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TRP Channels in Airway Sensory Nerves

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Abstract

Transient Receptor Potential (TRP) channels expressed in specific subsets of airway sensory nerves function as transducers and integrators of a diverse range of sensory inputs including chemical, mechanical and thermal signals. These TRP sensors can detect inhaled irritants as well as endogenously released chemical substances. They play an important role in generating the afferent activity carried by these sensory nerves and regulating the centrally mediated pulmonary defense reflexes. Increasing evidence reported in recent investigations has revealed important involvements of several TRP channels (TRPA1, TRPV1, TRPV4 and TRPM8) in the manifestation of various symptoms and pathogenesis of certain acute and chronic airway diseases. This mini-review focuses primarily on these recent findings of the responses of these TRP sensors to the biological stresses emerging under the pathophysiological conditions of the lung and airways.

Keywords

transient receptor potential channel; airway; lung; respiratory disease; vagus; C-fiber

1. Introduction

1.1. Airway sensory nerves

Activities of sensory nerves arising from the lung and airways are conducted in two separate neural pathways: 1) vagal nerves and their branches innervate the entire respiratory tract, from larynx, conducting airways to lung parenchyma, and project to the nucleus tractus solitarius in the medulla, and 2) sympathetic afferents innervate lung parenchyma, pulmonary vessels and pleural region, and travel via the white rami communicants to the dorsal root ganglia (DRG) of spinal cord cervical and thoracic segments. An important role of vagal bronchopulmonary afferents in regulating the functions of the respiratory system

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under both healthy and disease conditions has been extensively studied and well documented [1–3]. These afferents are grossly classified into three major subgroups: slowly and rapidly adapting receptors conducted by myelinated fibers, and bronchopulmonary C-fibers [1,4]. The primary function of these afferents is to maintain homeostasis by regulating breathing pattern, bronchomotor tone and other essential cardiopulmonary functions. In comparison, transduction properties and regulatory functions of the sympathetic afferents are less clearly defined [2], and further investigations are warranted.

Another important function of vagal bronchopulmonary C-fibers and a subset of rapidly adapting receptors is to detect inhaled irritants and certain endogenous chemical substances; and elicit centrally mediated defense reflexes such as cough, mucous secretion and reflex bronchoconstriction [2,5]. In addition, intense or sustained stimulation of bronchopulmonary C-fibers by chemical irritants is known to evoke the release of neuropeptides including tachykinins and calcitonin-gene related peptide (CGRP) from their sensory terminals, which can in turn interact or act on a number of effector cells in the airways, trigger local “axon reflexes” and neurogenic inflammation resulting bronchoconstriction, protein extravasation, inflammatory cell chemotaxis [6]. These actions of tachykinins on airway functions are extensively documented in various airway diseases, but a marked difference in their potencies between different species has also been well recognized [6].

1.2. TRP channels in respiratory tract

The mammalian transient receptor potential (TRP) superfamily consists of 28 non-selective cation channels that can be divided into six subgroups on the basis of protein and nucleotide sequence homology: canonical (TRPC, 7 channels), vanilloid (TRPV, 6 channels), ankyrin (TRPA, 1 channel), melastatin (TRPM, 8 channels), polycystin (TRPP, 3 channels) and mucolipin (PRTML, 3 channels) families. Each of them contains six transmembrane spanning regions (S1–S6) with a pore-forming loop between S5 and S6 regions [7,8]. They are expressed in various cell types of the mammalian organ systems and also located in the plasma membrane of a number of cell organelles (e.g., endoplasmic reticulum, etc.) [9]. In the respiratory tract, they are found in sensory nerves (e.g., TRPV1, TRPA1, TRPM8), airway and vascular smooth muscles (TRPV4, TRPC3 & C6), airway epithelial cells and capillary endothelial cells (TRPV1 & V4, TRPC6), fibroblasts (TRPV4, TRPA1), alveolar macrophages (TRPV2 & V4), and neutrophils (TRPV4) [8,10,11]. It is extensively documented that these TRP channels play an important role in detecting a diverse range of biological signals and regulating the function of these cells.

Upon activation of TRP channels in the airway sensory nerves, the influx of cations can generate depolarization of the neuronal membrane leading to activation or inactivation of voltage-gated ion channels, and modulate the cell excitability. Increasing evidence continues to reveal the important biological properties and functions of these TRP channels, their involvements in regulating the physiological responses to various physicochemical stresses, and the up-regulation of their sensitivity and expression during airway inflammation.

Several comprehensive reviews of the roles of TRP channels as therapeutic targets in respiratory diseases have been published in the last decade [8,11–14]. In view of increasing new findings on the following TRP channels: TRPV1, TRPV4, TRPA1 and TRPM8, this

brief review will focus specifically on their respective roles in the neural control of airway functions. Particular emphases have been given to their potential involvements in the development of pathophysiological conditions in the lung and airways.

2. TRP channels expressed in airway sensory nerves

The cell bodies of vagal sensory neurons innervating the respiratory tract are located in two separate but adjacent vagal sensory ganglia: nodose and jugular ganglia. It has been clearly documented that the neurons within these two ganglia are of different embryological origins and distinct phenotypes, including the differences in their distributions in the lung and airway structures and expression of TRP channels [3]. An in-depth review of this important and complex subject is presented in another article by Taylor-Clark et al. in this special issue and therefore not included in this mini-review.

2.1. TRPV1

TRPV1 is recognized as a “molecular gateway” to nociceptive sensation in somatic and visceral tissues and can be activated by a wide range of nociceptive chemical (e.g., acid), physical (e.g., heat) and biological stimuli (e.g., capsaicin) [8,15].

