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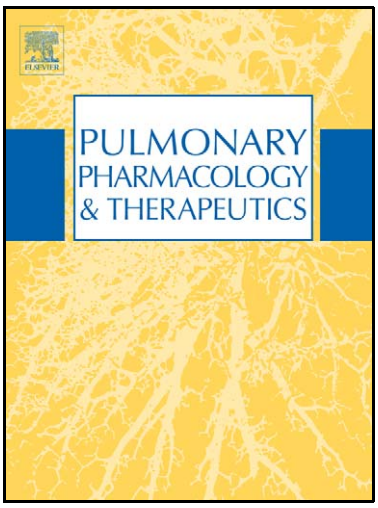

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Title: **Is TRPV-1 a useful target in respiratory diseases?**

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Abstract

This review focuses on the transient receptor potential vanilloid 1 (TRPV1). TRPV1 is a non-selective cation channel predominantly expressed in the cell membranes of sensory afferent fibers, which are activated multi-modally. In the mammalian respiratory system, immunohistochemical and electrophysiological studies have revealed heterogeneous localizations of TRPV1 channels in the airways and their presence in pleural afferents. TRPV1 channels in afferents are not only involved with sensory inputs, but also release several neuropeptides upon stimulation. These processes trigger pathophysiological effects (e.g. reflex bronchoconstriction, hypersecretion, cough, etc.) that cause various symptoms of airway diseases. Recent studies have identified several endogenous and exogenous substances that can activate TRPV1 in the lung. Because of its key role in initiating inflammatory processes, TRPV1 receptor antagonists have been proposed as therapeutic candidates. Therefore, a critical update of recent therapeutic results is also given in this review.

Key words: Neurogenic inflammation, bronchoconstriction, mucus secretion, cough, apoptosis, therapy

Introduction

Non-myelinated (C-) fibers represent the majority of vagal afferents that innervate the airways and lungs [1]. The afferent activity arising from C-fiber endings plays an important role in regulating respiratory functions under both normal and pathophysiologic conditions. Capsaicin, a pungent ingredient of chili peppers, is known to activate airway C-fibers, and this activation has long been associated with the initiation of several central reflexes, including increases in respiratory rate, parasympathetic bronchoconstriction, mucus hypersecretion, vasodilation, as well as urge to cough sensations and sensations of dyspnea [2, 3].

Recent immunohistochemical studies have revealed the presence of nerve endings, presumably C fibers, that contain tachykinins, such as substance P (SP) and neurokinin A (NKA), and calcitonin gene-related peptide (CGRP) in the airway mucosa [4, 5]. In many species, including humans, these neuropeptides are synthesized in the cell bodies of airway neurons of the trigeminal, jugular and nodose ganglia, and are then transported to and stored in the peripheral endings. The neuropeptides that are released locally from C-fiber endings upon stimulation play important roles in the human respiratory system. They have potent effects on the tone of airway smooth muscle, airway secretions, edema of airway mucosa and on inflammatory and immune cells that mediate neurogenic inflammation via binding tachykinin ligands (NK_1, NK_2 and NK_3) or CGRP receptors [6-14]. Thus, responses evoked by activating C-fiber afferents are mediated both by central reflex pathways and by local or axon reflexes involving the release of tachykinins from sensory endings.

Transient receptor potential vanilloid (TRPV) 1 is a multi-modal, non-selective

cation channel with a high permeability to Ca^{2+} [15, 16]. In the respiratory system, TRPV1 is predominantly found in afferent sensory neurons. It has been hypothesized that TRPV1, together with tachykinin, is responsible for the release of neuropeptides from the sensory terminals, thereby initiating local neurogenic inflammation [14]. To clarify the roles of TRPV1, experiments using selective receptor antagonists and targeted gene deletions in mice have demonstrated the important roles of TRPV channels, particularly TRPV1 in the regulation of airway function [17, 18]. This review will outline our current knowledge of TRPV1 and its potential roles for respiratory medicine.

