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Review Article

Transient Receptor Potential Vanilloid 1 and Transient Receptor Potential Vanilloid 2 in the Spotlight: Understanding their Significance in Disease Mechanisms

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Received: August 04, 2023; **Published:** September 01, 2023

Abstract

Transient receptor potential vanilloid 1 (TRPV1) and TRPV2 are prominent members of TRPV group of transient receptor potential family of ion channels. These channels play crucial roles in various physiological processes and are implicated in several illnesses. TRPV1 primarily contributes to itch, inflammation, pain perception, respiratory disorders, eliciting itching sensations, promoting inflammation, and transmitting pain signals. In contrast, TRPV2 is associated with pain, cancer, and neurodegenerative diseases, exhibiting heightened pain sensitivity and sensitization following nerve injury, though its exact role in pain remains incompletely understood. This in-depth review explores the functions of TRPV1 and TRPV2 in diverse array of diseases, such as cancer, neurodegenerative diseases, and respiratory conditions. The review provides insights into their mechanisms of action and the impact of different stimuli on their activation. Furthermore, it explores the potential therapeutic applications of targeting TRPV1 and TRPV2, offering prospects for their utilization in the treatment of pain and related conditions. Insights into ongoing clinical studies investigating TRPV1 and TRPV2 modulators for the treatment of pain and other related conditions are also provided by the review. For the advancement of precision medicine techniques and the development of targeted therapies, it is essential to comprehend the roles of TRPV1 and TRPV2 in diseases.

Keywords: *TRPV1; TRPV2; Disease; Pain Sensation; Inflammation; Therapeutic Targets*

Introduction

The mammalian genome contains 28 TRP channel genes that code for the diverse Transient Receptor Potential (TRP) superfamily. Based on DNA and protein sequence homology, these genes are categorized into six subfamilies which are Transient Receptor Potential Canonical (TRPVC), Transient Receptor Potential Vanilloid (TRPV), Transient Receptor Potential Melastatin (TRPM), Transient Receptor Potential Ankyrin TRPA), Transient Receptor Potential Polycystin (TRPP), and Transient Receptor Potential Mucoliptin (TRPML) [1,2]. Na^+ and Ca^{2+} which are necessary ions, can pass across the plasma membrane more easily due to transient receptor potential (TRP) channels, which have significance in human physiology [3]. There are six known TRPV channel subtypes (TRPV1-6), which can be further split into Ca^{2+} selective TRPV channels (TRPV5, TRPV6) and thermo TRPV (TRPV1-4) [4-6].

The TRPV1 gene, which is found on chromosome 17p13, codes for the human TRPV1 protein. TRPV1, also known as the capsaicin receptor and vanilloid receptor 1 (VR1), is a member of the transient receptor potential channel vanilloid subfamily. Each subunit of TRPV1 has six trans membrane segments, a pore-forming loop between the fifth and sixth trans membrane domains, cytoplasmic C- and N-terminal domains. TRPV1 primarily forms a homotetramer [7]. It was described in 1997 by Julius group as a receptor of capsaicin, a spicy chemical found in chili peppers. According to research, lipopolysaccharide (LPS), protons, and temperature (with a threshold of 43°C) can also activate TRPV1 [8,9].

TRPV2 (transient receptor potential vanilloid type 2) is a non-selective cation-permeable cation channel that is triggered by heat (above 52°C), ligands like cannabidiol, 2-APB, and probenecid, as well as mechanical stressors [3,10]. TRPV2 is expressed by a variety of immune cells, including mast cells, neutrophil granulocytes, dendritic cells, epidermal Langerhans cells, lymphocytes, and macrophages. Numerous biological processes, including somatosensation, osmosensation, and innate immunity, have been linked to TRPV2 [11]. Both TRPV1 and TRPV2 have numerous roles that are further discussed in this review.

Role of TRPV1 and TRPV2 in diseases

TRPV1 and TRPV2 are ion channels belonging to the transient receptor potential (TRP) family. They play important roles in various diseases and conditions. TRPV1 is important in respiratory disorders, itch, inflammation, and pain perception. Its activation causes itching sensations, causes inflammation, and transmits pain signals. Cancer, neuropathic pain, is all linked to TRPV2. Here's an overview of the roles of TRPV1 and TRPV2 in diseases.