In the respiratory tract, although the expression of TRPV1 is also found in other cell types such as airway epithelial cells [16] and airway smooth muscles [17], TRPV1 is predominantly expressed in the sensory nerves, particularly in the C-fibers that represent a majority (>70%) of the vagal bronchopulmonary afferents [18]. In fact, TRPV1 is known as a reliable biomarker for identifying the C-fiber sensory neurons [2,19]. Indeed, one of the most distinct characteristics of these C-fiber afferents is their exquisite sensitivity to capsaicin, the pungent extract of hot peppers and a selective and potent activator of TRPV1 [15,19]. In contrast, their myelinated counterpart of the vagal pulmonary afferents, slowly and rapidly adapting receptors, exhibit either no or negligible sensitivity to capsaicin when the reflex contraction of airway smooth muscles is prevented in intact animals under normal condition [2,19].

TRPV1 is a polymodal transducer that can be activated directly or indirectly by a number of endogenous chemical substances such as hydrogen ion [20], anandamide [21,22], bradykinin [23], lysophosphatidic acid [24] and lipoxygenase metabolites [25]. TRPV1 can also detect physicochemical perturbations in the airway tissues; for example, TRPV1 expressed in the respiratory tract are extremely sensitive to a slight increase (Δ = ~3 °C) in tissue temperature within the normal physiological range [26,27]. More recent studies further revealed that TRPV1 and TRPA1 can be activated by air borne particulate matters [28,29] and volatile anesthetics such as isoflurane [30]. The superficial and strategic locations of these TRPV1-expressing sensory terminals in the airway mucosa [31] render them an important sensor to detect inhaled chemical irritants and elicit the protective airway reflexes.

Bronchial hypersensitivity, characterized by exaggerated sensory (e.g., airway irritation) and reflex mediated responses (e.g., cough, bronchoconstriction) to inhaled irritants and certain endogenous inflammatory mediators, is a prominent pathophysiological feature in patients with airway inflammatory diseases such as asthma. Increasing evidence reported in recent

studies suggested a pivotal role of TRPV1 in the manifestation of various symptoms of bronchial hypersensitivity in these patients [32–34]. For example, certain endogenous TRPV1 activators such as H^+, lipoxygenase metabolites (e.g., 12S- and 15S-hydroperoxyeicosatetraenoic acid), bradykinin and sphingosine-1-phosphate are consistently detected in the bronchoalveolar lavage fluid, sputum and/or exhaled breath condensate of patients with asthma [9,25,35–38]. Cough sensitivity to TRPV1 activators was markedly elevated in patients with asthma or other airway inflammatory diseases [39,40]. Furthermore, certain endogenous inflammatory mediators and cytokines (e.g., prostaglandin E_2, tumor necrosis factor α [TNFα], etc.), though not a TRPV1 activator themselves, can enhance the sensitivity of TRPV1 [34,41]; TRPV1 has several consensus phosphorylation sites that can be phosphorylated by protein kinases A (PKA), PKC and PKG, tyrosine kinase, etc. [41–44]. It is evident that TRPV1 functions not only as a transducer but also an integrator of biological actions generated by multiple endogenous activators and modulatory molecules.

Recent studies have further revealed that the allergic inflammation-induced airway hyperresponsiveness was associated with an enhanced bronchopulmonary C-fiber sensitivity to TRPV1 activators [45,46], accompanied by an upregulation of TRPV1 expression in Aδ vagal afferents of nodose ganglionic origin [46–48], mainly rapidly adapting receptors. As such, a near-threshold level of stimulation is expected to evoke a greater afferent discharge of bronchopulmonary C-fibers and consequently more intense sensory and reflex responses, resulting in bronchial hypersensitivity [34]. For example, a recent report showed that a slight increase in airway temperature triggered vigorous coughs and a transient bronchoconstriction mediated through cholinergic reflex pathway in patients with mild asthma, but not in heathy individuals [49].

2.2. TRPV4

TRPV4, originally identified as an osmosensor on mammalian cells [50], is now recognized as a molecule integrator of diverse stimuli [51]. It can be activated by physical stimuli including hypotonicity, moderate heat and shear stress, as well as a number of endogenous and exogenous chemical stimuli, such as acidic pH, anandamide, arachidonic acid metabolites, 4α-PDD and GSK1016790A [52]. TRPV4 is widely expressed in respiratory track, including vascular smooth muscle, endothelial cells, epithelial cells of alveoli, trachea and bronchi, and inflammatory cells such as macrophages and neutrophils [13,51]. Although TRPV4 mRNA has been detected in pulmonary sensory neurons [26], the functional expression of this TRP channel in vagal bronchopulmonary afferents and its role as a peripheral nociceptor in the lungs and airways are yet to be unequivocally defined.

In anesthetized rats, right atrial injection of selective TRPV4 agonist GSK1016790A evoked a slowly-developing rapid shallow breathing and an increased pulmonary chemosensitivity to capsaicin. The stimulating and sensitizing effects were abolished by sectioning and perineural capsaicin treatment of both cervical vagi, TRPV4 antagonist GSK2193874, or by systemic infusion of the COX inhibitor indomethacin. Surprisingly, patch clamp recordings showed that GSK1016790A or 4α-PDD failed to activate or sensitize isolated bronchopulmonary sensory neurons [53]. These results suggested that activation of TRPV4

regulated the respiration in rats through an indirect stimulation of vagal bronchopulmonary afferents, likely via the effect on other TRPV4-expressing cells, e.g., macrophages, epithelial or endothelial cells in the lungs and airways. Similarly, in a study of airway sensory nerves, Bonvini et al. [54] showed that TRPV4 agonists induced Ca^{2+} flux in guinea pig nodose ganglion neurons, depolarization of guinea pig, mouse and human vagus nerves, discharge of Aδ fibers (not C-fibers), and coughing in conscious guinea pigs. However, the single-cell RT-PCR study showed that TRPV4 was expressed on 1 out of 32 and 0 out of 32 guinea pig nodose and jugular ganglia neurons, respectively, suggesting that TRPV4 exerted its effects on accessory cells and acted on sensory neurons via an indirect mechanism. The study further proposed the TRPV4-ATP-P2X3 interaction as a key osmotic sensing pathway involved in airway sensory nerve reflexes [54].