TRPVs: A brief overview

Studies with Drosophila opened the door to understanding the roles of transient receptor potential (TRP) channels. The term TRP derives from a transient, rapid decline of electrical potential in photoreceptor cells of mutant *Drosophila* following prolonged stimulation with light [19, 20]. To date, 28 ion channels have been identified for the TRP family, which are classified in six subfamilies based on their homologies and activation characteristics. All TRP channels are comprised of six transmembrane domains that assemble as tetramers to form cation-permeable pores. Upon adequate stimulation, the channel opens and allows ions to pass through. Only a small conformational change in the TRP channel protein is required for pore opening, which allows > 10^6 ions per second to flow through each channel and initiate a nerve impulse [15, 16] (Fig 1 Ref [16]).

In mammals, TRP channels are ancient sensory receptors that are ubiquitously expressed in tissues and organs. Not only are they involved in the classical sensory

transduction processes of multicellular organisms, such as vision, olfaction, taste, thermosensation and other stimuli, but they are also engaged at the single cell level [15]. One TRP subfamily, the transient receptor potential vanilloid subtype (TRPV), consists of six non-specific cation channel receptors [21-23]. The best known member of this family is TRPV1, initially called vanilloid receptor (VR)1. Caterina and co-workers cloned TRPV1 from a rat sensory neuron cDNA library and showed that the receptor is expressed in both the dorsal root (DRG) and trigeminal ganglia (TG) [24]. TRPV1 has also been cloned from humans [25], guinea pigs [26], rabbits [27], mouse mice [28] and dogs [29].

Expression of TRPV-1 in the respiratory system

Several immunohistochemical studies have described the distributions of TRPV1 within the central nervous system [30], skin [31], gastrointestinal tract [32] and nasal mucosa [33]. Much is known about the mapping of TRPV1 receptors in the animal lung. Recently, an investigation using immunofluorescence and confocal microscopy found a unique distribution and co-localization of TRPV1 and two neuropeptides (CGRP, substance P) in the extra- and intrapulmonary airways of guinea pigs.

TRPV1 positive axons represented only a small fraction of the total number of PGP9.5 staining nerves within the tracheal epithelium of the guinea pig, and only half of the TRPV1 positive axons also stained positive for substance P. In the intrapulmonary airways, most TRPV1 positive neurons co-localized with substance P and CGRP within and beneath the epithelium, around blood vessels, within airway smooth muscles and alveoli. TRPV1 is predominantly found in sensory nerves that contain neuropeptides, and it is heterogeneously expressed in the airways of guinea pigs [34, 35].

TRPV1 expression in the lung is not confined to sensory nerves, as this receptor is

also present in immortalized human bronchial epithelial cells [36-38], airway smooth muscle cells [35] and mast cells [39]. Recently, parietal pleura afferents were found in the intercostal nerves of rabbits, and these myelinated and unmyelinated fibers had multi-modal properties [40]. In addition, a very recent study demonstrated the presence of acid-sensitive channels, TRPV1 and acid sensing ion channel-3 (ASIC3) in rat DRG neurons projecting to the pleura.

Groth et al. investigated to what extent they were expressed by rat DRG neurons projecting to the lung and pleura using retrograde labelling with antisera against TRPV1, ASIC3 and neurofilament 68 (marker for myelinated neurons) injected into the lung or applied to the costal pleura. It was found that 22% of pulmonary spinal afferents expressed neither TRPV1 nor ASCI3 channel-immunoreactivity. In contrast, only 3% of pleural afferents expressed neither TRPV1 nor ASCI3. $TRPV1^{+}/ASIC3^{-}$ neurons with slow conduction velocity (small soma, neurofilament 68-negative) were significantly more frequent among pleural (35%) than pulmonary afferents (20%). $TRPV1^{-}/ASIC3^{+}$ neurons were found in between 44% (lung) and 48% (pleura) of the neurons, and half of these presumably conducted in the A-fibre range (large soma, neurofilament 68-positive) [41].

In contrast to animal tissue or cultured cells, much less is known about the mapping of TRPV1 receptors in the human lung. One study showed specific staining of nerve profiles for TRPV1 in the subepithelial and epithelial layers in human bronchial tissue obtained by fiberoptic bronchoscopy, but there was little evidence of TRPV1 expression in non-sensory nerve sites [42].

