due to infection and can be also triggered by trauma, ischemia, severe injury, burns, or pancreatitis, which participate in the pathogenesis of this systemic inflammatory response syndrome.

The pathogenesis of sepsis is characterized by an excessive production of inflammatory mediators, mainly cytokines, chemokines, lipid mediators, and oxygen radicals. In a normal inflammatory response, these molecules are necessary to enhance leukocyte infiltration at the site of infection, to destroy the pathogen and repair tissue damage. However, in sepsis, this uncontrolled production of inflammatory mediators ends up with excessive vasodilatation, capillary leakage, hypotension, tissue injury, and finally lethal multiple organ failure.^{150–152} Clinical and experimental studies have emphasized the role of apoptosis in sepsis. Programmed cell death constitutes an active process to control cell removal, but also plays an important role in several pathological states. Activation of intracellular cascades finally leads to DNA degradation, a process regulated by a cascade of caspases, which are critical molecules in programmed cell death.^{153,154} Accelerated apoptosis of lymphocytes has been observed in animal models of sepsis and in autopsies of patients who died from sepsis.¹⁵⁵

Different studies have demonstrated that the immune system is not the only system activated in sepsis. For instance, it is well known that a complex interaction exists between inflammation and coagulation in sepsis. The inflammatory response in sepsis skews the balance to a procoagulant state, promoting thrombus and clot formation. Indeed, patients with increased coagulation factors and reduced anticoagulation factors as a result of sepsis are prone to thrombus formation, compromising tissue perfusion and driving towards organ failure.^{151,156}

In addition to activation of the coagulation cascades, extensive bidirectional communication exists between the immune and nervous systems in all inflammatory processes, which involves a huge diversity of molecular mechanisms.^{156,157} Release of inflammatory molecules can activate or influence sensory nerve function, which, in turn, can stimulate or inhibit the immune system by the release of neurotransmitters. In patients with sepsis, plasma levels of substance P and calcitonin gene-related peptide are significantly increased, providing evidence that sensory nerves are activated in this pathology.^{158–160} These bioactive neuronal agents are able to induce inflammation by directly acting on immune cells, mast cells, vascular smooth muscle, or other cell types.^{118,119} Substance P is known to increase vascular permeability,¹⁶¹ and calcitonin gene-related peptide is a potent vasodilator and hypotensive agent.¹⁶² Therefore, both neuropeptides have been mainly considered to be involved in the development of inflammation. However, it has also been shown that calcitonin gene-related peptide can mediate

anti-inflammatory and immunosuppressive activities. For instance, it modulates cell adhesion and migration, increases some anti-inflammatory mediators, such as interleukin-10 or prostaglandin I₂, and inhibits proinflammatory mediators, such as tumor necrosis factor alpha, among others.^{163–168} Consistent with these findings, administration of calcitonin gene-related peptide attenuated the development of some inflammatory and organ failure models.^{169,170} Neuropeptides, such as somatostatin, have also been recently reported to be increased in plasma from septic patients,¹⁷¹ but others, such as endothelin-1 or vasoactive intestinal peptide serum levels, seem to remain unmodified during sepsis.¹⁷² However, despite these observations, progress towards understanding the potential involvement of sensory nerves in sepsis and defining the exact role of neuropeptides in the development of this pathology is quite limited.

Is TRPV1 involved in sepsis?

Cumulative evidence associates TRPV1 channel activity with a protective effect in experimental models of sepsis. The role of the TRPV1 channel in sepsis was first evidenced by using its known agonist, capsaicin, and its antagonist, capsazepine. Injection of capsaicin was shown to diminish mortality during abdominal sepsis, suggesting an important role for nociceptive system in the host response to infection.¹⁷³ A small dose of capsaicin reduced the systemic inflammatory response in septic rats by increasing anti-inflammatory cytokines and attenuating proinflammatory cytokines,¹⁷⁴ which was consistent with previous *in vitro* results in lipopolysaccharide-activated peritoneal macrophages.¹⁷⁵ In contrast, TRPV1 blockade with capsazepine reduced channel-mediated protection against endotoxin-induced hypotension and mortality in septic rats.¹⁷⁶ Later, similar beneficial effects were also shown in a different rat model of sepsis, where capsaicin significantly attenuated systemic inflammation and multiple organ damage caused by sepsis, and protected against mortality.¹⁷⁷ Other TRPV1 agonists and antagonists have also been evaluated in different models of sepsis, all showing a consistent decrease in the development of sepsis or a reduction in some of the pathological symptoms when TRPV1 is activated.^{178–180}