2.3. TRPA1

TRPA1 is expressed in a sub-population of TRPV1-expressing airway neurons [55,56] (e.g., Fig. 1A), and is considered as the major airway irritant sensing receptor [57]. TRPA1 can be activated by cold temperature (< 17°), a wide range of pungent compounds and environmental irritants such as allicin, allyl isothiocyanate (AITC), cannabinoids, acrolein, ozone, formaldehyde, cinnamaldehyde, crotonaldehyde, commonly used tear gases, heavy metals zinc, cadmium and copper, and anesthetics isoflurane, lidocaine and nicotine [13,57,58]. It can also be activated by a variety of endogenous mediators such as hydrogen sulfide [59], reactive and electrophilic byproducts of oxidative (ROS), nitrative (RNS), and carbonilyc (RCS) stress [14,60,61]. A recent study demonstrated a direct interaction between diesel exhaust particles and airway C-fiber afferents in guinea pig and human vagus nerves that was mediated through an oxidative stress pathway and activation of TRPA1 channels expressed on these airway afferents [62]. In addition, TRPA1 has been suggested to play a crucial role in detection of lipopolysaccharides (LPS), a microbial signature molecule, by sensory neurons in flies and mammals [63].

2.4. TRPM8

TRPM8 is gated by cool and noxious cold temperatures, and can also be activated by the cooling compounds menthol, icilin, and eucalyptol [64]. It is predominantly expressed in a subset of primary afferent neurons within the DRG and trigeminal ganglia that are largely distinct from neurons expressing TRPV1 and TRPA1 [65,66]. The expression of TRPM8 in vagal bronchopulmonary sensory neurons seems relatively sparse. In a study of vagal afferent nerves innervating the mouse lungs, there was little evidence of TRPM8 expression [56]. In acutely dissociated vagal ganglion neurons innervating rat airways and lungs, 16% neurons expressed TRPM8 as demonstrated by both cold and menthol sensitivity [67]. Using an ex vivo rat lung preparation, another study showed that a similar small fraction (15.3%) of afferent nerves were activated by both cold temperature and menthol, but not a TRPA1 agonist, cinnamaldehyde [68]; this is an interesting distinction since TRPA1 can also be activated by either cold or menthol in vitro (57).

3. Interaction between TRP channels and its implications

As described above, a majority of these TRP channels are polymodal transducers; for example, TRPV1 can be activated by low pH, high temperature, anandamide, bradykinin and other endogenous inflammatory mediators; TRPA1 by various environmental chemical irritants, ROS, bradykinin and other inflammatory mediators; TRPV4 by hypotonicity, shear stress, anandamide, etc. As such, more than one TRP channels can be activated in the same cell by the same chemical mediator. Furthermore, because both TRPA1 and TRPV1 can be activated by a number of endogenous inflammatory mediators, it is highly probable that they can be activated simultaneously during airway inflammatory reaction. In addition, both TRPV1 and TRPA1 are abundantly and selectively expressed in vagal pulmonary C-fiber sensory nerves [56] (Fig. 1), and interestingly, their co-localization in the same cells increased from 55% to 80% in trigeminal ganglion neurons after a treatment of nerve growth factor [69]. More importantly, recent studies showed that simultaneous activations of TRPA1 and TRPV1 with their respective selective agonists at near-threshold concentrations evoked an abrupt and striking potentiating effect; this synergistic effect was clearly illustrated in both studies of vagal bronchopulmonary C-fiber recording in intact animals [70] and in isolated bronchopulmonary sensory neurons [71]. The synergism was completely abrogated in isolated neurons when Ca^{2+} was removed from the extracellular solution [71], suggesting an involvement of activation of certain intracellular signaling pathway(s) and molecule(s) initiated by the Ca^{2+} influx conducted through these channels (Fig. 2). Such an important role of intracellular Ca^{2+} as a mediator regulating the interaction between the TRPA1 and TRPV1 channels has been reported in the nociceptor neurons during acute inflammatory hyperalgesia [72,73], as illustrated in Fig. 2 [74].

A recent study further revealed that Tmem100, a two-transmembrane adaptor protein with a putative TRPA1 binding site at its C-terminus, can alter the physical association between TRPA1 and TRPV1, and thereby regulate the excitability of the TRPA1-TRPV1 heteromeric channel complex [75]. In the presence of Tmem100, the physical association between TRPA1 and TRPV1 was weakened and the sensitivity to TRPA1 agonist was enhanced in a TRPV1-dependent manner (Fig. 2C). Taken together, these findings suggest a potentially important role of the TRPA1-TRPV1 interaction in regulating the excitability and function of bronchopulmonary C-fiber sensory nerves during airway inflammatory reaction [70,71,74].