Activation of TRPV1 in the lung

TRPV1 in the lung may be experimentally activated by a variety of stimuli, such as

electrical stimulation of the vagus nerve, mechanical stimuli or chemical irritants. Capsaicin is a potent, selective stimulus for the TRPV1 channel. TRPV1 is also activated by acid [43-45], heat [24], arachidoynlethanolamide (AFA and anandamide) [46, 47]and the lipoxygenase metabolites of arachidonic acid, including leukotriene B4 (LTB4), 12- and 15-(*S*)-hydroperoxyeicosatetraenoic acid [12-(S)-HPETE), 15-(S)-HPETE] and 5- and 15-(*S*)-hydroxyeicosatetraenoic acids [5-(S)-HETE), 15-(S)-HETE] [48].

In addition to exogenous stimuli, TRPV1 is sensitized by a number of endogenous inflammatory mediators. TRPV1 has several consensus phosphorylation sites where phosphorylation by protein kinases A, C and G (PKA,C and G) or tyrosine kinase might take place [49-51]. Also, adenosine 5-triphosphate (ATP) and bradykinin enhance TRPV1 activity through a PKC-dependent pathway (See ref. [52] for details on each TRPV1 activator and modulator).

Role of TRPV1 in the respiratory tract under pathophysiological conditions

1. Thermal sensing

The body temperatures of mammalian species are usually maintained within relatively narrow physiological ranges. However, hyperthermia can occur under various conditions. For example, body core temperature can exceed 41℃ during strenuous exercise, such as marathon running, or in some pathological cases with severe fever [53, 54]. TRPV channel subtypes play important roles in thermal sensing. In mammals, six thermosensitive ion channels have been reported, all of which belong to the TRP subfamily. The TRPV1, TRPV2, TRPV3 and TRPV4 channel subtypes are the primary thermal sensors, and each TRPV subtype is activated in a different temperature range [22]. TRPV1 exhibits general sensitivity to

extreme temperatures over 43 ℃, which are painful to humans [24, 55]. However, TRPV1 may be activated at even lower temperatures within the normal physiological range.

The temperature threshold for TRPV1 stimulation is lowered by anandamide or ATP through a PKC-dependent pathway [50, 51]. A recent study by Ni et al. showed that isolated rat vagal pulmonary sensory neurons can be directly activated by increases in temperature (35 ℃ to 41 ℃) as demonstrated by the evoked inward currents. Stimulation was only partially attenuated by pre-treatment with capsazepine or AMG9810, which are selective TRPV1 antagonists. In contrast, after treatment with ruthenium red, a blocker of TRPV1-4 channels, activity was almost completely abolished. In addition, TRPV1-4 channel mRNA and protein expression was evident in these neurons. This indicates that TRPV1, as well as other thermo- sensitive TRPV channel subtypes, are activated within the normal physiological range and play a primary role in regulating the response of pulmonary sensory neurons to hyperthermia [56]. However, the relative contributions of these different TRPV channel subtypes to the thermal sensitivity of these neurons remain to be determined, and the effects of these neurons' activation under normal or pathophysiological condition await future studies.

2. Acid sensing

Acidification of pulmonary tissue can commonly occur due to excessive CO_2 production (e.g., exercise), impaired CO_2 clearance from the lungs (e.g., COPD) [57, 58] or excessive lactic acid production caused by tissue ischemia or hypoxia [59]. In asthmatic patients with acute exacerbations, the pH of exhaled breath condensates is reduced to 5.23, as compared to 7.65 in healthy subjects [60]. Low pH in the

exhaled breath condensate, which reflects the lining fluid pH of the lower airways, has been found in various respiratory diseases, such as obstructive sleep apnea [61], chronic cough [62], cystic fibrosis [63], a acute lung injury [64].

Airway acidification induces the release of neuropeptides from bronchopulmonary C fibers [65, 66]. Two well-established mechanisms for activation of sensory nerves by acid are TRPV1 and ASICs. The airway C-fiber response to acid has both transient and sustained components. Electrophysiological and pharmacological studies show that the TRPV1-mediated response to acid is sustained, while most of the ASIC-type receptors mediate brief transient responses [45, 67].

The transient component is inhibited in a dose-dependent manner by the ASIC blocker amiloride, whereas the sustained component is attenuated, but not abolished by selective TRPV1 antagonism. In addition, there appear to be no interactions between these two chemicals when simultaneously applied to neurons [65, 68]. In an experiment using TRPV1 knock-out mice, the fact that sustained activation of C-fibers was evoked by acid suggested that ion channels other than TRPV1 can also generate potentials in C-fibers in response to decreases in tissue pH. Little is known regarding the mechanism for the TRPV1-independent response to acid in pulmonary C-fibers. But, numerous acid-sensitive ion channels may contribute to this response, such as TRPV4 [69] and certain types of voltage-gated potassium channels [70].

