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Review

TRPV1: The key bridge in neuroimmune interactions

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ABSTRACT

The nervous and immune systems are crucial in fighting infections and inflammation and in maintaining immune homeostasis. The immune and nervous systems are independent, yet tightly integrated and coordinated organizations. Numerous molecules and receptors play key roles in enabling communication between the two systems. Transient receptor potential vanilloid subfamily member 1 (TRPV1) is a non-selective cation channel, recently shown to be widely expressed in the neuroimmune axis and implicated in neuropathic pain, autoimmune disorders, and immune cell function. TRPV1 is a key bridge in neuroimmune interactions, allowing for smooth and convenient communication between the two systems. Here, we discuss the coordinated cross-talking between the immune and nervous systems and the functional role and the functioning manner of the TRPV1 involved. We suggest that TRPV1 provides new insights into the collaborative relationship between the nervous and immune systems, highlighting exciting opportunities for advanced therapeutic approaches to treating neurogenic inflammation and immune-mediated diseases.

Introduction of Transient Receptor Potential Vanilloid Subfamily Member 1 (TRPV1)

The transient receptor potential (TRP) channel superfamily consists of over 30 subtypes that function as polymodal signal integrators, which detect diverse environmental and physiological signals in mammals.[1] TRP channels are involved in diverse physiological processes, including transducing chemoreception, injury sensing, and mediating the release of cytokines and the release of neuropeptides, all of which contribute to the maintenance of immune homeostasis.[2,3] TRPV1 was the first member of the TRP channel family to be identified, making it the most thoroughly characterized TRP channel. Additionally, the structure and functional properties of TRPV1 are well-known in the literature.

TRPV1 was originally known as a capsaicin receptor wherein it is activated by capsaicin, sodium, and calcium ions influx to depolarize nociceptive neurons, leading to the action potential firing and the sensation of pain.[4] In 1997, Michael et al.[5] first cloned TRPV1 from rat dorsal root ganglia and identified its role as a “noxious heat” sensor. Subsequently, several studies have revealed the structure and functional properties of TRPV1. The TRPV1 protein is encoded by the *TRPV1* gene located on chromosome 17p13 and has a molecular weight of 95 KD. It is a tetrameric protein consisting of four monomers, each of which consists of six transmembrane segments (S1–S6) with cytoplasmic C- and N-terminal domains and a pore region between the S5 and S6 domains.[5]

Besides being sensitive to capsaicin, as a polymodal nocisensor par excellence, TRPV1 is essential to nociception, thermosensation, and chemaesthesis. Various biotins derived from plants and animals are TRPV1 activators. DkTx, a toxin from the Earth Tiger tarantula, is an irreversible TRPV1 activator. DkTx has a bivalent nature; it traps TRPV1 in the open state by interacting with residues in the presumptive pore-forming region of the channel.[6] Resiniferatoxin (RTX), a phorbol ester isolated from the irritant lattices of the Moroccan cactus, showed exquisite sensitivity to TRPV1, which may make the channel more permeable to cations, ultimately leading to an analgesic effect through channel desensitization.[7,8] Additionally, RTX, piperine, gingerol, zingerone, camphor, eugenol, ethanol, etc., can also activate TRPV1 channels.[8] The endoge-

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nous ligands of TRPV1 are mainly lipid-derived molecules, such as N-arachidonoyl-dopamine, N-oleoyldopamine, oleoylethanolamide, 12-(S)-hydroperoxyeicosatetraenoic acid, and 15-(S)-hydroperoxyeicosatetraenoic acid.[9] Moreover, it can be activated by proalgesic pathways, such as noxious heat (>40 °C) and acidic solutions (pH <6.5)[10] and by divalent cations Mg^{2+} and Ba^{2+}.[11]

Previous studies have shown that TRPV1 is mainly distributed in sensory neurons, including dorsal root neurons, trigeminal neurons, and small- and medium-sized neurons of the vagal ganglion.[10] TRPV1 has also been found in the neurons and glial cells of the central nervous system (CNS), where it is associated with thermoception and nociception. Additionally, TRPV1 expression has been detected in non-neuronal tissues such as heart, liver, lung, kidney, adipose tissue, skeletal muscle, and intestine.[12-14] Thus, it has been associated with many disease processes, such as neuroinflammatory diseases, autoimmune diseases, and hypersensitivity reactions. The function of TRPV1 has also been studied in various physiological and pathological processes, including vascular activation, inflammatory response, anxiety and depression, cell proliferation, and apoptosis.

An Introduction to Neuroimmunity

Neuroimmune cross-talking is an emerging hotspot for medical and life science research. The two systems involved—the nervous and immune systems—are highly complex and integrated and can receive and process signals from all types of physical and chemical stimuli in the environment. With human evolution, neuroimmune cross-talking is becoming increasingly complex and advanced in response to environmental harms to protect tissues from damage.

