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·Minireview·

Research progress in transient receptor potential vanilloid 1 of sensory nervous system

Da-Lu LIU[1], Wen-Ting WANG[2], Jun-Ling XING[2], San-Jue HU[2]

[1] class 2005, School of the Stomatology, [2]Institute of Neurosciences, Fourth Military Medical University, Xi'an 710033, China

Abstract: The transient receptor potential vanilloid subfamily member 1 (TRPV1) is a protein mainly expressed in sensory neurons and fibers, such as in trigeminal ganglion and dorsal root ganglion, and has been indicated to be involved in several physiological and pathological processes. Studies on thermal activation have revealed that phosphorylation is involved in TRPV1 activation and 2 putative phosphorylation sites, Ser residues 502 (Ser-502) and Ser residues 800 (Ser-800), have been recently confirmed to possess the capability of resensitizing TRPV1. In addition to acidification, alkalization has also been proved to be a highly effective stimulator for TRPV1. TRPV1 could be regulated by various physical and chemical modulators, as well as the chronic pain. TRPV1 plays a crucial role in the transmission of pain signals, especially under inflammation and the neoplasm conditions, and it can also modulate nociceptive afferents by reinforcing morphine tolerance. The present review mainly focused on the structural and functional complexities of TRPV1, together with its activation and modulation by a wide variety of physical and chemical stimuli. Its pharmacological manipulation (sensitization/desensitization) and therapeutical targets were also discussed.

Keywords: TRPV1; sensory nervous system; pain; thermal; phosphorylation; alkalization

1 Introduction

The transient receptor potential vanilloid subfamily member 1 (TRPV1) is a ligand-gated nonselective cation channel that belongs to the transient receptor potential family of ion channels. Research in TRPV1 originates from a study of a ligand-activated receptor by Caterina[1]. Since its ligands such as capsaicin and resiniferatoxin (RTX) all have the vanilloid structure, the receptor was once called the Vanilloid Receptor 1 (VR1), and later it was renamed as TRPV1. The activation of TRPV1 can induce non-selective cation currents, including Ca^{2+} influx, which contributes to the transmission of intracellular signals and triggers the basic cellular activities.

Recently, TRPV1 has been found in the cardiovascular system and the central nervous system, indicating its new functions. However, many studies are still focused on its role in the sensory nervous system, in which sensory neurons generate and propagate signals to the central nervous system in response to stimuli. In sensory nervous system, TRPV1 can be activated by a plethora of stimuli, such as pain stimuli, inflammatory mediators, tissue damaging stimuli, high temperature (> 43 ℃), and acid pH. In many pathological conditions, the changes in TRPV1 expression indicate that the membrane protein in the signal pathways might be involved in the pathologies of some diseases and the intracellular functional disorders[2].

2 Molecular structure and ion permeability

TRP receptors are tetrameric in structure and each monomeric subunit component contains 6 transmembrane (TM)

Corresponding author: San-Jue HU
Tel: 86-029-84774590
Email: sjhu@fmmu.edu.cn
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domains (S1-S6) with a pore domain between the fifth TM domain (S5) and sixth TM domain (S6), while S1, S2 and S3 are lipidic areas. By binding with the lipophilic part of the ligand, S2 and S3 domains initiate the conformational alteration of the receptor. The voltage-dependent movement of the S4 TM domain activates the receptor and opens the ion channel, followed by the transmembrane flow of the cations[3]. Recently, 2 putative phosphorylation sites on TRPV1 have been identified, namely Ser residues 502 (Ser-502) and Ser residues 800 (Ser-800). Ser-502 is a non-selective substrate of multiple enzymes, including protein kinase A (PKA), protein kinase C (PKC) and Ca^{2+}/CaM-dependent kinase II (CAMK II), while Ser-800 is specific for PKCδ-induced phosphorylation. Phosphorylations of Ser-502 and Ser-800 have been implicated in re-sensitizing TRPV1 and are considered as novel potential therapeutic targets[4].