There is little available information regarding acid-sensing channels in the pleura. Rat pleural afferents express at least two different acid-sensitive channels, TRPV1 and ASIC3, with a higher prevalence of $TRPV1^{+}/ASIC3^{-}$ neurons among pleural afferents compared to pulmonary afferents. Different expression patterns of these acid sensing channels may make them suitable to monitor tissue acidification. A higher incidence of the $TRPV1^{+}/ASIC3^{-}$ pattern might reflect the high sensitivity of

the parietal pleura to sustained, painful stimuli. However, direct experiments regarding the specific function of this neuron subclass remain to be done [41].

3. Airway smooth muscle constriction

Bronchoconstriction is a clinically important feature resulting from neurogenic inflammation. Atropine-resistant bronchoconstriction has been shown in guinea pig airways. It is completely blocked by the simultaneous administration of NK_1 and NK_2 receptor antagonists both *in vitro* [71, 72] and *in vivo* [73]. Tachykinins cause bronchoconstriction through NK_2 receptors, and to a lesser extent NK_1 receptors, in the guinea pig [74]. In allergic animal models, pre-treatment with capsaicin, which degenerates the airway TRPV1-expressing afferents and depletes sensory neuropeptides, inhibits allergen-induced bronchoconstriction in sensitized guinea pigs [75]. These effects are ascribable to non-cholinergic bronchoconstriction via activation of TRPV1. An analogous non-cholinergic bronchoconstriction has not been consistently demonstrated in humans.

Tachykinergic innervation is absent, or very sparse, around human airway muscle [76]. Electrical field stimulation of human isolated bronchi leads to cholinergic contractions, but not to tachykinergic contractions [77]. A few studies found a small contraction of human bronchi to capsaicin, but a direct role for tachykinins was not investigated [78, 79]. Other studies have shown that capsaicin either does not contract human bronchial tissue or only causes contractions at non-selective concentrations by mechanisms that do not involve neurokinin receptors [80, 81].

Recently, functional TRPV4 channels in human airway smooth muscle cells have been reported. Jia and co-workers showed a hypotonicity-induced airway contraction that was independent of tachykinin-containing sensory nerves in isolated intact human and guinea pig airways [82]. From their work, a direct action on airway

smooth muscle via TRPV4 excitation followed by Ca^{2+} influx may be suggested. TRPV1 channels were unlikely to have been involved in the Ca^{2+} response in cultured human smooth muscle cells, as TRPV1 mRNA was not expressed and a TRPV1 agonist and an antagonist had no effects on Ca^{2+} influx. However, a recent study showed that TRPV1 is up-regulated in airway smooth muscle in patients with chronic cough [83]. Whether or not the direct action via TRPV1 excitation on airway smooth muscle applies to pathological conditions in human airways, such as asthma or COPD, remains to be determined.

4. Cough

Several studies support a linkage between TRPV1 and cough. Inhalation of the well-known TRPV1 agonist capsaicin consistently and reproducibly elicits cough in animals and humans [84-86]. TRPV1 receptors are found on sensory airway nerves that play important roles in the cough reflex [13, 42, 52, 87]. Groneberg et al. found a significant correlation between the capsaicin tussive response and the numbers of TRPV1 positive nerves in patients with chronic cough of diverse causes, suggesting that TRPV1 receptors contributed to the enhanced cough reflex [42].

In some studies, TRPV1 antagonists inhibited coughs elicited by capsaicin and citric acid in guinea pigs [88, 89] and by aerosol exposure to ovalbumin in sensitised guinea pigs [90]. More direct evidence linking TRPV1 channel activity to airway sensory neurons innervating inflammatory airways was recently provided by McLeod et al. who demonstrated the effects of airway inflammation induced by sulfur dioxide (SO_2) exposure on TRPV1 receptor activity in vagal sensory neurons and cough. Using a subacute SO_2 exposure model in guinea pigs, intracellular Ca^{2+} responses in nodose ganglia cells evoked by capsaicin were significantly augmented in SO_2 exposed animals compared to nodose ganglia from control guinea pigs. This

response was blocked by the TRPV1 antagonist capsazepine (1μM). In addition, cough responses elicited by aerosolised capsaicin and the numbers of BAL neutrophils were significantly increased in SO_2 -exposed guinea pigs compared to controls [91]. This study suggests that up-regulated TRPV1 may play an important role in cough under inflammatory conditions.