Both TRPA1 and TRPM8 can be activated by cold temperature, but at different temperature thresholds (25–28 °C in TRPM8 and 17 °C in TRPA1), in addition to their respective specific chemosensitivities. However, they are expressed in two distinct populations of sensory neurons in DRG [65]: TRPA1 is expressed in nociceptive neurons containing tachykinins, whereas TRPM8 does not co-express with tachykinins [76]. In addition, in rat DRG neurons all TRPM8-expressing cells also express TrkA, whereas the expression of TRPA1 is independent of TrkA expression [55]. Despite a lack of evidence of their co-expression in the same neurons, a selective activation of TRPM8 by menthol or eucalyptol, was able to inhibit or attenuate the irritant effect evoked by activating TRPA1 or TRPV1 in mice and in isolated murine DRG neurons, but the underlying mechanism was not entire clear [77].

4. Roles of TRP channels in pathophysiological conditions

4.1. Cough hypersensitivity

TRPV1.—The reproducible dose-dependent cough responses to inhalation of aerosolized capsaicin has been extensively reported in both animal and human studies, without serious short- or long- term side effects [78,79]; as such, capsaicin inhalation challenge has been commonly used for testing the cough reflex sensitivity in humans [80]. There is a significant correlation between cough sensitivity and the density of TRPV1-expressing nerves in the mucosa of chronic cough patients [17,81]. These observations led to the assumption of TRPV1 expressed in the airway sensory nerves is likely the cough sensor mediating the pathophysiological condition of cough hypersensitivity [82]. However, in clinical trial studies, despite the profound inhibitory effects the TRPV1 antagonists, SB-705498 and XEN-D0501, on capsaicin-evoked cough, neither of them has proven to be effective in the treatment of patients with refractory chronic cough [83,84]. These results raised the questions about the precise role of TRPV1 in the pathogenesis of refractory chronic cough and/or the possible involvements of multiple cough sensors in this disease.

TRPA1.—Activation of TRPA1 in airway sensory nerves can evoke cough in both animals and humans. Acrolein, cinnamaldehyde, crotonaldehyde and AITC have been shown to cause cough in guinea pigs [85,86]. Cinnamaldehyde induces a concentration-dependent cough response in human volunteers [85]. TRPA1 blockade diminishes these responses as well as the coughing induced by endogenous mediators PGE2 and bradykinin [87]. Citric acid–induced cough response is similarly alleviated by selective TRPA1 blocker [88]. Based upon these observations, TRPA1 was suggested as a promising target for developing therapeutic treatment for chronic cough [10,89]. However, collective data indicated a distinctly lower efficacy of its selective agonists (e.g., AITC or cinnamaldehyde) as a tussive agent in awake guinea pigs [86] and also a markedly lower potency as a stimulant of isolated airway sensory neurons [56] or bronchopulmonary C-fibers [70] than capsaicin, a selective agonist of TRPV1 (Fig. 1). Furthermore, the clinical trial of the selective TRPA1 antagonist, GRC 17536, has not yielded successful outcome in patients with chronic cough [90], once again illustrating the unpredictability of success in translating animal experimental data to human clinical trial outcome.

TRPM8.—Breathing cold air can provoke cough, airway constriction, mucosal secretion and trigger an asthma attack [91], such responses are thought to be mediated by vagal afferent nerves [92,93], and through the activation of TRPM8 channels [67,94]. However, TRPM8 agonist menthol has been widely used as antitussive treatment. It can inhibit citric acid induced cough [95], decreases capsaicin cough reflex sensitivity [96], and is often used for suppressing respiratory irritancy [8]. It is worth noting that menthol can also affect a number of other ion channel targets besides TRPM8 that could in part account for its inhibition of irritating sensations or cough (97). It has been proposed that the antitussive effect of menthol may result from TRPM8-dependent activation of nasal trigeminal, rather than vagal bronchopulmonary sensory nerves [66]. In a recent pilot clinical study, a TRPM8 agonist, AX-8, given as a lozenge significantly reduced cough frequency during waking hours in refractory chronic cough patients compared with baseline (no therapy),

accompanied by reductions in the patient-reported outcomes of cough severity, throat irritation and urge-to-cough [98].

4.2. Asthma

TRPV1.—Cumulative evidence have suggested potential involvement of TRPV1 in the pathogenesis of asthma. A general hypothesis has been as follows: inhaled irritants (e.g., acid) or endogenous TRPV1 activators (e.g., lipoxygenase metabolites) activate TRPV1 that are overexpressed and sensitized through intracellular pathways driven by inflammatory mediators, which leads to exaggerated TRPV1 activation and bronchopulmonary C- and Aδ-fiber discharges. The resulting various aspects of tachykinin-mediated “neurogenic inflammation” contribute to the manifestation of clinical features of asthma, including excessive cough [12,33]. Despite the extensive supportive results obtained from pre-clinical studies, the precise role of locally released tachykinins play in the pathogenesis of asthma and cough hypersensitivity remains uncertain as results obtained from clinical trials in testing the efficacy of tachykinin receptor antagonists have been largely either non-conclusive or disappointing [99,100].

In allergic animal models, pretreatment with capsaicin to degenerate airway TRPV1-expressing afferents inhibited allergen-induced bronchoconstriction in sensitized guinea pigs [101] and airway hyperresponsiveness in allergic rabbits [102]. Capsaicin pretreatment and depletion of sensory neuropeptides also inhibited inflammatory cells accumulation and airway hyperresponsiveness in a mouse model of non-atopic asthma [103]. An issue with the above mentioned studies is that they could not differentiate whether the effects are due to degeneration of TRPV1 channels specifically, or degeneration of all TRPV1-expressing sensory nerves [104], the subpopulation of which are known to also include TRPA1-expressing neurons [13,57]. Studies with TRPV1 antagonism supported an important role for TRPV1 in asthma. Two TRPV1 antagonists SB-705498 and PF-04065463 significantly inhibited airway hyperresponsiveness to histamine in ovalbumin (OVA)-sensitized guinea pigs [105]. In a mouse model of OVA-induced asthma, blocking the TRPV1 pathway by capsazepine or TRPV1 siRNA inhalation significantly alleviated airway hyperresponsiveness, allergic inflammation and airway remodeling [106].