According to previous studies, although TRPV1 is a nonselective cation channel, it is more permeable to divalent ions, such as Ca^{2+}. The transmembrane current not only induces the depolarization, but also gates the Ca^{2+} release from cytoplasm. Increased Ca^{2+} concentration regulates the cell behaviors, including cytoproliferation, gene-transcription, nerve excitation, apoptosis, and other important cytological events[5, 6].

3 Expression

The latest studies have revealed that TRPV1 is expressed not only in the widely realized sensory afferent neurons and fibers, but also in central nervous system regions that involve pathological and apoptotic alterations, such as the hippocampus[7,8]. The dorsal root ganglion (DRG) and the trigeminal ganglion caudate nucleus contain many sensory nerve cell bodies where TRPV1 is expressed at a high level. In the DRG and trigeminal, TRPV1 is expressed only by a subtype of neurons with medium or small sizes (with average size profile of 537±16 μm^2) and the unmyelinated C fibers or thinly myelinated A-δ fibers[9,10]. Both the neurons and the fibers also express some chemical markers (i.e. isolectin B4, IB4), fluoride-resistant acid phosphatase (FRAP), the P2X3 purinoceptor (a receptor provoked by ATP-induced nociception) and Ret, a glial cell line-derived neurotrophic factor receptor[11]. However, Hong *et al.* have reported that the DRGs of diabetic rats displayed an intensively positive immunoreactivity for TRPV1 on large myelinated A-β fibers and large-sized neurons[12]. It is assumed that TRPV1 in the nervous system is responsible for conducting nociceptive stimuli, initiating and maintaining the acute pain induced by inflammation, as well as establishing the chronic pain state[13].

4 Agonist and antagonist

Ligand-like agents and a plethora of unrelated stimuli act as agonists for TRPV1. The classical ligands capsaicin and RTX have been highlighted for their great efficiency in stimulating TRPV1. Besides, TRPV1 can be activated under noxious heat (≥ 43 ℃) and low pH (≤ 5.9) conditions. Moreover, 2 inflammatory mediators—arachidonic acids and the leukotrienes (LTs) have been implicated in activating TRPV1, suggesting the involvement of TRPV1 in inflammation[14].

5-Iodoresiniferatoxin (I-RTX) is the halogenide form of RTX and is commonly used as a potent selective pharmacological antagonist for TRPV1. Studies in bone tumor model have shown that I-RTX can relieve the pain-related behaviors in a dose-dependent way. Capsazepine is another widely used specific blocker for TRPV1, although it has a lower affinity to TRPV1 than I-RTX does[15]. 1-Isoquinolin-5-yl-3-[4-trifluoromethyl-benzyl]-urea (A-425619) is a novel antagonist that specifically inhibits TRPV1 activation induced by vanilloids, heat and proton, while exerts no effect in TRPV1 activation by other noxious stimuli[16]. The latest research has revealed mustard oil as another antagonist for TRPV1. Mustard oil treatment results in inward rectifier current and intracellular Ca^{2+} overload, and finally interruption in the downstream of TRPV1 signal pathway[17]. Some researchers have reported that agelenopsis aperta (a kind of spider venom) can cause thorough desensitivity of TRPV1, which sheds light on the toxicology concerning TRPV1[18].

5 Activation

5.1 Mechanical stimuli To study the mechanical hyperalgesia, repetitive noxious colorectal distension (CRD) was used to induce the visceral pain responses in rats. The

apparent increase of the viscerosomatic response that indicating the acute mechanical sensitization, could be successfully induced by 12 consecutive isobaric CRDs (80 mmHg). However, the sensitization is prevented by TRPV1 antagonist NGV-1 in a dose-related manner, with no hyperalgesic responses[19]. The mechanical hyperalgesia could also be induced by an eccentric exercise (ECC) without the infiltration of inflammatory cells into muscles. Intramuscular injection of capsazepine, a TRPV1 selective antagonist, could completely suppress the ECC-induced muscle hyperalgesia[20]. These findings suggest that TRPV1 may be greatly involved in the development of mechanical hypersensitivity.