The immune system consists of innate and adaptive immunity. When the innate immune system detects an invading pathogen or tissue damage, it sends signals to the adaptive immune system. The latter immediately exerts cellular and humoral immunity by mobilizing various immune cells and cytokines in the anti-inflammatory immune process.[15] Contrary to the immune system with mobile and dispersed cells, the organization of the nervous system is fixed and is divided into the CNS and the peripheral nervous system (PNS). Typically, sensory neurons are responsible for the translation of physical stimuli translation; stimuli such as touch, temperature, and exogenous or endogenous chemicals can be translated into electrical signals and then sent to the CNS.[16] The CNS rapidly integrates and processes the signals and directly activates muscle contraction and glandular secretion.[16] The nervous and immune systems are autonomous entities with unique characteristics, but they often work together, acting in an integrated and coordinated manner in host defense and, therefore, provide a more effective defense than when acting in isolation.[17] Specific spatial connections between neurons, nerve cells, and immune cells allow for easier and convenient communication between the two systems, especially in the skin and mucous membranes, which are rich in sensory neurons. In the mucosa of mice with allergic airway inflammation, dendritic cells (DCs) and T cells were either directly contacted by nerves or located near the nerve fibers, which greatly enhanced the efficiency and speed of signaling.[18] In the skin of psoriasis mice, most DCs are in close contact with nociceptive sensory neurons.[19] This close communication induces the secretion of more proinflammatory factors and the aggregation of various immune cells, which promotes local and systemic feedback activity, greatly increasing the body's efficiency and combativeness against inflammation and pathogens.

The synergistic effects with high efficiency and existing between the nervous and immune systems have been attributed to several factors. First, the two systems share "communication language," including cytokines, growth factors, and neuropeptides. Second, they share a variety of the same signaling receptor. Both systems share many recognition receptors for various pathogens, metabolites, and products of an inflammatory response, enabling timely reception and feedback of abnormal signals from the environment.[17,20–22] Third, they have their specialized roles. For instance, the nervous system responds more quickly to physical stimuli, while the immune system is more sensitive to chemical signals. The role of neuroimmunity in diverse disease contexts and the mechanisms involved are receiving increasing attention and focus, and the interaction involved in neuroimmunity is increasingly being implicated in the pathophysiology and pathological processes of tumors, neurological disorders, infectious diseases, metabolic diseases, etc. However, due to the different microenvironments, the functional role of the neuroimmunity interaction is also diverse. Thus, the mechanisms involved are complex and varied, and the results from animal and *in vivo* studies still require further clinical validation. Nevertheless, it is evident that an in-depth study of the cellular and molecular mechanisms involved in neuroimmune interactions may help discover novel therapeutic targets for diseases.[23]

TRPV1 and the Immune System

TRPV1 was originally thought to be exclusively neuronal, but now it appears indispensable for the immune system. As a key communication mediator between the nervous and immune systems, it is widely expressed in immune cells and regulates immune cell activity and immune molecule secretion in various ways. Hence, TRPV1 plays a wide range of regulatory roles in inflammatory responses and immune-related diseases (Figure 1). However, data about its exact role in the immune system are limited.

TRPV1 regulates the immune system through various mechanisms

Expression of TRPV1 in the immune system

TRPV1 expression is widely distributed in the nervous system, being found in astrocytes, microglia, and neurons. Recent studies have detected TRPV1 in the hippocampus, cortex, cerebellum, olfactory bulb, mesencephalon, hindbrain, and other sites of the mouse, rat, and human brain.[24,25] Furthermore, studies have found TRPV1 in intracellular organelles of astrocytes and microglia.[13,26] Additionally, using immunocytochemistry at the ultrastructural level, TRPV1 expression was also detected in astrocytes in the spinal cord.[26,27] The function of glial cells in the nervous system is similar to that of macrophages in the immune system. TRPV1 actively engages in proliferation, apoptosis, phagocytosis, and inflammatory fac-

