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Review Article

Transient Receptor Potential Vanilloid 1 in Acute Pain: A Literature Review

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ABSTRACT

Transient Receptor Potential Vanilloid 1 (TRPV1) is a protein that functions as a non-selective channel receptor that is widely expressed in skin tissue, including keratinocytes, peripheral sensory nerve fibers, and immune cells. Several structural features of TRPV1 are involved in heat-induced activation, where stimulation of TRPV1 elicits a burning sensation, reflecting the receptor's important role in pain. A TRPV1-mediated signalling pathway that functions as an endogenous pain resolution mechanism by inducing nuclear translocation of β-arrestin2 to minimize desensitization of μ-opioid receptors (MOR). TRPV1 agonists can reduce pain primarily by interfering with pain nerve conduction. Several TRPV1 antagonist drug candidates have failed in clinical trials because by interfering with the detection of the above-mentioned stimuli, they triggered serious side effects such as hyperthermia and painful impaired heat detection. In the case of agonists, systemic administration causes more severe side effects such as respiratory damage. Therefore, only topical preparations with limited effectiveness have been developed. The TRPV1 agonist capsaicin is currently the only one approved for the treatment of muscle, bone, neuropathic pain and migraine, and is only available as a low-concentration cream or as a transdermal patch.

Keywords: Agonis TRPV1, Capsaicin, pain, transient receptor potential vanilloid 1.

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INTRODUCTION

Transient Receptor Potential Vanilloid 1 (TRPV1) is a polymodal protein with a function that is closely related to the generation of pain [1, 2]. This protein functions as a non-selective channel receptor that is widely expressed in skin tissue, including keratinocytes, peripheral sensory nerve fibers, and immune cells [3]. These ion channels have been shown to be examples of functional and structural flexibility. Several agonists have been identified for TRPV1 and their presence and activity have been described in several organs [1,4]. TRPV1 is activated by various exogenous or endogenous inflammatory mediators, triggering neuropeptide release and a neurogenic inflammatory response [1,3].

Pain therapy conceptually has not progressed significantly since the opioid crisis, highlighting the risks of using opioids in the treatment of pain [5,6]. As an alternative to conventional painkiller-based treatments, a non-addictive strategy is to target receptors in the pain pathway, such as transient receptor potential (TRP) ion channels. One of the targets for pain therapy originating from the vanilloid TRP channel family is TRPV1 [7].

Various studies support the role of the TRPV1 receptor in pain and inflammation, making it one of the most critical targets for the development of new analgesics. Understanding the structure of the TRPV1 channel, the endovanilloid binding site, and the critical structural features of the endogenous ligand is of paramount importance in the development of new active agents to regulate the activity of this receptor [8]. Several studies showed extensive experimental evidence implicating the ion channel TRPV1, among other members of the TRP family, as a molecular sensor of chemical, thermal, and mechanical noxious stimuli to evoke the sensations of pain and itch [9].

Transient Receptor Potential Vanilloid 1

TRPV1 or capsaicin receptor was cloned by D. Julius in 1997 from mouse cDNA. Three years later a human ortholog was isolated and showed high similarity in sequence and function. TRPV1 is an integral membrane protein consisting of 4 subunits that usually assemble in a homotetrameric ion channel (Fig. 1), although heterotetramers with other TRP channels have been reported [9].

TRPV1 is structurally characterized as a homotetrameric channel. Each of the four subunits contains six transmembrane domains (S1-S6; Fig. 2). Each monomer chain consists of a total of 838 amino acids, with amino acid residues 433–684 forming the transmembrane domain. The transmembrane region consists of six helices (S1-S6) that form a voltage sensor-like domain (S1-S4) and an inner pore region (S5-S6). Transmembrane domains 5 and 6 are connected by a hydrophobic S4S5-linker loop and are involved in channel pore formation. Ion channel pores are formed by selectivity filters and pore helices. Residues from the bottom of helix S6 behave as activation gates. Different TRPV subtypes have different pore radii that regulate channel selectivity. The binding of the activating ligand causes sequential and allosterically coupled opening of both gates [8].