TRPV4.—Activation of TRPV4 is known to cause bronchoconstriction, a key symptom of asthma [107], but the underlying mechanism is not yet clear. McAlexander et al. [108] demonstrated that TRPV4 agonist GSK1016790A produced a slow-onset, long-lasting contraction of guinea pig and human isolated airways. This contraction could be blocked by TRPV4 antagonist, but also by cysteinyl leukotriene (cystLT) antagonists and a 5 lipoxygenase inhibitor, indicating that the activation of TRPV4 did not induce airway smooth muscle contraction directly, and instead reliant upon the production of cystLT. A recent study by Bonvini et al. [109] further suggested that activation of TRPV4 induced release of ATP from airway smooth muscle cells which triggered P2X4-dependent release of cysteinyl leukotrienes from nearby mast cells and resulted in airway smooth muscle contraction. It would be interesting to examine whether this novel TRPV4-ATP-cystLT axis is also involved in the indirect stimulation of bronchopulmonary sensory nerves upon TRPV4 activation.

TRPA1.—Exposure to certain chemical irritants such as ozone [110] and toluene diisocyanate [111], which are now known to activate TRPA1, has been shown to produce asthma-like symptoms such as cough, dyspnea, wheezing and subsequent hypersensitivity to chemical, physical and/or electrical stimuli [112–114]. Indeed, TRPA1-activating stimuli such as chlorine, aldehydes, ROS, and scents are among the most prevalent triggers of asthma [115]. Acetaminophen, via its reactive metabolite N-acetyl-pbenzo-quinoneimine, was reported to induce airway neurogenic inflammation through TRPA1 activation and subsequent release of sensory neuropeptides substance P and CGRP. The responses were abated by TRPA1 antagonism and absent in TRPA1-deficient mice, indicating that TRPA1-dependent neuronal inflammation may contribute to the increased risk of asthma and other atopic and inflammatory conditions that are associated with acetaminophen consumption [116].

In a non-allergic mouse model of asthma, the induction of airway hyperresponsiveness without bronchial inflammatory cells by exposure to hypochlorite-OVA was shown to result from a neuroimmune interaction between sensory neurons and mast cell activation which was significantly reduced in TRPA1-deficient mice [117]. In an OVA-induced mouse model of allergic asthma, the allergen-induced leukocyte infiltration, cytokine and mucus production as well as airway hyperreactivity were significantly attenuated in TRPA1-deficient mice or wild-type mice treated with TRPA1 inhibitor HC-030031 [115]. In both cases, the neuronal expression of TRPA1 channels was most probably responsible for disease symptoms [11]. The TRPA1-dependent airway inflammation shown in mouse OVA model of asthma has been reproduced in recently developed TRPA1-deficient rats [118].

TRPM8.—A TRPM8 gene polymorphism is positively associated with cold-evoked airway hyperresponsiveness, a characteristic feature of bronchial asthma [119]. TRPM8 is also responsible for cold-induced mucus hypersecretion through Ca2+- PLC-PIP2-MARCKS signaling pathway [120]. TRPM8 seems also contribute to airway inflammatory responses due to the activation of this channel in non-neuronal cells in the respiratory tract. The expression of TRPM8 in human bronchial epithelial cells is well established [120,121], activation of which by cold or menthol increases the expression of many pro-inflammatory cytokines, an effect inhibited by nonselective TRPM8 antagonist BCTC, and siRNA knockdown [122]. A recent in vitro study [123] demonstrated that the extracts of menthol cigarette smoke induced greater reactive oxygen species-sensitive, TRPM8-mediated, mitogen-activated protein kinase (MAPK) - dependent inflammatory responses in human lung epithelial cells, than those of non-menthol cigarette smoke. A follow up study [124] further showed that sub-chronic exposure in mice to menthol cigarette smoke induced greater TRPM8-mediated activation of MAPKs and lung inflammation than that to non-menthol cigarette smoke. The augmented inflammatory effects likely resulted from menthol-evoked additional stimulation of TRPM8 channels on lung epithelial cells. Furthermore, TRPM8 is expressed in mast cells, where it has been implicated in cold- and menthol-elicited histamine release [125], which offers an alternative explanation for the involvement of TRPM8 in the menthol- and cold-induced airway allergic and inflammatory responses.

4.3. COPD

The involvement of TRP channels in the development of COPD has been suggested [11,14]. TRPV1 and TRPV4 mRNA levels were increased in lung tissue samples from patients with COPD, and cigarette smoke exposure–induced ATP release from primary bronchial epithelial cells was attenuated by blockers of both TRP channels [126]. Polymorphisms in the TRPV4 gene have been associated with COPD [127]. Tiotropium, a drug widely prescribed for its bronchodilator activity in patents with COPD and asthma, inhibited neuronal TRPV1-mediated effects in guinea pigs through a mechanism unrelated to its anticholinergic activity [128].