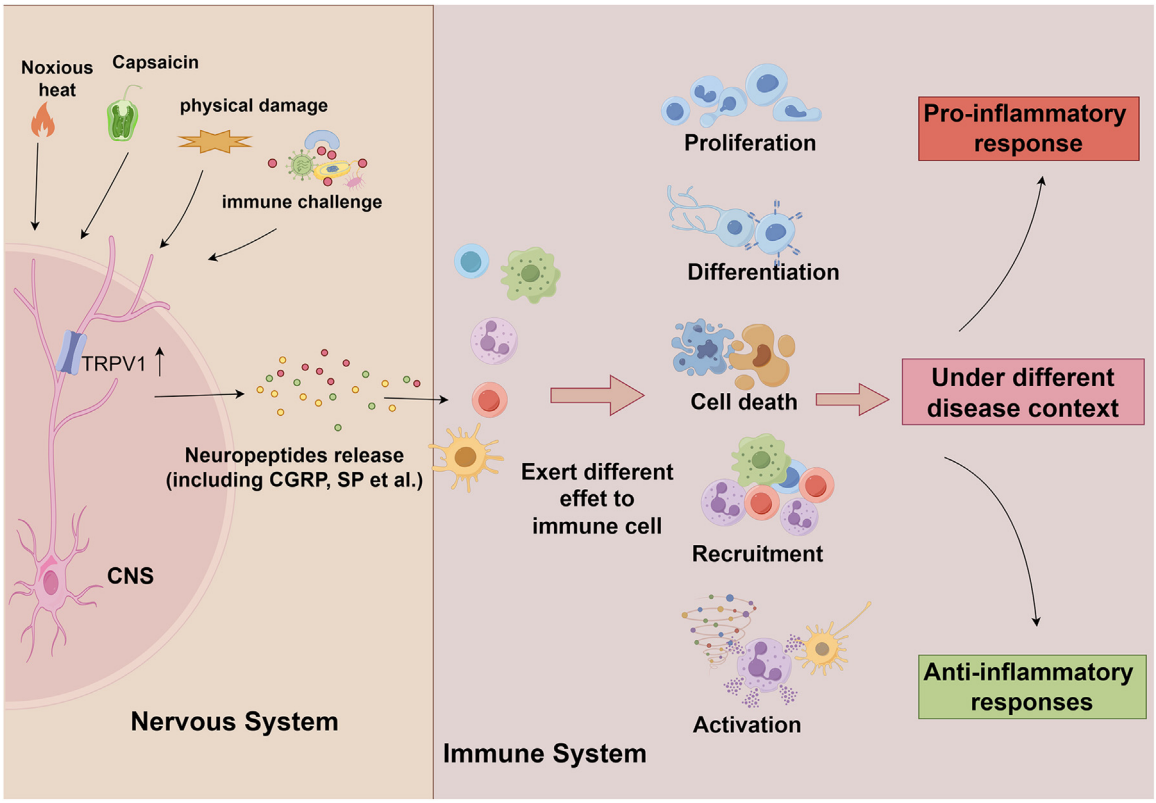

Figure 1. The effect of TRPV1 on the immune system. Many external factors, such as capsaicin, noxious heat, acidic solutions, and physical damage, as well as immune challenges, rapidly activate TRPV1, resulting in the release of neuropeptides such as CGRP and SP. These neuropeptides activate immune cells, including macrophages, T cells, and neutrophils, and exert various effects that influence immune cell proliferation, differentiation, death, recruitment, and activation. These changes in cell activity may lead to proinflammatory or anti-inflammatory effects under different disease contexts (The picture was made using Figdraw).
CGRP: Calcitonin gene-related peptide; CNS: Central nervous system; SP: Substance P; TRPV1: Transient receptor potential vanilloid subfamily member 1.

tor secretion in microglia and astrocytes.[28] For instance, Hassan et al.[29] found that cannabidiol enhances microglial phagocytosis via TRPV1 channel activation, while inhibition of microglia TRPV1 promotes interleukin (IL)−6 release and nuclear factor-kappa B (NF-κB) activation.[30] Similarly, in the peripheral immune system, since the first detection of TRPV1 in human peripheral blood mononuclear cells,[31] many studies have revealed the expression and role of TRPV1 on various immune cells. TRPV1 expression has been detected in T lymphocytes, macrophages, DCs, natural killer (NK) cells, neutrophils, and other immune cells in human and mouse immune organs and blood.[32–34]

TRPV1 promotes the secretion of neuropeptides to regulate the immune system

TRPV1-expressing sensory neurons mediate the neuroimmune cross-talking by releasing neuropeptides to innervated tissues and immune cells. TRPV1 activation can lead to the release of calcitonin gene-related peptide (CGRP), substance P (SP), somatostatin, and other neurotransmitters, and these neuropeptides can mediate a range of immunological responses. CGRP is a critical and highly expressed sensory signal, making it important in neuroimmune communication pathways. One of the primary outcomes of TRPV1 activation is the release of CGRP.[35] Similar to TRPV1, CGRP is expressed in sensory neurons and $CGRP^+$ neurons have also been detected in many immune organs and immune cells.[36,37] TRPV1 agonists (rutaecarpine, capsaicin and its derivatives, etc.) stimulate the secretion of CGRP and the antagonists inhibit the release of CGRP.[33,38,39] Activation of TRPV1 by protons leads to the upregulation of CGRP via calcium/calmodulin-dependent protein kinase II (CaMKII) and CREB in dorsal root ganglion (DRG), while CGRP expression is reduced in TRPV1-deficient mice.[40] CGRP modulates the systemic immune response through various mechanisms. For instance, CGRP promotes DC motility, reduces phagocytic capacity,[41] and affects antigen-delivery function.[42] It also regulates lymphocyte differentiation and cytokine production [43] and affects the migration and adhesion of T cells and monocytes.[44] Jonathan et al.[45] fully illustrated the role of CGRP in the inflammatory response under TRPV1 induction. TRPV1 neuron activation elicited the type 17 immune response and increased secretion of CGRP—which is accompanied by the increased secretion of type 17-related inflammatory factors IL17A and IL22—while CGRP antagonism decreased the secretion of these inflammatory factors, suggesting that TRPV1-induced CGRP release is required for the induction of type 17 inflammation.[45]

SP is a neuropeptide with immunomodulatory effects, which is stored in peripheral sensory neurons and mainly released after pain stimuli.[46] SP is mainly expressed in neurons, glial cells, and non-neurological sites, including some immune cells, such as T cells, DCs, and macrophages. The widespread expression of SP in diverse cell types suggests that it plays key roles in many physiological and pathological processes by activating several signaling pathways.[47,48] In allergic diseases, allergens

directly activate TRPV1$^+$ neurons, inducing SP release and the DC migration to lymph nodes.[48] Allergens also activate Mas-related G protein-coupled receptor B2 in skin mast cells to initiate anaphylactic responses [49] and promote leukocyte adhesion.[46] The above-mentioned data indicate that SP has proinflammatory functions, although some studies have reported contrasting findings. Giovanna et al.[50] found that SP significantly reduces the production of proinflammatory cytokines and enzymes, such as tumor necrosis factor (TNF)-α, IL-6, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2, and facilitates migration of and phagocytic properties in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. Also, SP stimulates the anti-inflammatory effects of macrophages by suppressing NF-κB activation and inducing hemeoxygenase-1 expression. These findings suggest a diverse role for SP in immune response.

In addition to the release of neuropeptides, TRPV1 promotes the release of other immunomodulatory factors to modulate the immune response. For instance, Raffaele et al.[51] found that TRPV1 activation leads to the release of miR-21–5p in the exosomal fraction by DRG neurons; miR-21–5p is readily phagocytosed by macrophages in which increased miR-21–5p expression promotes a proinflammatory phenotype.