Several structural features of TRPV1 are involved in heat-induced activation. Although this phenomenon is not entirely understood, thermal activation appears to be based on conformational changes in the outer pore tower. Receptor activation causes the influx of cations resulting in the transfer of action potentials

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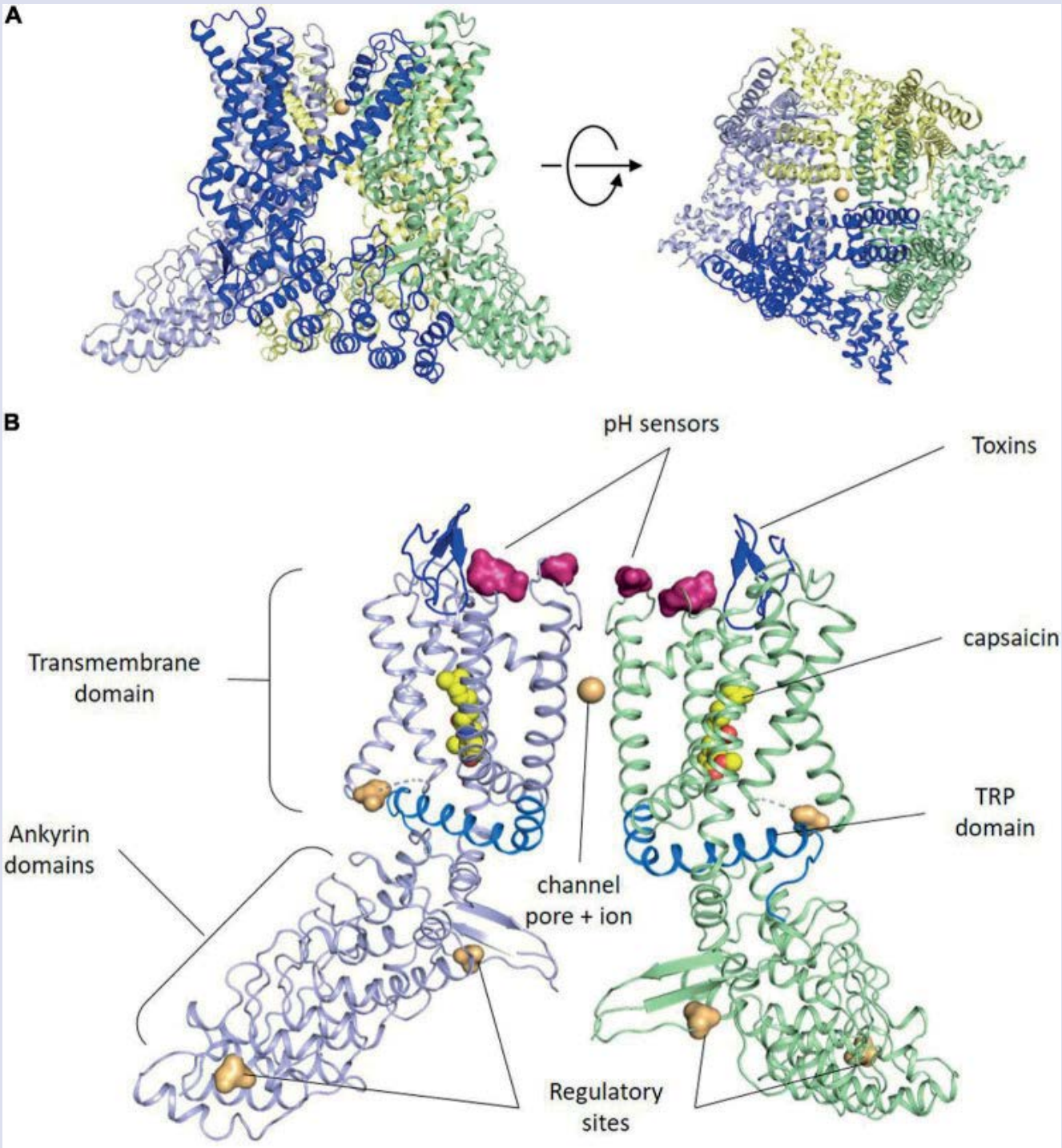

Figure 1. TRPV1 structure. (A) Side and top views of the full-length human TRPV1 tetrameric array in the closed state. Each TRPV1 channel subunit consists of six transmembrane domains. The pore circle is located between segments S5 and S6. The N and C termini are located intracellularly. Sodium ions are shown as orange spheres. Contacts between monomers occur mainly in the membrane domain and in the C-terminal coiled-coil domain located around the central axis and surrounded by the N terminus. (B) Side view of the band structure model of two opposing TRPV1 channel monomers. The other two monomers are not shown for clarity. Amino acid residues specific for capsaicin and proton activation, as well as residues important for toxin binding, phosphorylation by protein kinases A and C (PKA, PKC) and Ca2+-calmodulin-dependent kinase II (CaMKII) are highlighted in both intra-cytoplasmic regions[9].