Recent evidence indicates that TRPA1 could be the primary TRP channel implicated in the pathogenesis of COPD [129]. TRPA1 is a major neuronal sensor of oxidative stress, which is known to be substantially increased in COPD [130]. The vast majority of COPD patients are smokers. Crotonaldehyde, α,β-unsaturated aldehydes and acrolein contained in cigarette smoke, the major causative factor of COPD, cause irritation and inflammation in the respiratory tract, via activation of TRPA1 [73,131]. Cigarette smoke extract increases TRPA1 expression and induces IL8 release in human bronchial epithelial cells, the latter can be attenuated by TRPA1 inhibitor HC-030031 or TRPA1 siRNA [132]. Nicotine, the major chemical constituent of cigarette smoke, has also been reported to activate TRPA1 directly; however, this action required a concentration of nicotine much higher (>100 folds) than that delivered by cigarette smoke [133,134].

Exposure to biomass fuels and biomass smoke is also a risk factor for COPD development [11,135]. Wood smoke particulate matters has been shown to cause calcium influx in trigeminal sensory neurons through TRPA1 activation [136]. Diesel exhaust particles activate TRPA1 channels in airway C-fiber afferents in guinea pig and human vagus through an oxidative stress pathway [62]. Ample evidence suggests that TRPA1 antagonism might be a promising option in clinical management of COPD [89].

4.4. Airway viral infection

In addition to the injury of alveolar walls and lung parenchyma cells, respiratory viral infection induces inflammatory reaction in the airway mucosa that is densely innervated by TRPV1-expressing sensory nerves [31], which can lead to the development of airway hypersensitivity. Indeed, cough sensitivity to inhalation of TRPV1 activators, capsaicin or citric acid aerosol, was markedly elevated in patients during and recovering from upper respiratory infection [39,40]. The evidence of a pronounced upregulation of TRPV1 expression was found in the airway mucosa of patients with chronic cough during recovery from respiratory tract infections caused by rhinovirus, respiratory syncytial virus and measles virus [81,137,138]. In addition, the viral infection increased the tachykinin synthesis in C- and Aδ-fiber airway afferents and upregulated the neurokinin receptor expression on the target cells in the lung [139–141]; it also inhibited the preganglionic muscarinic M2 autoreceptors in the airways [142]. Together, they augmented the reflex bronchoconstriction mediated through both cholinergic and tachykininergic mechanisms as well as the cough responsiveness to TRPV1 activation.

In the current pandemic of coronavirus (COVID-19) infectious diseases, one of the major causes of mortality is respiratory failure [143]; possible involvements of abnormal function of TRPV1 and TRPV4 in the development of lung dysfunction have been suggested [144,145]. The “cytokine storm”, a primary pathogenic factor of acute respiratory distress syndrome (ARDS) and multiple organ failures in COVID-19 patients, is triggered by a dysregulated and severe immune reaction as indicated by excessively high levels of inflammatory markers and cytokines in the plasma [146,147]. Some of these endogenous mediators (e.g., prostaglandins, leukotrienes) and cytokines (e.g., TNFα, interleukin-1β) are known to activate pulmonary C-fibers [148–151] via sensitization or direct stimulation of TRPV1 receptors [149–150], which in turn leads to airway constriction, increased alveolar capillary permeability and inflammatory cell chemotaxis through both centrally-mediated and local axon reflexes [2].

TRPV4 is also abundantly expressed on alveolar epithelial and capillary endothelial cells (Section 2.2). A recent clinical trial phase-1 study has demonstrated effective protective actions of the TRPV4 inhibitor in the treatment of cardiogenic pulmonary edema [152], suggesting a possible role of TRPV4 in regulating the integrity of the alveolus/capillary barrier [153,154]. In view of the fact that a disruption of the alveolus/capillary barrier integrity can lead to alveolar edema and other serious detrimental consequences of the ARDS, it seems plausible that a selective TRPV4 antagonist may provide a potentially effective therapeutic action on the alveolar edema caused by COVID-19 infection [144].

5. Conclusion

The new information obtained from these recent studies has provided valuable insights and broadened our knowledge about the potential involvements of these TRP channels in the development of certain pathophysiological conditions in the lung and airways, but many important and challenging questions still remain. First and foremost, it is imperative that these new findings be tested in clinical trial studies to further evaluate their significance and impact on developing the new therapeutic strategies for treating patients with these respiratory diseases.

It is well documented that TRP sensors are also expressed in a wide spectrum of non-neuronal cells in the respiratory tract as described earlier (Section 1.2.). Although their actions and interactions with sensory neurons are beyond the scope of this brief review, existing evidence clearly indicates their important roles in regulating the overall function of airway nervous system under both normal and pathophysiological conditions, which cannot be overlooked. For example, it is well recognized that both nervous and immune systems are the cornerstones of the important pulmonary defense function. Despite the clear evidence of expression of various TRP channels (e.g., TRPC1, TRPC3, TRPA1, TRPV1, TRPV4) in a number of immune and inflammatory cells (T-cell, B-cell, mast cell, neutrophil, macrophage, etc.) [155,156], the role of these TRP channels in modulating the interaction between neural and immune cells and thereby regulating the function of pulmonary defense mechanisms is certainly very important and requires further investigations.

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Highlights

- Transient Receptor Potential (TRP) channels expressed in airway sensory nerves function as transducers and integrators of a diverse range of sensory inputs including chemical, mechanical and thermal signals.
- These TRP sensors are extremely sensitive to inhaled irritants as well as endogenously released chemical substances.
- They play an important role in generating the afferent activity carried by these sensory nerves and regulating the centrally mediated pulmonary defense reflexes.
- This review focuses primarily on the recent findings of the responses of these TRP sensors to the biological stresses emerging under the pathophysiological conditions of the lung and airways.