Recent elegant experiments performed in TRPV1 knockout mice lend further support to the protective role of the vanilloid channel in the onset of sepsis. In these animals, there was an enhanced development of the pathological features and biomarkers of the systemic inflammatory response. Early onset, decreased body temperature, and enhanced hypotension were shown, together with an increased level of some

inflammatory mediators in peritoneal exudates.^{181,182} At the same time, protective effects were also shown in another septic model in which TRPV1 null mice showed greater infiltration, more histological lesions, bronchial hyperactivity, and increased myeloperoxidase levels in the lungs.¹⁸³

The neuropeptides involved in the protective effects of TRPV1 in sepsis remain to be exactly defined. Although it was initially suggested that TRPV1 mediated the effects of sepsis via substance P and the NK1 receptor,¹⁷⁶ the regulatory role of the channel in sepsis was shown to be independent of substance P in mice lacking TRPV1.¹⁸¹ Alternatively, because calcitonin gene-related peptide, a potent vasodilator, was shown to be elevated in endotoxin-treated rats,¹⁸⁴ it has been considered a critical factor in the development of septic shock.¹⁸⁵ Moreover, an essential role has been claimed for somatostatin, because somatostatin receptor blockade aggravates sepsis in the lungs of wild-type mice, while the process is attenuated by injection of this neuropeptide in TRPV1 knockout mice.¹⁸³

It should be noted that these results have been obtained from different models of sepsis in rats or mice, using several research and pharmacological tools which could explain the differences observed in neuropeptides participating in the effects of TRPV1. Moreover, the tissue parameters and/or biomarkers analyzed in each model are different, which could also contribute to the observed differences in the role of neuropeptides. In addition, it should not be forgotten that endotoxin-induced fever was shown to be initiated via the TRPV1 channel.^{186,187} However, an overall protective role of TRPV1 in sepsis has been proposed in most of these studies, and the increased levels of some neuropeptides in septic patients could be due to compensatory mechanisms of the organism when trying to control the systemic inflammatory process.

Although understanding of the pathogenesis of inflammation and sepsis has improved, this has not translated into clinical benefit. Therapies for severe sepsis are mainly focused on eradication of infection and on maintenance of systemic perfusion. Despite advances in adjuvant treatments, mortality remains high. In past decades, therapeutic attempts have been focused on inflammatory mediators and processes, but they have failed to translate into efficacy in clinical trials, although animal models have shown promising and successful results. The benefit of corticosteroid therapy in severe sepsis and septic shock remains controversial. Activated protein C, one of the coagulation factors, is the only treatment for sepsis approved by the Food and Drug Administration, which is projected to be useful only in a small subset of patients with

severe sepsis. The proposed protective role of TRPV1 implies that antiseptic treatments should preserve its channel activity. Thus, until the role of TRPV1 in sepsis is well understood, potent channel antagonists should be used with caution to treat the septic inflammatory process.

Conclusion

It is becoming clear that TRPV1 contributes to the pathophysiology of inflammatory processes. Intriguingly, this channel may have both a proinflammatory and anti-inflammatory action, depending on the disease. Thus, although it was widely accepted that TRPV1 blockers will become a new generation of anti-inflammatory and analgesic drugs to treat a plethora of human diseases, their clinical use must be reconsidered, because of the newly identified protective roles assigned to TRPV1. We are learning that some of the protective anti-inflammatory effects of TRPV1 were most probably ignored or misinterpreted. Therefore, the better we understand how TRPV1 works and how it contributes to human physiology and pathology, the more challenging it will be to find compounds that target pathological proinflammatory TRPV1 channels, without altering physiologically working and anti-inflammatory subpopulations of channels. Perhaps targeting inflammatory expression and/or recruitment of channels may provide a superior therapeutic paradigm to attenuate inflammation.

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Disclosure

The authors report no conflicts of interest in this work.

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