TRPV1 activates Ca^{2+} channels to modulate the immune system

Calcium acts as a second messenger in most immune cells, and resting cells maintain a low concentration of Ca^{2+}. However, the engagement of antigen receptors, such as the T-cell receptor, B-cell receptor, chemokine, and co-stimulatory receptors, induces calcium influx from the extracellular space.[52,53] TRPV1 promotes Ca^{2+} influx into immune cells, such as DCs and T cells,[33,54] while TRPV1 deficiency results in reduced Ca^{2+} influx.[34,55] Calcium signaling is key to many cell functions, including apoptosis, mobility, and immune responses. Thus, TRPV1 may regulate immune cell activity by modulating Ca^{2+} signaling. TRPV1-induced Ca^{2+} influx attenuated M1 macrophage polarization, as TRPV1 promoted the phosphorylation of CaMKII and facilitated the nuclear localization of nuclear factor-erythroid 2-related factor 2 (Nrf2), ultimately inhibiting M1 macrophage polarization.[56] Ca^{2+} is also thought to regulate autophagy. TRPV1 activation causes Ca^{2+} influx into the microglia, activating ATG5 and Ca^{2+}/CaMKK2/AMPK/mTOR signaling pathways and promoting microglia phagocytosis.[57] TRPV1 blockade results in sustained perturbation in intracellular calcium, which induces a rapid increase in mitochondrial reactive oxygen species production and mitophagy and mitochondrial damage.[58] Although TRPV1 regulates immune responses through Ca^{2+} signaling, it cannot fully control the function of Ca^{2+} signaling. Rebecca et al.[59] showed that elevated hydrostatic pressure induced a significant increase in microglial intracellular Ca^{2+}, which in turn induced increased microglial IL-6 and cytosolic NF-κB; however, TRPV1 activation by capsaicin alone was not sufficient to increase IL-6 levels. This indicates that TRPV1 and Ca^{2+} can functionally compensate for each other, but their roles differ.

In summary, TRPV1 expression can be detected in immune cells. TRPV1 can regulate the function of immune cells through the release of neuropeptides or calcium signals because immune cells respond to TRPV1 agonists by promoting Ca^{2+} influx and neuropeptides such as CGRP and SP release. Additionally, TRPV1 antagonists or TRPV1 knockdown significantly inhibits Ca^{2+} influx and neuropeptide release. Finally, Ca^{2+} or neuropeptides upregulated by TRPV1 induce subsequent marker activation and cytokine release to participate in immune regulation and homeostasis. However, uncertainties persist about whether Ca^{2+} and neuropeptides such as CGRP act alone or in synergy with each other. Nonetheless, it is becoming clear that TRPV1 can accelerate nerve/immune cell cross-talking through a range of pathways.

Effect of TRPV1 on immune cells

TRPV1 has been shown to affect various aspects of immune cells, such as proliferation, differentiation, and signal transmission. It exerts direct and rapid regulation of immune processes and inflammatory signaling pathways and exerts diverse effects under different disease backgrounds, demonstrating the substantial functional diversity of the TRPV1 channel.

TRPV1 and proliferation and differentiation of immune cells

The effect of TRPV1 on proliferation varies according to the immune cells. Capsaicin, the ligand of TRPV1, regulates the proliferation of immune cells. Oral administration of capsaicin to mice promotes the proliferation of macrophages and results in an altered macrophage activation state.[60] In contrast, Feng et al.[61] found that TRPV1 knockdown significantly increased the number of macrophages, suggesting that the effect of TRPV1 on macrophage proliferation varies by disease type. TRPV1 also regulates the number and activation state of NK cells. In malaria-infected mice, capsazepine treatment increased the circulating NK population without interfering with natural killer T (NKT) cell numbers and blood NK and NKT activation.[62] However, capsazepine reduced CD69 expression in spleen NKT but not NK cells,[62] suggesting the effect of TRPV1 on DC proliferation in different organs is diverse. A study investigating the effect of TRPV1 on lymphocyte proliferation showed that capsaicin can inhibit the proliferation of T cells in pancreatic lymph nodes.[60] Another ligand of TRPV1, piperine, inhibited B-cell proliferation and activation. However, the inhibitory effect of piperine on B-cell proliferation was not mediated through TRPV1, as piperine also inhibited the proliferation of B cells in TRPV1 knock-out (KO) mice.[63]

TRPV1 and immune cell death

TRPV1 affects the cell death modality. TRPV1 KO mice displayed autophagy dysfunctions, as TRPV1 induces autophagy through the Atg6/Beclin-1 pathway.[64,65] Treatment with the autophagy inducer rapamycin failed to reverse autophagy, indicating that TRPV1 knockdown significantly inhibited autophagy. Additionally, there is an interplay between autophagic survival and apoptotic cell death under the influence of TRPV1, as the level of apoptosis significantly increased after autophagy inhibition and the apoptotic regulator Atf4 transcription factor and ERp57 protein levels were upregulated.[66] Further studies found that capsaicin affected thymocyte death in a dose-dependent manner: low concentrations (5 μmol/L) of CPS induced apoptosis, whereas high concentrations (25 μmol/L) induced necrosis. The mechanism involved is related to TRPV1-induced Ca^{2+} influx, phosphatidylserine exposure, and mitochondrial permeability transmembrane pore opening.[67] TRPV1 also regulates macrophage apoptosis. In peritoneal macrophages

from TRPV1 KO mice, the expression of the apoptosis-associated molecule FAS, as well as the apoptosis effectors p53 and caspase-3, were significantly upregulated, suggesting that reduced TRPV1 expression significantly promotes macrophage apoptosis.[68]