Role of TRPV1 and TRPV2 in respiratory disorders

TPRPV ion channels are widely distributed in the airways. Airway smooth muscle and epithelial cells, in addition to sensory neurons, express TRPV1 channels. TRPV1 is believed to play a vital role in bronchitis, cough, allergic asthma, Chronic obstructive pulmonary disease (COPD) and other airway diseases [12]. It has been shown that TRPV1 controls the inflammatory and activating characteristics of CD^{4+} cells that play a significant role in allergic asthma. It has been reported by Baker, 2016 that IgE levels, airway inflammation, and alterations in lung function tended to decrease when TRPV1 was targeted using GM mice or a pharmaceutical inhibitor [13]. It is well established that the chronic airway inflammation and disease process of COPD are influenced by an increased generation of certain endogenous cytokines [14,15]. There is indirect evidence that some of these pro-inflammatory cytokines may stimulate lung afferents that express TRPV1[16]. TRPV2 plays an equally important function as TRPV1 in respiratory illness. TRPV2 expression is profoundly down regulated in alveolar macrophages at early time points of cigarette smoke exposure. Reduced TRPV2-mediated phagocytic function renders the lung susceptible to cigarette smoke-induced alveolar space enlargement. TRPV2 may provide a therapeutic target for COPD induced by cigarette smoke [17]. In asthma patients with hypo- and hyperosmotic airway hyper responsiveness, TRPV1 and TRPV2 are up-regulated at the mRNA level, which may indicate their participation in the development of osmotic airway responses and asthma [18].

Role of TRPV1 and TRPV2 in cancer

Human primary brain cancers have been shown to express TRPV1 more than brains without tumors. Additionally, the grading of malignancies strongly correlates with its expression [19]. Human pancreatic cancer and chronic pancreatitis both have significantly higher levels of TRPV1 mRNA expression than in a healthy pancreas [20]. Furthermore, increased TRPV1 expression has been demonstrated in breast cancer, prostate cancer, and squamous cell carcinoma of the human tongue [21-24].

Numerous studies have shown that cannabidiol (CBD), a ligand for the transient receptor potential vanilloid 2 (TRPV2), has anti-cancer properties both *in vitro* and *in vivo*. TRPV2 has been linked to increased cell proliferation and aggressiveness, which is frequently dysregulated in malignancies [25-27]. TRPV2 may be a new candidate marker for type II Endometrial Cancer (EC), particularly high-grade

and serous cancers. Its expression also made EC more aggressive, improving migratory ability by activating AKT/mTOR. As a TRPV2 ligand, CBD has the potential to be an effective adjuvant therapy to boost the effectiveness of chemotherapeutic medications and stop the spread of cancer cells [28]. According to some research, TRPV2 has oncogenic activity in leukemia blast cells (LBC) that is connected to changes in its molecular expression profile. Targeting TRPV2 may influence the signaling pathways that control LBC growth, proliferation, and chemotaxis, which has led to the evaluation of TRPV2 as a pharmacodynamics biomarker in the context of aggressive stages of leukemia that may be associated with a high risk of lung hyper inflammation from LBC infiltration [29].

Role of TRPV1 and TRPV2 in neurodegenerative diseases

Ca^{2+}'s critical role in neurodegenerative disease pathogenesis: Ca^{2+} homeostasis is required for neurons to live, develops, and differentiates. As a result, increased Ca^{2+} dyshomeostasis may eventually lead to neuronal death. A rising amount of evidence implies that abnormal Ca^{2+} levels disrupt intracellular signaling, ultimately leading to neuron death. As a result, disturbance of Ca^{2+} homeostasis in neuronal cells leads to ROS formation and ATP depletion, as seen in neurodegenerative diseases such as AD, PD, HD, and ALS. Interestingly, TRPV channels are vital in the regulation of calcium ions (Ca^{2+}) within cells associated pathogeneses of various neurodegenerative diseases. With an increase in Ca^{2+} and other pathogenic processes, such as a deposition, an imbalance between ROS and antioxidant activity, and mitochondrial dysfunction [30]. TRP channels are widely expressed in almost every mammalian cell, predominantly in the central nervous system, gastric intestinal tract, and keratinocytes [31]. TRPV1 is expressed not only in the plasma membrane but also in the ER and calcium storage vesicles. TRPV1 is phosphorylated by PKC and is found in the ER. TRPV1 activation may cause a rise in intracellular calcium levels, which may worsen neuronal cell death. TRPV1 agonists such as capsaicin (CAP) and resiniferatoxin (RTX) promote apoptosis in microglia cells. Dopamine release is dependent on mechanosensitive TRPV1 channels triggered in dopaminergic neurons by cannabinoid receptor activation. Through the activation of TRPV1 and CB1 receptors, capsaicin, a TRPV1 agonist, causes the death of mesencephalic dopaminergic neurons and leading to cytochrome-c release, caspase-3 cleavage, and mitochondrial disruption [30]. TRPV2 Role in Bell's palsy: TRPV2 is essential for the growth of motor neurons and neural synapse and generation of the myelin sheath. TRPV 2 is associated with Peripheral facial palsy (also known as Bell's palsy) is a cranial nerve disorder with clinical manifestations including unilateral facial muscle weakness or paralysis caused by facial nerve dysfunction. Its predisposing factors include diabetes, hypertension and dyslipidemia. Immunity, infection, ischemia are potential factors leading to the onset of peripheral facial paralysis. Although the exact cause of Bell's palsy has not been elucidated, the mechanism of autoimmune demyelination mediated by myelin cells has been suggested as the pathogenesis of Bell's palsy. TRPV2 expressed in Schwann cells as a membrane protein. A study showed that TRPV2 protein could be secreted by Schwann cells. The expression of TRPV2 protein was significantly decreased under the sharp cool-hot temperature difference showed that cold stress inhibited the expression of TRPV2 in the Schwann cells. Therefore, the imbalance of Schwann cell homeostasis caused by the sharp change in temperature may be one of the contributing factors to the dysfunction of nerve signaling and the development of peripheral facial paralysis [32].