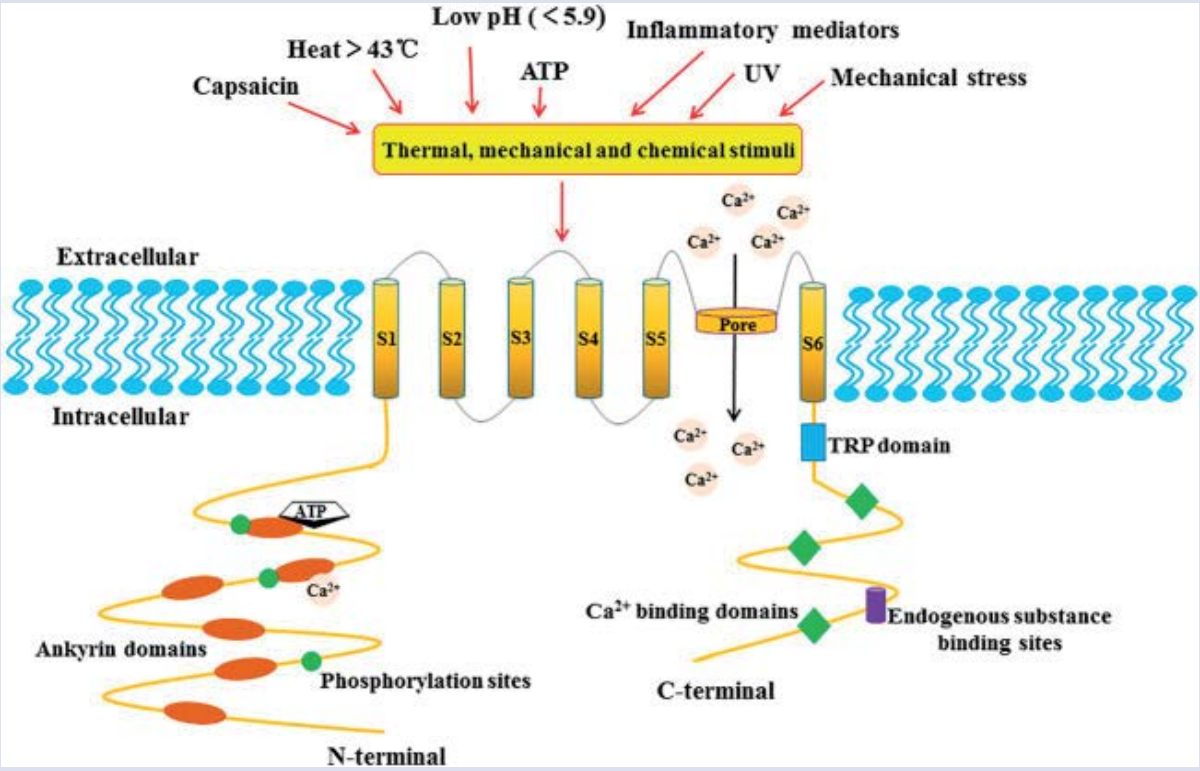

Figure 2. Structure of TRPV1 channel subunits. TRPV1 is a homo-tetramer, and each subunit consists of six transmembrane domains (S1–S6) with pore-forming hydrophobic groups. The long N-terminus contains several phosphorylation sites and six ankyrin repeat domains. The C-terminus has a TRP domain, several calmudulain binding domains, and endogenous substance binding sites[3].