TRPV1 and immune cell recruitment

TRPV1 neurons affect the recruitment of immune cells. TRPV1 inhibited the recruitment of neutrophils. After using RTX to chemically denervate and ablate TRPV1$^+$ neurons, RTX-treated mice displayed greater lung neutrophil recruitment and higher CD4 T cells number.[69] Similarly, TRPV1 KO mice showed increased neutrophil numbers, as well as increased expression of chemokines for neutrophil recruitment (KC and macrophage inflammatory protein 2) and key adhesion molecules ICAM-1.[70] Different TRPV1 ligands may regulate the effect of TRPV1 on neutrophil aggregation. Some of the constituents in essential oils from *Ferula akitschkensis* are agonists, and some are antagonists for neutrophil aggregation; hence they exert different effects on neutrophil migration and cell viability.[71] TRPV1 also regulates the aggregation of macrophages and T cells. Capsaicin reduced the macrophage and T-cell infiltration in the rat sciatic nerve, thereby exerting an anti-inflammatory effect.[72] In contrast, capsaicin treatment resulted in a dose-dependent inhibition of T-cell proliferation in the colon of mice. More unexpectedly, the TRPV1 antagonist BCTC also showed a dose-dependent inhibition of T-cell proliferation.[73] We, therefore, conclude that capsaicin regulates T-cell proliferation by a TRPV1 receptor-independent way. However, this has not been fully confirmed, and the role and mechanism of TRPV1 on T-cell proliferation still deserve to be further explored.

TRPV1 and immune cell activation

TRPV1 is involved in regulating immune cell activation. TRPV1 is expressed in primary human T cells and primary murine splenic T cells, and its expression increases during T-cell activation. In contrast, knockdown or inhibition of TRPV1 activity results in reduced secretion of cytokines (including TNF, IL-2, IL-6, and IL-17) and the downregulation of the phosphorylation of T-cell antigen receptor activates related molecules,[54,74] suggesting that inhibition of TRPV1 activity attenuates T-cell activation. Consistently, TRPV1 knockdown decreases the expression of CD4$^+$ T-cell surface activity markers (CD25 and human leukocyte antigen-DR) in mice.[75] Collectively, these data indicate that the TRPV1 channel plays an essential role in the activation and the acquisition of inflammatory properties by T cells. T-cell activation by TRPV1 was associated with Ca^{2+} signaling, as inhibition of TRPV1 channels reduced Ca^{2+} influx and T-cell activation.[54] TRPV1 also regulates macrophage activation. Some TRPV1 antagonists such as AMG9810 and CPZ significantly inhibited macrophage activation and macrophage secretion of inflammatory factors such as IL-6, IL-1β, and IL-18, whereas some antagonists such as SB366791 and BCTC had no significant effect on macrophage activity.[76]

TRPV1 regulates inflammatory response

TRPV1 plays a role in different inflammatory diseases by exerting proinflammatory or anti-inflammatory responses depending on the disease context. This section briefly discusses the clinical implications of TRPV1 immunobiology for allergic diseases and sepsis, where there is growing research interest in neuropeptides.

TRPV1 is expressed in a large subset of sensory nerves, especially in the skin and airway,[19] where they integrate numerous noxious stimuli.[77] Allergens like endogenous mediators (eicosanoids, cytokines, and histamines) and exogenous substances (injurious heat or cold, ultraviolet [physical factors], and chemical irritants or allergens) can further activate or sensitize TRPV1,[78] resulting in the rapid release of neurotransmitters.[79] The released neuropeptides act on skin and airway cells, leading to degranulation, vasodilation, and extravasation of plasma proteins and leukocytes, which enhance allergic reactions. Many studies have shown that TRPV1 has a proinflammatory effect in allergic inflammation. In atopic dermatitis, IL-31 induces itch by directly activating TRPV1$^+$ neurons in the skin; TRPV1 facilitates the transmission of itch sensations [80] and regulates the inflammatory response.[80,81] In psoriasiform skin inflammation, TRPV1 promotes IL-23 secretion by dermal DCs, thereby promoting the recruitment of circulating neutrophils and monocytes to provoke psoriasis-like inflammation.[19] The effect of TRPV1 on allergic reactions was further confirmed by TRPV1 antagonists. The TRPV1 antagonist PAC-14,028 cream (Asivatrep: C21H22F5N3O3S) significantly inhibited cutaneous inflammation and scratching behavior by decreasing the expression of inflammation factors.[82] Similarly, TRPV1 deficiency reduced the levels of inflammatory factors, decreased eosinophil numbers, and attenuated allergic responses in allergic rhinitis mice [74]; it also alleviated airway hyperresponsiveness and inflammation in asthma murine.[83] In summary, these results indicate that the TRPV1 antagonist acts as an anti-inflammatory factor in allergic reactions like allergic dermatitis, rhinitis, and asthma. The TRPV1 receptor may be a potential drug target for chronic inflammation.