Role of TRPV1 and TRPV2 in pain

TRPV1and TRPV2 has role in noxious heat sensation and thermoregulation [33]. TRPV participate in transduction of painful stimuli. TRPV1 is a non-selective cation channel that is triggered by a number of stimuli such as heat (> 43°C), acidic pH, and some chemical substances such as capsaicin. TRPV2 (activated at temperatures over 52°C). When TRPV1 is activated, calcium and sodium ions can enter the cell, which causes the creation of pain signals and their transmission to the central nervous system [10]. TRPV1 activation causes the nociceptors to release a variety of neuropeptides, including substance P and calcitonin gene-related peptide (CGRP), which activate secondary order neurons in the dorsal horn of the spinal cord and cause neurogenic inflammation at the periphery. Several pro-inflammatory substances, including prostaglandins, serotonin (5-HT), bradykinin, activators of the protease-activated receptors (PAR), ATP, nerve growth factor (NGF), histamine, calcitonin-gene-related peptide (CGRP), tumour necrosis factor (TNF), and granulocyte colony stimulating factor (G-CSF) activate TRPV1 channels. Through their associated G protein-coupled receptors (GPCR), these allogeneic

mediators cause conformational changes in the TRPV1 [34]. Neuropeptides like CGRP and SP can be released from central and peripheral nerve terminals as a result of TRPV1 activation [35]. The pain perception process and neuropathic pain conditions may be affected in some ways by TRPV2. Increased pain sensitivity and sensitization in response to nerve injury have been linked to TRPV2 activation in sensory neurons [36].

TRPV1 AND TRPV2 modulators in clinical trials

TRPV1 is activated or sensitized by a variety of endogenous stimuli, including bioactive lipids, noxious heat, and extracellular protons, which result of tissue injury and inflammation. Thus, inhibition of TRPV1 receptor is modulated by desensitization (decrease TRPV1 activity by prolonged exposure to the agonist), which results in excessive calcium to enter the nerve fiber, initiating reversible impairment of nociceptor function, which provides relief from pain. Resiniferatoxin (RTX), which activates TRPV1 and induces apoptosis by affecting mitochondrial function, depolarization, and increasing the production of reactive oxygen species (ROS) others are endogenous stimuli, including bioactive lipids, noxious heat, and extracellular protons [37,38]. Despite the potential therapeutic interest of TRPV2 modulation, thus far, only two-channel modulators have shown promising pharmacological results, namely probenecid and tranilast as activator and inhibitor respectively.

TRPV 1	Compound	Mechanism	Route	Indication	Phase
	SB-705498	Antagonist	Oral	Migraine	II Completed
	SB-705498	Antagonist	Oral	Dental pain	II Completed
	SB-705498	Antagonist	Oral	Non-allergic Rhinitis	II Completed
	AZD-1386	Antagonist	Oral	Osteoarthritis knee pain	II Terminated
	NEO-6860	Antagonist	Oral	Osteoarthritis knee pain	II Completed
	PAC-14028	Antagonist	Topical	Rosacea	II Completed
	AG-1529	Antagonist	Topical	Pruritus	Pre-clinical
	Capsaicin	Agonist	Topical	Burning mouth syndrome	Not applicable
	RTX	Agonist	Intrathecal	Cancer pain	I Recruiting
	SYL-1001	TRPV1 siRNA	Ophthalmic	Dry eye	II Completed
TRPV2	Pebenecid	Agonist	oral	Heart Failure	II Completed
	Tranilast	Antagonist	Oral	Cardiomyopathy of muscle dystrophy	Pilot study

Table 1: *TRPV1 and TRPV2 Modulators (Inhibitors and activators) in clinical trials [37-40].*

Conclusion

Overall, understanding the roles of TRPV1 and TRPV2 in disease is crucial for advancing precision medicine techniques and developing novel therapeutic strategies to improve patient outcomes in pain management and related conditions, cancer, and neurodegenerative diseases.

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Volume 12 Issue 9 September 2023