5.2 Thermal stimuli The function of noxious heat stimuli has been a focus since the early period of TRPV1 research. Recent studies concentrate more on TRPV1 expression, activity and structure during thermal signal transmission and also in response to cold and heat stimuli in body.

TRPV1-KO and TRPV1-mutant models exhibit significant deficiency in encoding noxious heat stimuli. Eckert[21] has reported that none of the spinal lamina I neurons of mutant mice respond to temperature of 40 ℃ (15% for WT neurons), while only 8% respond to temperature of 45 ℃ (96% for WT neuron) and 44% respond to 49 ℃ (100% for WT neurons), and the rest mutant neurons (56%) respond to 55 ℃ heat stimuli.

Others report that TRPV1-KO mice have a lower proportion of spontaneous activity (SA) positive afferents after the plantar incision. SA positive afferents have a lower temperature threshold compared with SA negative afferents, which suggests the inverse relationship between the firing rate of SA and the temperature threshold for heat, indicating that TRPV1-KO mice may have a lower sensitivity to heat[22].

Fasting usually leads to progressive daytime hypothermia (hence saving some energy) with night-time core temperature being maintained at normothermia. As revealed by recent studies in fasting heterothermia, the daytime core temperature in WT mice is significantly decreased as compared with that in TRPV1-mutant mice under fasting conditions. Besides, the WT mice exhibit an earlier onset of changes in locomotive activity rhythm and core temperature than TRPV1-mutant mice do. These findings suggest that TRPV1 is responsible for temperature regulation under short-term energy lack conditions[23].

5.3 pH On stimulations by protons, the majority of rat capsaicin-sensitive DRG neurons display acid-sensing ion channels (ASICS) like large inward currents. For both DRG neurons and the unmyelinated nociceptors, their sensitivities to acid are significantly attenuated in TRPV1-KO or mutant mice[24]. Acidic condition (pH < 7.0) or capsaicin could induce a sustained inward current on rat vagal sensory neurons, which could be inhibited by treatment of 10 μmol/L capsazepine[25]. These studies indicate that the acid afferents depend on the expression of TRPV1 on DRG neurons and the nociceptors, and proton may either directly evoke TRPV1 or maintain the activation of TRPV1. Moreover, capsazepine can inhibit the increase in cytosolic calcium concentration ($[Ca^{2+}]_c$) elicited by either acidic condition or capsaicin. The increase in $[Ca^{2+}]_c$ may lead to cell apoptosis via the release of reactive oxygen species[26]. TRPV1 also seems to have the ability of interfering with basic cellular behaviors under acidic conditions.

An up-to-date study reveals that TRPV1 can also be activated by alkaline chemicals, eliciting severe pain and inflammation. The ammonia-induced intracellular alkalization (pH 8.0) causes 4.1±0.8 fold increase in TRPV1 activity as compared with that in control conditions (pH 7.3). Besides, when cultured under conditions with high extracellular pH of 7.8, 8.3 and 9.5, the DRG neuron activity shows 5-fold, 40-fold and 45-fold increases, respectively. All the alkaline-induced TRPV1 activations can be inhibited by TRPV1 antagonist BCTC (300 nmol/L)[27]. Although the underlying mechanisms remain unclear, the alkalization may act as a new approach for TRPV1 research. As mentioned previously, TRPV1 is the first identified ion channel that has high sensitivities to both the acidic and alkaline stimuli.

6 Regulation

6.1 Modulators Pharmacological agonists and antagonists are commonly applied as modulators for TRPV1 activity. The capsaicin treatment on DRG neurons induces the 2.65-fold increase in heat-induced currents (I_{heat}), from -161±17 pA of pre-treatment to -353±60 pA during sustained heat stimulation. The heat response in capsaicin group (-353±60

pA) is also apparently higher than that of the control group (from -135±16 pA to -145±19 pA)[28]. These results indicate that the changes in TRPV1 activity can modulate the transmission of temperature signal.