TRPV1 plays a protective role in sepsis, as TRPV1 deficiency disrupts immune homeostasis in septic mice. TRPV1 KO mice displayed increased neutrophil recruitment, increased serum cytokines (such as TNF-α, IL-1β, and IL-6), and elevated serum levels of creatinine and alanine aminotransferase, indicating liver and kidney organ dysfunction. Additionally, enhanced hypotension, decreased core temperature, and edema suggest worse circulatory failure systemic control.[84] A further study showed that the mortality of TRPV1-deficient septic mice exceeded that of wild-type mice, suggesting that TRPV1 KO may lead to a fatal outcome in septic mice.[85] The inhibitory effect of TRPV1 on inflammation is related to the Ca^{2+}/phosphatidylinositol 3-kinase (PI3K)/threonine protein kinase B (PKB; also known as AKT)/endothelial nitric oxide synthase (eNOS)/nitric oxide (NO) pathway.[86] Additionally, TRPV1 agonists are protective in sepsis. In contrast, antagonists promote septic inflammation. 20-Hydroxyeicosateraenoic acid, a TRPV1 activator, reduces heart damage caused by sepsis in mice,[87] whereas prolonged treatment with capsazepine or the selective TRPV1 antagonist SB366791 increased mortality in septic wild-type mice.[88]

TRPV1 and the Nervous System

TRPV1 is widely distributed in the nervous system, including the PNS and CNS. As a multimodal receptor, it can be activated

by physical and thermal stimuli and chemokines.[45] TRPV1 is like a functional switch. Activation of TRPV1$^+$ sensory neurons triggers the action potential and subsequent neurogenic responses. TRPV1$^+$ neurons at different locations play different roles in organ function, with the most recognized function being the "polymodal nociceptor" in the PNS. As research progressed, TRPV1$^+$ neurons were found to mediate several important functions in the CNS and in different peripheral and visceral tissues.

The function of TRPV1 flows in the nervous system

Since the TRPV1 channel is widely expressed in neurons and nerve cells of the central and PNS, it has diverse functional roles, acting as "polymodal nociceptor" in the PNS and "emotional lane" and "learning flow" in the CNS.

The role of TRPV1 in PNS functions

In the PNS, TRPV1 is highly expressed in a subset of primary sensory neurons of the trigeminal, vagal, and DRG with C- and A-δ fibers, which is found in various sensory fibers in the skin, airway,[89] bone,[90] viscera, etc. TRPV1 is best known for its role in nociceptive sensory transmission, as it can be rapidly activated by noxious stimuli.[5] Their activation excites the terminals of primary sensory neurons, resulting in their depolarization and the initiation of action potentials, ultimately contributing to pain- and itch-associated responses. The role of TRPV1 in pain control has been most studied. TRPV1-expressing neurons related to pain in diverse sites (skin, visceral, limb, etc.) and different types (inflammatory pain, neuropathic pain, and visceral pain) have been proposed in several diseases. The results demonstrated that TRPV1 collectively plays a critical facilitating role.[91] A recent study reported that two individuals with TRPV1 functional loss showed impaired heat pain- and cold pain-detection thresholds and absent capsaicin-induced neurogenic inflammation,[92] providing strong evidence for the involvement of TRPV1 in pain processing. TRPV1-targeted drugs are, therefore, widely used as clinical routine analgesic medication.[93] TRPV1 also serve as a promoter in itchy sensation transmission. It is involved in acute and chronic itch and in histaminergic and non-histaminergic itch.[94] Additionally, it has been implicated in several itch-related diseases, including neuropathic itch,[95] atopic dermatitis, allergic contact dermatitis, and psoriasis.[96] TRPV1 expression positively correlates with itch intensity,[97] while TRPV1 KO mice showed impaired itch and pain sensation.[98] However, in humans, TRPV1 inhibitors cannot improve chronic itch in patients.[99]

Apart from pain and itch, TRPV1$^+$ axons are also involved in diverse other stimuli in various organs and tissues. In the respiratory system, TRPV1 is expressed in the sensory nerves of the airway wall and has been implicated in the airway smooth muscle constriction,[100] airway hyperresponsiveness,[101] and mucus secretion.[102] Hence, it enhances the cough reflex in chronic persistent cough of diverse causes [103] and worsens asthma.[104] In the circulatory system, TRPV1 is involved in the modulation of thermoregulation and vasodilation; vasodilators like anandamide exert their effects by activating TRPV1 on perivascular sensory nerves.[105] Eliminating TRPV1 expression in sensory neurons abrogates capsaicin-induced body temperature perturbations and hyperthermia in mice.[106] In the urinary tract, TRPV1$^+$ neurons mediate the mechanosensation of the bladder during its filling.[107] The gastrointestinal system is known to be rich in capsaicin-sensitive sensory nerves. As a capsaicin receptor, TRPV1 has been extensively studied for the visceral sensations (urge to pain, defecate, burning, and warmth sensation) mediated by ingested capsaicin.[108] On this basis, studies related to TRPV1 expression levels, axonal distribution density, and pain severity at different sites and in different models of the digestive system have shown that TRPV1 plays a crucial facilitating role in pain induced by mechanical and chemical proalgesic factors. Additionally, TRPV1$^+$ sensory nerves have been implicated in gastrointestinal motor activity, abdominal thermoregulation, nausea, and vomiting caused by toxic ingested food or drugs.[109,110] Furthermore, the activation of TRPV1$^+$ axons induced the release of CGRP and SP substances, thereby promoting vasodilatory mucus secretion by the gut and achieving the purpose of protecting the gastrointestinal mucosa. It is, therefore, a potential target for drug action in digestive diseases.[111]