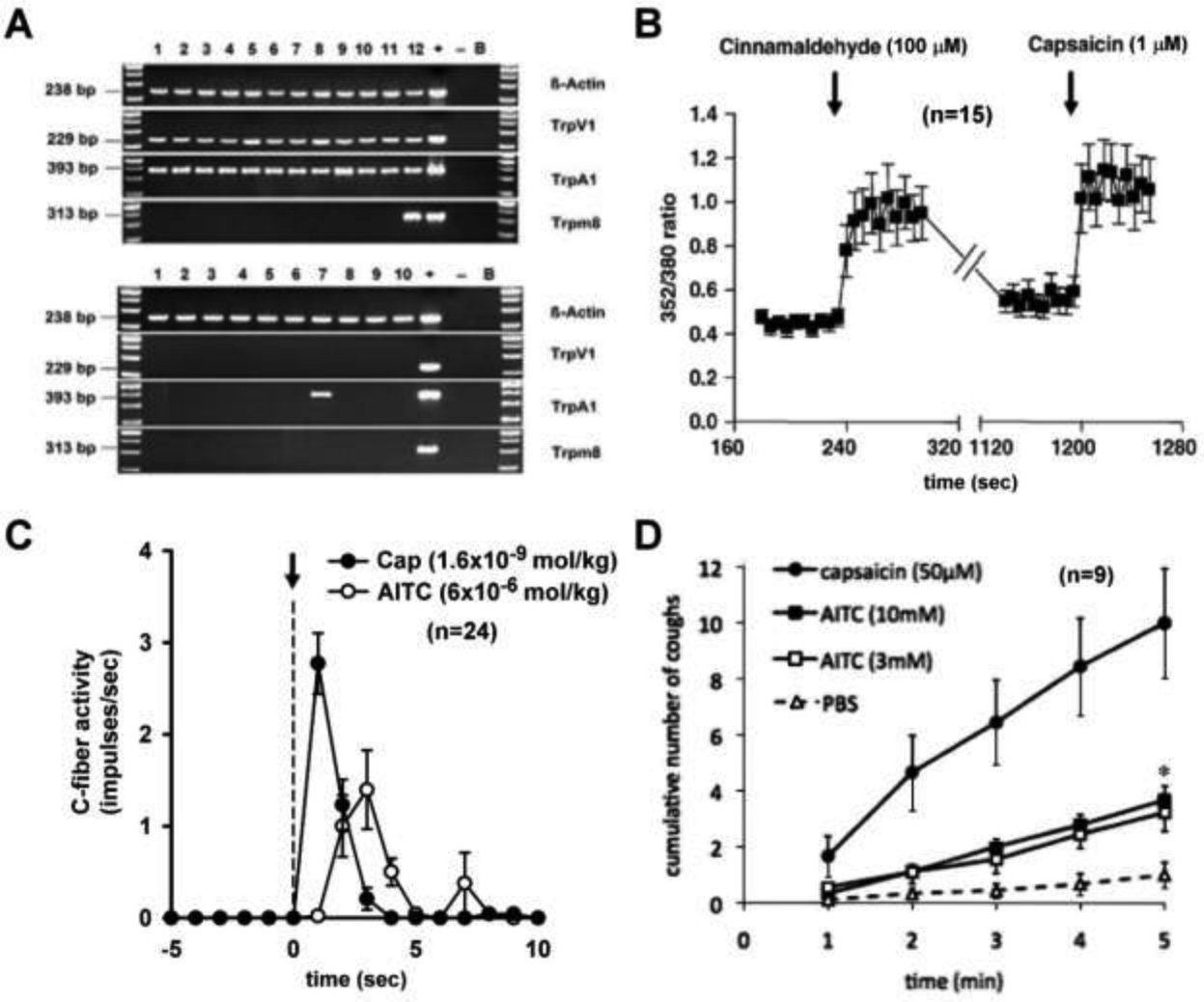

Fig. 1. Co-expression of TRPV1 and TRPA1 in airway sensory neurons and a comparison of neural and cough responses to their respective agonists.

A: Single cell RT-PCR of TRPV1+ (top) and TRPV1− (bottom) mouse jugular/nodose cells retrogradely labelled from the lung and airways. Samples in which the reverse transcriptase was omitted ('−') served as negative control. cDNA obtained from a whole jugular/nodose ganglion served as positive control ('+'); B: bath solution was used as a template. ***B***: Effect of cinnamaldehyde and capsaicin, selective agonists of TRPA1 and TRPV1, respectively, on intracellular $[Ca2+]_{free}$ (expressed as 352/380 ratio) in dissociated DiI-labelled jugular/nodose neurons from mouse lung. ***C***: Responses of pulmonary C-fibers activity to intravenous injections (dashed line) of allyl isothiocyanate (AITC; ave 6×10^{-6} mol/kg), a selective agonist of TRPA1, and capsaicin (Cap; ave 1.6×10^{-9} mol/kg) in anesthetized rats. Note that the potency of the stimulatory effect of Cap on bronchopulmonary C-fibers is >1000-fold higher than that of AITC. ***D***: Time course of the cough induced by inhalation of AITC and capsaicin (paired study, n=9) in awake guinea pigs. Note that increasing the concentration of AITC from 3 mM to 10 mM did not further increase cough frequency, indicating that the maximally effective concentration of AITC was attained; AITC (10 mM) was significantly less effective in inducing cough than capsaicin (50 μM); *, P<0.05, Cap vs

AITC. Data are means ± SEM; n is shown in each panel. (***A***&***B***, ***C*** and ***D*** modified from references 56, 70 and 86, respectively)