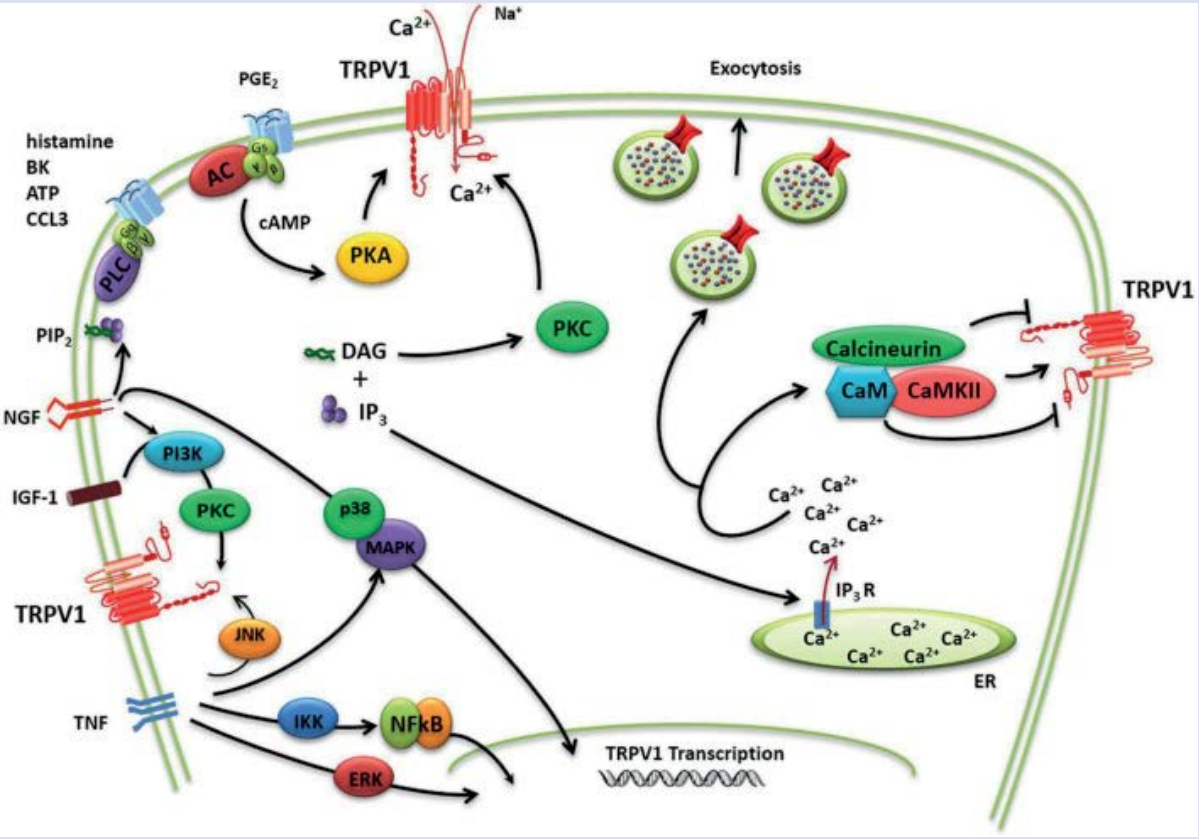

Figure 3. TRPV1 Modulation[9].

to neurons and then to the brain. This is why TRPV1 agonists this mechanism triggers an open channel state, causing a burning, stinging, or tight sensation. In contrast, capsazepine blocks TRPV1 receptors, inhibiting calcium influx induced by VBP-binding agonists but not by other painful stimuli such as heat or acid [8].

RPV1 is one of the best characterized and most widely validated members of the TRP family that plays important roles in pain physiology, neurogenic inflammation, and non-neuronal cell types such as mast cells, epidermal and hair follicle keratinocytes, and dendritic cells. TRPV1 in keratinocytes is involved in proliferation, differentiation, homeostasis, and immunological functions of the skin associated with pruritis and inflammation [10].

The Role of Transient Receptor Potential Vanilloid 1 in Acute Pain Pathways

TRPV1 is mainly expressed by Trigeminal Ganglion (TG) neurons and small diameter neurons in sensory ganglia such as the dorsal root ganglion (DRG) and its activation is essential for pain response [1,11]. TRPV1 is found in the somatosensory system, specifically primary afferent neurons that respond to nociceptive stimuli. Stimulation of TRPV1 produces a burning sensation, reflecting the important role of this receptor in pain [4].

TRPV1 was first reported to have polymodal properties, responding differently to stimuli than noxious heat (>43 °C) and capsaicin, triggering pain responses in animals and humans. It was later discovered that TRPV1 was also activated by low extracellular pH (pH ≤5.9). Importantly, when multiple stimuli are present simultaneously, TRPV1 activation becomes stronger [1,2].