Many potential TRPV1 interaction partners, also known as "TRPV1 chaperones," influence the expression, sensitivity, and activation of TPRV1. These molecules are mostly structurally co-expressed/co-distributed/co-localized with TRPV1 in neurons, for example, the scaffolding protein AKAP79/150,[112] GABAA receptor associated protein,[113] anoctamin 1,[114] voltage-gated K channel accessory subunit beta 2,[115] Ankyrin-rich membrane-spanning protein,[116] Whirlin,[117] inducible kinin B1 receptor,[118] N-methyl-D-aspartate receptors,[119] and Toll-like receptor 4.[120] Some of these molecules are distributed in sensory fibers, DRG, or the spinal cord. The interaction of TRPV1 and these chaperones may modulate aspects of TRPV1 function, enhancing TRPV1 sensitivity to capsaicin, thermal hyperalgesia, inflammatory or neuropathic pain transmission, and histamine-induced itch. Other members of the TRP family also interact with TRPV1 in some aspects to augment TRPV1 activity. The most prominent is transient receptor potential ankyrin 1 (TRPA1),[94] which can be activated simultaneously by many nociceptive stimuli,[121,122] *in vitro* mediators,[123,124] and *in vivo* inflammatory factors.[55]

The role of TRPV1 in peripheral central system functions

The putative role of TRPV1 as a nociceptor in the PNS is well established, but its role in the CNS is less clear. TRPV1 is present in several brain areas, mainly in a contiguous band of cells within and adjacent to the caudal hypothalamus in extremely low levels,[125,126] where it modulates the synaptic transmission of nociceptive signals from the periphery. Besides the brain, TRPV1 was also found in the spinal cord and trigeminal ganglia.[127] Capsaicin-sensitive sensory neurons transmit nociceptive information from the periphery into the CNS, implicating TRPV1 in the CNS in pain processing, rendering this channel a potential target of brain-acting drugs for pain relief.

Later studies showed that TRPV1 in CNS has some exciting possibilities, as it may be involved in the control of emotions, learning, and satiety. TRPV1 phosphorylation induced control conditioned place aversion in mice,[128] while TRPV1 KO mice showed reduced anxiety, conditioned fear,[129] antidepressant-like, anxiolytic, abnormal social, and reduced memorial behaviors.[130] These findings highlight the role of TRPV1 as an "emotional lane," exaggerating depressed emotions or feelings.[131] Besides, TRPV1 was shown to induce "learning flow," protecting

learning and memory.[132] Downregulated TRPV1 expression is correlated with learning and memory impairments following biliary cirrhosis,[133] while capsaicin or TRPV1 upregulation reversed memory deficits and ameliorated cognitive by regulating microglia functions in mice with Alzheimer's disease.[134,135] Additionally, TRPV1 plays a role in modulating synaptic plasticity and ameliorating synaptic functions [136]; TRPV1 activation channels enhanced excitability, while TRPV1 inhibition suppressed ongoing electrographic seizures.[137,138] In summary, TRPV1 is involved in numerous critical neuropathic responses, but the mechanisms involved are still unclear. However, previous studies suggest that the functional role of TRPV1 is closely linked with the region of the CNS in which it is expressed. It is, therefore, involved in the regulation of many nervous system functions, as it is ubiquitously expressed in the CNS.

Implications of the immune system (inflammatory mediators) in TRPV1 and neurological disease

TRPV1 promotes the secretion of inflammatory factors but can also be sensitized by many inflammatory mediators, including cytokines, chemokines, and neurotransmitters. Most inflammatory mediators enhance TRPV1 activity, while sustaining inflammation might mediate a positive feedback loop of neuroinflammation and exacerbate neurological disorders (Figure 2).

Itch typically includes degrees of burning, prickling, and stinging. As one of the prime noxious heat sensors, TRPV1 is responsible for itch-sensing. Some immune mediators are known to activate TRPV1 and cause pruritus. Histamine is the main cause of itching in patients with dermatitis. Won-Sik Shim et al.[139] showed histamine excites sensory neurons by activating TRPV1, while scratching behavior was markedly less frequent in TRPV1-deficient mice. Similarly, leukotriene B4 is abundantly expressed in patients with atopic dermatitis.[140,144] Leukotriene B4 can activate TRPV1 and induce itch-associated responses; hence, it is presumed that the itching it causes may be associated with TRPV1.[145] Insulin-like growth factor-1 (IGF-1) is a cytokine secreted by T cells. Cutaneous and intrathecal injections of IL-31 evoked intense itch, while mice lacking TRPV1 showed markedly reduced IL-31-induced scratching compared with wild type.[81] These results indicate that TRPV1 plays a key role in mediating the pruritogenic action.

Some substances enhance the activity of TRPV1 and consequently facilitate pain. TRPV1 plays a role in inflammation, cancer, and neuropathic pain. In the rat model of arthritis, TNF-α increased the proportion of neurons that express TRPV1 and thus contributed to the generation and maintenance of inflammatory pain.[141] IGF-1 is also a hepatokine. In a rat model of bone cancer pain, IGF-1 induced the upregulation of TRPV1 expression and enhanced cancer-related pain.[142] In addition to mediating pain and the itchy sensation, TRPV1 potentiates epileptogenesis. Huang et al.[143] reported that increased levels of proinflammatory factors, including IL-1β, IL-6, TNF-α, and high mobility group box-1 protein (HMGB1), resulted in TRPV1 activation and frequently repetitive febrile seizures. TRPV1 is believed to act as a polymodal nociceptor. Inflammatory mediators cause sensitization of nociceptors, which interact with the CNS to amplify the perception of heat, pain, etc. Additionally, TRPV1 promotes the secretion of neuropeptides that modulate the inflammatory response.