The latest research at molecular level confirms that phosphorylation is critical in intracellular signal transduction. Ser-800 is a substrate of PKC and acts as a novel phosphorylation site on TRPV1[4]. Recent studies have revealed that the activation of Ser-800 is a potential regulatory approach of TRPV1. The injection of endothelin-1 induced a fall of thermal threshold via Ser-800, which could be attenuated by the antagonist of PKC[29]. PKC has also been indicated in mediating the interaction between TRPV1 and neurokinin-1 receptor, leading to multiple intracellular signal events, from activation of the G-protein-coupled receptor to membrane translocation of PKCε. The downstream events lead to the heat hyperalgesia, which can be completely prevented by PKCε inhibitor[30].

These findings indicate that the phosphorylation of TRPV1 may trigger cascaded effects in the sensory neurons that result in heat hyperalgesia. Therefore, it is assumed that TRPV1 may possess far more chemical sites as potential targets for thermal hyperalgesia, via interfering with the intracellular signal at molecular level, providing new clues for clinical treatment.

6.2 Chronic pain conditions In the process of inflammation-induced pain, nociceptors are activated by released chemical factors and inflammatory mediators, as well as by inflammation-related tissue swelling and hyperemia.

Studies on TRPV1-KO mice have revealed that the inflammatory reactions in the arthritic TRPV1-KO mice, such as mild joint swelling, are more attenuated than that in WT mice.The ratio of the weight distribution between the hind limbs in TRPV1$^{-/-}$ mice is also apparently less than that in WT mice[31]. Likewise, subcutaneous injection of turpentine oil (an inflammatory mediator) into rat facial area causes significant decreases in both the head withdrawal thermal latency and the head withdrawal cold latency. Meanwhile, TRPV1-positive neurons are more frequent and denser in the trigeminal sensory nuclei caudalis[32]. In the model of chronic osteitis, TRPV1 induces the expression of c-fos, a widely recognized switch of the activation of spinal nociceptive sensory neurons[33, 34]. As a downstream component of c-fos pathway, the mitogen-activated protein kinases (MAPK) has been recently highlighted for its potential role in the pathological pain via post-translational, translational and transcriptional regulations[35]. Taken together, the studies indicate that (1) both the maintenance of inflammation and the transduction of inflammatory signal depend at least partly on the expression of TRPV1; (2) TRPV1 as a potential inflammatory medium may be associated with phosphorylation, in which MAPK might be involved. TRPV1 might provide a novel pharmacologic target in the treatment of inflammation-induced pain.

The neoplasm-induced pain is a primary factor compromising the life qualities of cancer patients. As confirmed by western blot and RT-PCR assays, TRPV1 expression is significantly increased in the ipsilateral DRG with sarcoma implantation, together with a significant increase in the proportion of TRPV1 positive neurons (31.2±1.3%, compared with 24.3±1.3% in sham mice) which is revealed by immunohistochemical analysis, providing a classical model to study the cancer pain. And TRPV1 is detected not only in small neurons but also in medium and large neurons in the tumor lateral DRG after sarcoma injection. The most impressive finding is that i.p. administration of I-RTX can apparently attenuate the ongoing and movement-evoked bone cancer-related pain behaviors[36]. In conclusion, TRPV1 activation plays a vital role in the generation of bone cancer pain. Furthermore, the extended spectrum of TRPV1 distribution, as well as the increased number of TRPV1 positive Aδ fibers from large neurons, may reinforce the nociceptive transmission, and hence maintain the cancer-related pain behaviors.

Moreover, Chen has initially found that the nociceptive opioid system could attenuate the up-regulation of TRPV1 expression induced by the complete Freud's adjuvant, a chronic inflammatory mediator[37]. It has been shown that presynaptic μ opioid receptors are highly intensively co-expressed with TRPV1 on DRG neurons[38]. These findings shed light on the relevancy of TRPV1 to the opioid receptor-like 1 in the pain.