Acute pain is defined as an unpleasant sensory and emotional experience associated with tissue damage [12]. Neuropathic pain occurs when there is injury or dysfunction to the peripheral or central nervous system and is a condition that is difficult to treat. One mechanism thought to modulate neuropathic pain is TRP channels that detect noxious, irritant, and inflammatory stimuli. Of these channels, TRPV1 has long been the focus of attention [13,14].

TRPV1 is a pressure-sensitive Ca2+ channel protein and is widely distributed in various tissues of the human body. TRPV1 agonists can reduce pain primarily by interfering with nerve conduction that transmits pain signals [15]. Previous studies have shown that the total number of TRPV1 channels in neurons, especially primary sensory neurons, regulates channel sensitivity [16]. Figure 3 depicts a schematic of the complex regulation of TRPV1 involved in pain transduction. TRPV1 channels can also increase neuronal excitability through the activation of intracellular signalling pathways. TRPV1 activity is controlled by many regulatory mechanisms that cause channel sensitization or desensitization. TRPV1 sensitization appears to be mediated by direct phosphorylation of intracellular domains of the protein by PKC, PKA, and other kinases. A dynamic balance between phosphorylation and dephosphorylation of TRPV1 by Ca 2+/ calmodulin-dependent kinase II and calcineurin appears to control the activation/desensitization state of the channel. TRPV1 activity can also be enhanced by Ca 2+ induced exocytosis recruitment to the cell membrane of the internal pool of vesicular TRPV1 [9].

Studies of TRPV1 Activation in Pain

The role of TRPV1 in pain and neurogenic inflammation has been well discussed in research. Duo et al found that TRPV1 mice showed apparent inhibition of thermal hyperalgesia after CFA-induced inflammation [16]. The discovery of capsaicin and the potency of TRPV1 has advanced the molecular understanding of the intestinal stimuli of noxious heat and inflammatory pain. TRPV1 channels are mainly expressed in somatic and visceral nociceptive neurons, but also in CNS neurons and immune system cells. In rodents, TRPV1 channels have been studied extensively, and their activity is mainly associated with the detection of noxious heat and the development of inflammatory hyperalgesia [17].

Basso et al. found that activation of potential TRPV1 channels stimulates the mitogen-activated protein kinase (MAPK) signaling pathway that also involves the transport of the scaffold protein β-arrestin2 to the nucleus. Translocation of β-arrestin2 to the nucleus inhibits the interaction of β-arrestin2 with the μ-opioid receptor (MOR), resulting in decreased internalization of agonist-bound MOR and reduced MOR activity that plays a role in receptor desensitization. In testing using Freund's adjuvant (CFA) inflammatory pain models in mice, they found that naloxone methiodide (Nal-M), a peripherally restricted, nonselective, and competitive opioid receptor antagonist, slowed recovery from CFA-induced hypersensitivity. in wild type mice. However, this effect was not affected by the presence or absence of TRPV1 [18].

A similar study showed that inflammation can also prolong morphine-induced antinociception in a mouse model of opioid receptor desensitization, a TRPV1-dependent process. Together, these study data reveal a TRPV1-mediated signaling pathway that functions as an endogenous pain resolution mechanism by inducing nuclear translocation of β-arrestin2 to minimize MOR desensitization. This previously uncharacterized mechanism may underlie peripheral opioid control of inflammatory pain. Dysregulation of the TRPV1-β-arrestin2 axis may contribute to the transition from acute to chronic pain [18].

TRPV1 Study in Analgesic Drug Development

TRPV1 is a heat-activated cation channel modulated by inflammatory mediators, which is closely related to pain and serves as a potential analgesic target [2]. TRPV1 is phosphorylated by Ca2+/calmodulin-dependent protein kinases C, A, D, and II, affecting its sensitivity, desensitization, and functional ligand interactions. TRPV1 is activated or sensitized by various endogenous stimuli, including bioactive lipids, noxious heat, and extracellular protons, which are generated because of tissue injury and inflammation so that TRPV1 receptor inhibition is modulated by desensitization (decreased TRPV1 activity due to prolonged exposure to an agonist) resulting in calcium influx. excessively to the nerve fibers, causing reversible disruption of nociceptor function thus relieving pain. TRPV1 is activated by exogenous stimuli such as capsaicin and resiniferatoxin (RTX) [10].