Indeed, TRPV1 play a key "switch" role in neuroimmune interactions. Its effect generally contributes to the amplification of

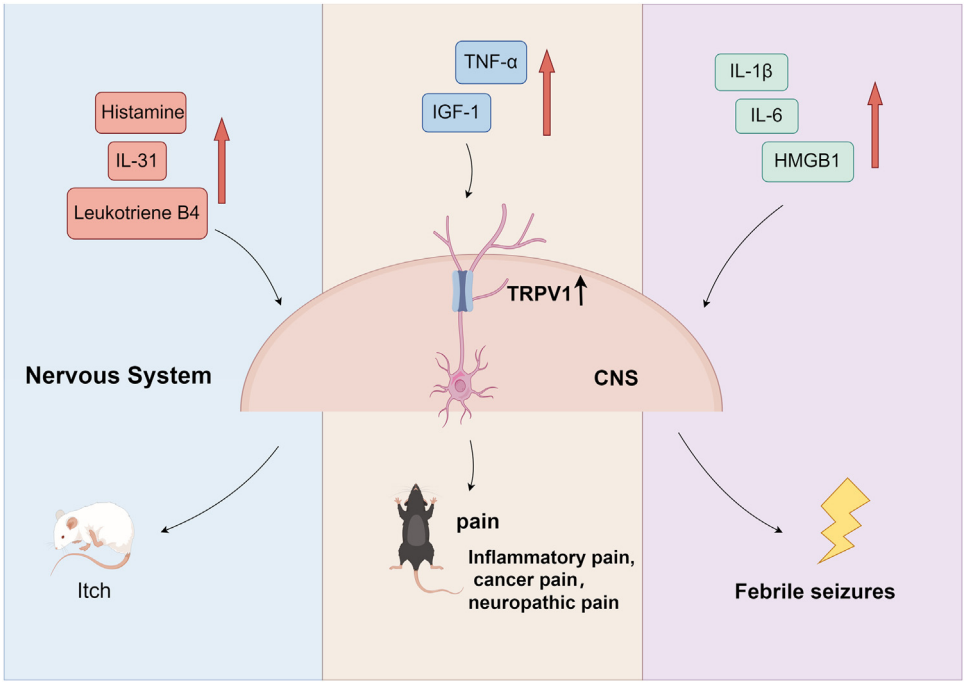

Figure 2. The effect of inflammatory mediators on TRPV1 and neurological disease. TRPV1 can be sensitized by many inflammatory mediators and exacerbate neurological disorders. For example, elevated levels of histamine, Leukotriene B4, and IL-31 lead to TRPV1 activation and induce itch.[81,139,140] Increased TNF-α and IGF-1 induced the upregulation of TRPV1 expression and enhancement of pain.[141,142] Increased levels of proinflammatory factors, including IL-1β, IL-6, TNF-α, and HMGB1, resulted in TRPV1 activation and frequently repetitive febrile seizures.[143] (The picture was made using Figdraw).
CNS: Central nervous system; HMGB1: High mobility group box-1 protein; IGF-1: Insulin-like growth factor-1; IL: Interleukin; TNF-α: Tumor necrosis factor-α; TRPV1: Transient receptor potential vanilloid subfamily member 1.

maladaptive feedforward inflammatory loops, enabling the development of allergy, autoimmunity, itch, and pain. During bacterial infection, the pore-forming toxin Streptolysin S secreted by *Streptococcus pyogenes* directly activates TRPV1 neurons to induce pain, while increasing the release of CGRP from TRPV1$^+$ neurons and impairing neutrophil recruitment and bactericidal activity.[146] Thus, during the body's defense against *S. pyogenes*, TRPV1 acts as a transmitter between the nervous and immune systems, accelerating the immune response. Similarly, formylated peptides and alpha-hemolysin (Hla) secreted by *Staphylococcus aureus* directly activated TRPV1 neurons and promoted the release of CGRP from TRPV1$^+$ neurons, thereby modulating pain and immune response, while TRPV1 antagonists reduced pain and inflammatory responses such as leukocyte infiltration and inflammatory factor secretion,[147] demonstrating the bidirectional regulatory role of TRPV1 on the nervous and immune systems.

Summary and Conclusions

The nervous and immune systems are close in spatial location. They are functionally interconnected, intimately communicating with each other, and bidirectionally regulated. The two systems communicate through common neuropeptides and use unique sensing mechanisms to detect environmental danger signals to terminate damage and restore organismal homeostasis, which is fundamental for the organism to defend against pathogens and maintain homeostasis. TRPV1 is a key bridge in neuroimmune interactions, expressed in neuroimmune axes and directly regulates immune cell function. Besides, it promotes the secretion of CGRP, SP, and other neuropeptides and immunomodulatory factors. Hence, it plays a critical role in the regulation of immune diseases and neurological-related disorders such as pain and itching. The role of TRPV1 in strengthening the interaction between the two systems provides insights into our understanding of neuroimmune interactions. Many unknowns remain regarding neuroimmune interactions, and the related mechanism of TRPV1 involvement has not been completely understood. Additionally, the clinical translation of TRPV1 into practical applications still needs further exploration. In summary, TRPV1 in neuroimmune interactions offers a deeper understanding of organismic immunity and opens new directions and opportunities for diagnosis and treatment.

Author Contributions

Jianwei Chen: Writing – review & editing. **Wenqian Sun:** Writing – original draft. **Youjia Zhu:** Writing – original draft. **Feng Zhao:** Writing – original draft. **Shuixiang Deng:** Writing – original draft. **Mi Tian:** Writing – review & editing. **Yao Wang:** Writing – review & editing. **Ye Gong:** Writing – review & editing.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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