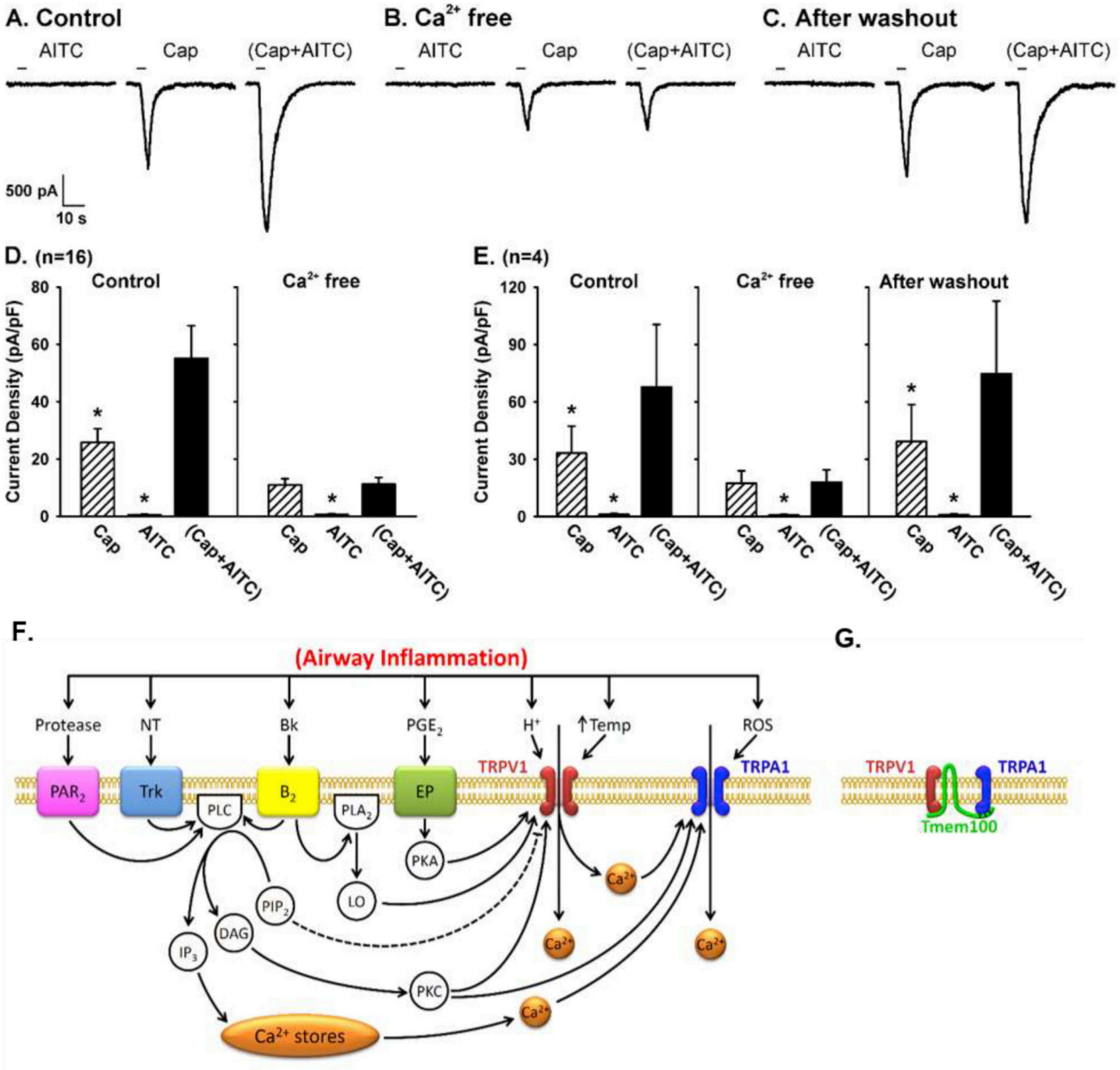

Fig. 2. Synergistic effect of simultaneous activations of TRPA1 and TRPV1 channels in pulmonary sensory neurons.

A: experimental records illustrating the positive interaction of TRPA1 and TRPV1 channels during control in a jugular neuron (27.4 pF). ***B***: the positive interaction was completely abolished after the same neuron was perfused by Ca^{2+}-free ECS for 10 min. ***C***: the positive interaction returned after the same neuron was perfused by regular ECS again for 20 min. ***D***: group data of the responses (n=16) when neurons were perfused with regular ECS (Control) and Ca^{2+}-free ECS, respectively. ***E***: in 4 of these 16 neurons, group data were also obtained after the Ca^{2+}-free ECS was washed out. Data are means ± SEM. *, significantly ($P < 0.05$) different from the response to (Cap+AITC). ***F***: hypothesized mechanisms involved in the TRPA1-TRPV1 interaction in pulmonary sensory neurons during airway inflammation.

Dashed line depicts an inhibitory pathway. Bk, bradykinin; B_2, bradykinin B_2 receptor; DAG, diacyglycerol; EP, prostanoid EP receptors; IP_3, inositol 1,4,5-triphosphate; LO, lipoxygenase products; NT, neurotrophins; PAR_2, protease-activated receptor-2; PGE_2, prostaglandin E_2; PLC, phospholipase C; PLA_2, phospholipase A_2; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; ROS, reactive oxygen species; Temp, temperature; Trk receptors, tryosine receptor kinase receptors A and B. ***G***: potential physical interaction between TRPA1 and TRPV1 subunits in a heteromeric A1/V1 channel complex; Tmem100, a two-transmembrane adaptor protein. (***A***-***E*** and ***F***-***G*** are modified from references 71 and 74, respectively)