5. Mucus secretion

Chronic mucus hypersecretion is indicative of poor asthma control and is an important characteristic of chronic obstructive pulmonary disease (COPD) [92, 93]. Up-regulation of the lung sensory neural pathways has been implicated in asthma and COPD. Tachykinins released from sensory nerves act mainly through NK_1 receptors in sensory glands, and mediate mucus hypersecretion, edema, vasodilatation and the release of pro-inflammatory cytokines [94, 95]. Pre-protachykinin (PPT)-A, a precursor of SP, NKA and NK_1, is expressed at high levels in human COPD airway extracts. NK_1 protein, PPT-A mRNA and SP protein are even more abundantly expressed in human COPD airway tissue [96].

A recent *in vivo* study found evidence of a role for TRPV1 in mucus secretion in capsaicin-evoked airway inflammation of rats. Karmouty-Quintana et al. showed that the TRPV1 antagonist capsazepine completely inhibited the fluid signals detected by magnetic resonance imaging and reduced mucin levels in BAL fluid induced by capsaicin. Furthermore, pre-treatment with a dual NK1/NK2 receptor antagonist completely inhibited the mucus release induced by capsaicin [97]. Taken together, these results suggest that the activation of TRPV1 may promote the release of tachykinins, SP and NKA, resulting in mucus secretion through NK_1 and/or NK_2 receptors.

6. Apoptosis and TRPV1

In vitro studies using human bronchial epithelial cells have demonstrated increased production of pro-inflammatory cytokines, such as interleukin-6 and interleukin-8, and oncotic cell death associated with TRPV1 activation [37, 98]. Other studies have also demonstrated that particulate matter increases intracellular Ca^{2+} and induces apoptosis of cultured lung epithelial cells via activation of TRPV1 [38, 99]. These results indicate that TRPV1 is a mediator of lung injury and inflammation. However, the detailed molecular mechanisms associated with cell death have not been established.

A very recent study addressed the effects of TRPV1 on the endoplasmic reticulum (ER) regarding stress and cell death in human bronchial epithelium and alveolar cells [100]. TRPV1 agonist (nonivamide) treatment induced calcium release from the ER and changed the transcription of growth arrest- and DNA damage-inducible transcript 3 (GADD153, GADD45alpha, GRP78/BiP, ATF3, CCND1 and CCNG2) in a manner similar to prototypical ER stress-inducing agents. Also, the TRPV1 antagonist N-(4-tert-butylbenzyl)-N'-(1-[3-fluoro-4-(methylsulfonylamino)-phenyl]ethyl) thiourea (LJO-328) inhibited mRNA responses and cytotoxicity. These results indicated that TRPV1 activation caused cell death and tissue damage via the ER stress pathway, and provided novel insights into the mechanisms of how exogenous and/or endogenous TRPV1 agonists may affect lung cell pathophysiology.

7. Protective role of TRPV1

Several studies support the notion that activated TRPV1 elicits inflammation and cell injury in lung epithelial cells. Accordingly, inhibition of TRPV1 receptors has potential benefits to prevent certain pathological actions and toxicity [101]. However, more recently, counter-regulatory functions of TRPV1 have been described in an endotoxin-induced sepsis model in the TRPV1 knock-out mouse. In TRPV1 knock-

out mice after intraperitoneal injection of lipopolysaccharide (LPS), Clark et al. demonstrated enhanced hypotension, hypothermia and mediator levels in peritoneal exudates, which indicated a loss of protective effects [99]. Helyes et al. also investigated the role of TRPV1 in endotoxin-induced airway inflammation and subsequent bronchial hyperreactivity in TRPV1 knock-out mice using intranasal LPS administration. They showed that bronchial hyperreactivity, inflammatory indices (edema, inflammatory cell infiltration, goblet cell hyperplasia in airway) and myeloperoxidase activity were significantly greater in TRPV1 knock-out mice compared to wild type mice. Furthermore, these results were attenuated by the exogenous administration of somatostatin in TRPV1 knock-out mice [102]. Several studies have shown that somatostatin released from capsaicin-sensitive sensory nerve terminals reaches the circulation and elicits systemic anti-inflammatory effects [103-105].