TRPV1 also reinforce morphine tolerance, as proved by

the inhibitory effect of RTX on TRPV1 during the consecutive intrathecal morphine injection. On day 1 and day 14 after morphine injection, the RTX-treated rats exhibit much higher threshold than control rats do under the noxious pressure. Further, the threshold of the vehicle-treated rats has fallen to the pre-injection level 1 week after morphine treatment. In contrast, the effect of morphine is largely sustained in RTX-treated rats during the 14-day period of daily injection. It is also found that the RTX-treated rats have low level of PKC γ in the spinal cord dorsal horn[39]. These results indicate that (1) TRPV1 may desensitize μ opioid receptors, which then leads to the attenuation of the analgesic effect and the hyperalgesia in the rats; (2) the morphine analgesic tolerance can be delayed in the absence of primary afferent neurons expressing TRPV1. TRPV1 may cooperate with the opioid tolerance to strengthen pain and reduce analgesic effect of morphine by regulating its phosphorylation in neurons. Therefore, TRPV1 is a promising pharmacologic target for studying pain mechanisms, providing potential clinical application to modulate the analgesic effect of morphine.

7 Conclusion

TRPV1 is a non-selective cation channel, firstly found in the sensory nerves that transmit various sensory signals. In sensory nerves, TRPV1 serves as a mediator in the transductions of intracellular and extracellular signals and modulates the organism functions through its activation by a variety of endogenous and exogenous stimuli, such as mechanical stimuli, noxious heat, proton, and capsaicin. The relevance of TRPV1 to some diseases, such as diabetes, suggests its important role in physiological and pathological processes. TRPV1 expression and activity are modulated under some chronic pain conditions, including inflammation and neoplasm, and then the persistent hyperalgesia is prompted. Therefore, further research on TRPV1 will cast light on clinically new pharmacological applications and novel therapeutics.

Besides, TRPV1 has recently been detected in various brain regions and in other systems. In cardiovascular system, TRPV1 can potentially prevent the hypertensions by releasing some neuropeptides, such as SP and CGRP[41]. TRPV1 may also elicit inflammation in the colon plexus, muscle and vein in some inflammatory bowel diseases[40]. TRPV1 on Sertoli cells contributes to the maintenance of the acidic milieu in spermatogenetic microenvironment that is crucial for male fertility[42].

However, doubts still exist calling for further investigations. How does alkalization evoke TRPV1 sensitization? How does TRPV1 alter the activity of the μ opioid receptor to regulate the nociceptive afferent pathway? By which way does TRPV1 interact with other TRP family members? Solving these problems will help discover the mechanisms of pain and TRPV1 might become a novel target in the treatment of hyperalgesia.

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感觉神经系统 TRPV1 受体的研究进展

刘大路[1]，王文挺[2]，邢俊玲[2]，胡三觉[2]
第四军医大学[1]2005 级口腔医学系，[2] 神经科学研究所，西安 710033

摘要：瞬时受体电位香草酸受体 1（transient receptor potential vanilloid subfamily member 1，TRPV1）主要表达于感觉神经元及其纤维，如背根神经节和三叉神经节，并参与多种生理病理过程。对热刺激的研究使得细胞磷酸化水平在TRPV1活化过程中的作用被逐渐认识。最新的分子学实验发现了 TRPV1 磷酸化的两个新位点，即 Ser-502（Ser residues 502）和 Ser-800（Ser residues 800）位点，两者都具有使失活的 TRPV1 通道重活化的作用。另外，继酸被发现可以激活 TRPV1 后，目前碱也被证实是一种高效的 TRPV1 刺激因子。研究发现 TRPV1 在神经系统疼痛信号传导整合中发挥重要作用，尤其是在炎症或肿瘤情况下。吗啡耐受作用的加强也被认为是 TRPV1 介导的疼痛信号的调节机制之一。本文主要对 TRPV1 的结构、表达、激活及调节因素作一综述，并对 TRPV1 在生理与病理条件下的活动改变及其机制，以及 TRPV1 相关的新药理学和治疗靶点进行了讨论。

关键词：TRPV1；感觉神经；疼痛；热；磷酸化；碱