TRPV1 antagonists demonstrate analgesic effects in animal models of inflammation, neuropathic pain, and pain associated with cancer or osteoarthritis. Agonists also have analgesic effects through reversible channel desensitization. Both agonists and antagonists have reached clinical trials for the treatment of various types of pain, including pain in muscles and bones, neuropathic, dental, eye and rectal pain, as well as pain in migraines, postherpetic neuralgia and osteoarthritis [8]. The available TRPV1 channel structures facilitate the search for small molecules with high affinity for the capsaicin binding site via virtual screening (VS) on a broad set of compounds, which can include millions of compounds. This approach has become very important in drug discovery, allowing the identification of potential candidates for the development of analgesics and other treatments [11].

Capsaicin is used as a topical analgesic in "low concentration" creams (0.1% or ~3 mM) that has poor efficacy in the treatment of neuropathic pain. or increased efficacy of "high concentration" patches (8%). or ~260 mM). This dose is several orders of magnitude higher (>50,000, lower limit) than that required to activate the human TRPV1 isoform. At high concentrations, off-target effects become significant and a precise mechanism for the analgesic effect is difficult to ascertain. Capsaicin and capsazepine also modulate other membrane receptors and ion channels, especially the voltage-dependent Cav channel [19].

Several TRPV1 antagonist drug candidates have failed in clinical trials because by interfering with the detection of the above-mentioned stimuli, they triggered serious side effects such as hyperthermia and painful impaired heat detection. Thus, successful TRPV1 modulators need to selectively interfere with only some of these activation modalities, so that other modalities are not disrupted [20].

Treat et al describe the synthesis of capsaicin analogues, their in vitro activity in Ca 2+ assays, and studies of the in vivo pungency and feasibility of the capsaicin analogues YB-11 and YB-16 as analgesics. Our results showed that male and female mice treated with the capsaicin analogue YB showed reduced pain-related behavior in the spontaneous formalin test as well as reduced thermal sensitivity in the hotplate test [20].

In the case of agonists, systemic administration causes more severe side effects such as respiratory damage. Therefore, only topical preparations with limited effectiveness have been developed. The TRPV1 agonist capsaicin is currently the only one approved for the treatment of muscle, bone, neuropathic pain and migraine, and is only available as a low-concentration cream or as a transdermal patch. The antagonist successfully reached phase II and III clinical trials. Despite its analgesic effectiveness, most clinical trials have been suspended due to the occurrence of side effects such as severe hyperthermia and dangerous heat sensation disorders [8,21].

Structural studies suggest that the analgesic and side effects are produced by different TRPV1 activation modes. Thus, through spatially distinct mechanisms, TRPV1 can be activated by capsaicin, protons (low pH) and heat. The canonical vanilloid agonist capsaicin binds to voltage-sensing subdomains in intracellular channel leaflets. The proton sensing mechanism is localized primarily to the extracellular loop of the pore subdomain of TRPV1. The mechanism of heat activation is not well understood, and there are some data indicating that it depends on amino acid residues located in the transmembrane region [8,22]. Duarte et al demonstrated that TRPV1 agonists different from capsaicin could be used to develop topical analgesics with faster onset and more substantial effects [11].

SUMMARY

TRPV1 is a non-selective channel receptor that is widely expressed in skin tissue, including keratinocytes, peripheral sensory nerve fibers, and immune cells. TRPV1 is one of the best characterized and most widely validated members of the TRP family that plays important roles in pain physiology, neurogenic inflammation, and also in non-neuronal cell types such as mast cells, epidermal and hair follicle keratinocytes, and dendritic cells. TRPV1 is mainly expressed by TG neurons and by small diameter neurons in sensory ganglia such as the DRG and its activation is essential for pain responses. TRPV1 is a pressure-sensitive Ca2+ channel protein and is widely distributed in various tissues of the human body. TRPV1 agonists can reduce pain primarily by interfering with pain nerve conduction. Studies have demonstrated that the TRPV1-mediated signaling pathway functions as an endogenous pain resolution mechanism by inducing nuclear translocation of β-arrestin2 to minimize MOR desensitization. Dysregulation of the TRPV1-β-arrestin2 axis may contribute to the transition from acute to chronic pain. Both TRPV1 agonists and antagonists are reaching clinical trials for the treatment of various types of pain.

AUTHOR CONTRIBUTION

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

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