Targeting TRPV 1 in the treatment of airway disease

Based on evidence suggesting that TRPV1 is a mediator for many lung pathologies caused by toxicants and endogenous agonists, and due to its central role in neurogenic inflammation, TRPV1 might be a good target for pharmacological intervention for pain, inflammation and preventing lung disorders [106, 107]. TRPV1 antagonists are under intense investigation in several animal models. Some pre-clinical studies suggest that TRPV1 antagonists may be useful as novel analgesic drugs, and may also be effective for bladder hyperactivity [106].

Chizh et al. reported the potential analgesic utility of the TRPV1 antagonist SB-705498 in men. They showed that orally administrated SB-705498 significantly reduced the area of capsaicin-evoked flare and elevated the heat pain threshold without any serious adverse events [104]. However, a more recent study revealed

that systemic use of the TRPV1 blockade AMG 517 elicited undesirable hyperthermia in susceptible individuals, which may limit its therapeutic use [108]. Also, AMG 517 has a long half-life in humans (13–23 days) [109]. Although the body temperature effects of TRPV1 blockade with a short half-life remain to be determined in humans, a short half-life compound may be more suited for clinical use. Or, there might be a place for anatomically-restricted administration of TRPV1 antagonists, either topically or by injection, that would prevent access to thermoregulatory visceral afferents [109, 110].

In respiratory medicine, pulmonologists have developed an interest in the possible role of the TRPV1 channel in respiratory diseases [111]. TRPV1 antagonists have potential indications for respiratory conditions, such as asthma, COPD and chronic cough [52]. However, a recent study showed the potential negative effects for therapeutic uses of TRPV1 antagonists in the lung. Johansen et al. found that prolonged treatment of BEAS-2B human bronchial epithelial cells with TRPV1 antagonists (LJO-328, SC0030 or capsazepine) for 24 hours significantly increased Ca^{2+} flux and cytokine gene expression (IL-6, IL-8), and cells exhibited greater cytotoxicity in response to the TRPV1 agonist nonivamide compared to cells that were not pre-treated with antagonists. However, TRPV1 mRNA levels in pre-treated cells showed no increase, and sensitisation was attenuated by brefeldin A (a Golgi transport inhibitor), but not by cycloheximide (a protein synthesis inhibitor) or by actinomycin D (a transcription inhibitor). These results suggest that the observed sensitisation of TRPV1 receptors by pre-treatment with a TRPV1 antagonist was probably due to an increased number of expressed receptors, which resulted from the translocation of existing receptors from the endoplasmic reticulum to the cell surface [112]. These results may add to our understanding of TRPV1 sensitization.

However, a previous study showed that expression of TRPV1 on epithelial cells was rare (< 1% of epithelial cells) in patients with cough [42], and there is no evidence that such a sensitization occurs for sensory nerves. Whether this phenomenon applies to other tissues or under *in vivo* conditions is unclear, but it warrants examination [113].

Conclusion

TRPs are ubiquitously expressed in tissues and organs, and they sense a diverse range of stimuli. TRPs are thought to play roles as intrinsic sensors of the cellular environment under normal and pathophysiological conditions. The cloning of TRPV1 in the last decade engendered a large amount of evidence that neurogenic inflammation may play an important role in the pathophysiology of pulmonary disease. Furthermore, it has stimulated studies revealing the roles for TRPV1 in respiratory medicine. Experiments that used selective receptor antagonists and targeted gene inactivation in mice have begun to reveal the essential mechanisms of TRPV channels. Still, however, only little is known regarding the precise role for TRPV1, especially in human airway diseases such as asthma or COPD. Ultimately, a better understanding of the mechanisms underlying TRPV1 activation and sensitisation will lead to the development of novel therapeutic strategies in the treatment of inflammatory diseases of the lung.

Conflict of interest

The authors declare no conflict of interest.

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Figure legend

Fig. 1 (A) Proposed tetrameric structure of transient receptor potential vanilloid 1 (TRPV1) in the plasma membrane. (B) Single-channel recordings after TRPV1 activation by capsaicin (*cap*, 100nM), heat (*44°C*) or protons (*pH 5.4*) at +40mV for the inside/out (protons) configuration. *Broken lines* indicate closed channel levels.

Figure 1: