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REVIEW

Transient receptor potential channels as potential drug targets in respiratory diseases

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A subpopulation of nociceptive primary sensory neurons expresses six different transient receptor potential (TRP) ion channels of the vanilloid (V1, V2, V3 and V4), melastatin (M8) and ankyrin (A1) subtypes. TRPV1 mediates the tussive action of capsaicin, which is widely used in cough provocation studies. The upregulation of TRPV1 expression and function has been reported in asthma and other inflammatory conditions. TRPA1 is targeted by a series of byproducts of oxidative and nitrative stress, including acrolein, 4-hydroxy-2-nonenal and hydrogen peroxide. Proinflammatory neuropeptides are released from nociceptive nerve terminals after TRPV1/TRPA1 stimulation, thereby causing airway neurogenic inflammation. In addition, the early inflammatory response to cigarette smoke is mediated entirely by neuronal TRPA1. TRPV1 and TRPA1 antagonists may therefore represent potential antitussive and anti-inflammatory therapeutics for respiratory airway diseases.

Keywords Airway, antitussive, anti-inflammatory, calcitonin gene-related peptide, drug target, respiratory disease, substance P, transient receptor potential channel, TRP channel, TRPA1, TRPV1, .

Introduction

A dense sensory innervation, originating from both trigeminal and vagal ganglia, supplies the upper and lower airways from the nose to the bronchioles. A portion of these neurons (50% in rodents) with unmyelinated C or scarcely myelinated A-δ fibers are sensitive to capsaicin, the principal active component in plants of the genus *Capsicum*. A proportion of capsaicin-sensitive sensory neurons contains the neuropeptides calcitonin gene-related peptide (CGRP) and the tachykinins substance P (SP) and neurokinin A (NKA). These neuropeptides are released from central and peripheral terminals of capsaicin-sensitive neurons, thus contributing to pain transmission and to neurogenic inflammation. Capsaicin and other capsaicinoids excite sensory neurons by activating the transient receptor potential vanilloid 1 (TRPV1) [1], which belongs to the TRP ion channel superfamily [2,3]. Resiniferatoxin, noxious temperatures (> 42°C), low extracellular pH, anandamide, *N*-arachidonoyl-dopamine, certain eicosanoids and other agents [4-7] also activate TRPV1. In addition to TRPV1, capsaicin-sensitive primary sensory neurons express a variety of ion channels and receptors on their plasma membranes with excitatory and inhibitory functions that regulate neuronal activity. Activation of excitatory channels causes irritation and pain, generates protective reflex responses, and promotes neurogenic inflammation. This review focuses on the functions of excitatory TRP channels expressed in primary sensory neurons of the respiratory tract, and on the role of these channels in health and diseases. The potential of drugs that target TRP channels as new medicines to treat inflammatory airway diseases and cough is also addressed.

TRP channels, primary sensory neurons and neurogenic inflammation

Vascular neurogenic inflammation encompasses arterial vasodilatation (mediated by CGRP and the calcitonin receptor-like/receptor activity-modifying protein [CL/RAMP1] receptor), as well as plasma protein extravasation in, and leukocyte adhesion to, the vascular endothelium of postcapillary venules (both mediated by the SP/NKA and NK1 receptors). Extravascular neurogenic inflammation in mammal airways includes trachea or bronchial smooth muscle contraction (mediated by the SP/NKA and NK2 receptors), mediator release from the airway epithelium, and secretion of mucus from airway glands (both mediated by the SP/NKA and NK1 receptors) [8]. Exogenously administered tachykinins, mainly acting ~~hrough~~ the NK2 and NK1 receptors, have been demonstrated to contract human airways both *in vitro* and *in vivo* [9,10]. However, there is no evidence that

endogenous tachykinins contract human airways. The activation of additional TRP channels, namely the TRPV2, TRPV3, TRPV4 and TRP ankyrin 1 (TRPA1) channels, may cause protective reflex responses, nociceptive behavior and neurogenic inflammation, because these channels are co-expressed by neuropeptide-containing and TRPV1-expressing sensory neurons [11-16]. In contrast, the TRP melastatin 8 (TRPM8) channel, which is activated by menthol and moderately low temperatures, is expressed by a different and TRPV1-negative neuronal subpopulation [12]. The TRPV2, TRPV3 and TRPV4 channels are gated by warm, non-noxious and noxious temperatures and by small reductions in tonicity. No evidence has yet been provided that these channels play a major role in inflammation and tissue injury in the respiratory system, but recent findings demonstrating that TRPV2 participates in early phagocytosis by macrophages [17] highlight a fundamental function in innate immunity for the TRPV2 channel expressed in non-neuronal cells. TRPA1, which is activated by isothiocyanate, thiosulfinate and cinnamaldehyde compounds that are the pungent ingredients present in mustard, garlic and cinnamo n, respectively [18-22], is rapidly gaining research interest as a primary proinflammatory mechanism in models of airway diseases [23,24].

The efferent and afferent functions of TRPV1-positive airway primary sensory neurons

The administration of capsaicin to guinea pigs causes bronchoconstriction, plasma protein and neutrophil extravasation, and cough ~~via~~ the activation of TRPV1, which is expressed by a dense network of subepithelial peptidergic sensory neurons [25]. Some of these responses are generated locally, produced by a calcium-dependent neurosecretion from peripheral sensory nerve terminals of tachykinins or CGRP, both of which activate specific receptors on smooth muscle, endothelial or other effector cells directly. Additional responses are generated by reflex mechanisms ~~via~~ the stimulation of TRP channels. These responses include cholinergic bronchoconstriction, secretion from seromucous glands, and cough. Notably, several of these reflex responses have also been documented in humans [26]. The ability of capsaicin to contract isolated human bronchi, which then undergo rapid tachyphylaxis, has been reported; however, the neurogenic nature of this response remains undetermined [27]. However, the pronounced effect of antagonists of the tachykinin NK2 and, in part, NK1 receptors in inhibiting SP/NKA-mediated bronchoconstriction in humans [10] has been associated with negative reports on the potential of these compounds to reduce bronchoconstriction in asthma provocation tests [28,29], thus limiting the initial enthusiasm for this class of drugs. One possible explanation for the diversity observed between guinea pig and human bronchi is that tachykinins are not released in sufficient amounts or at the correct anatomical site in humans to produce effects similar to those observed in rodents.

In contrast to the differing responses produced by activation of the efferent function (neuropeptide release) of airway terminals of primary sensory neurons in experimental animals and humans, cough evoked by capsaicin in guinea pigs demonstrates close similarities with the tussive response observed in healthy humans. The site of action of capsaicin-evoked cough in humans was initially identified to be localized to nerve terminals situated in the larynx [30]. However, more recent evidence suggests that the distribution of capsaicin aerosols is diffuse, located in both the central and peripheral airways [31]. Regarding the type of receptors responsible for capsaicin-evoked cough, rapidly adapting receptors (RARs) that conduct action potentials in the A-δ range have been demonstrated to respond to capsaicin or PGE_2 in cats *in vivo* [32]. In contrast to these findings, in a different experimental paradigm, RARs appeared to be unaffected by bradykinin or capsaicin, both of which can stimulate C-fibers, characterized by a high threshold for mechanical stimulation [33]. However, a distinction between aspiration-induced cough (evoked by rapidly adapting touch-sensitive A-δ fibers) and the itchy urge-to-cough that can be evoked by the stimulation of vagal C-fibers by capsaicin may be simplistic. In fact, interactions between these cough pathways have been described, as the selective stimulation of C-fibers could sensitize A-δ fibers to initiate the cough reflex in guinea pigs [34]. In addition, hypertonic saline-induced cough appears to be independent from TRPV1 [35,36], whereas citric acid-evoked cough, which can be inhibited by the TRPV1 antagonists capsazepine or iodo-resiniferatoxin, is likely mediated by TRPV1 channel activation [36,37]. Additional mechanisms, including activation of acid-sensing ion channels (ASICs), can contribute to acidic media-induced cough [38]. Thus, evidence gained from experimental animals and humans suggests that TRPV1 plays a major role in the mechanism that initiates the cough reflex. The TRPM8 receptor, which is not co-expressed in TRPV1-positive neurons, may subserve different or even opposing functions, including the paradoxical inhibition of the tussive response [39]. The other TRP channels (ie, TRPV2, TRPV3, TRPV4 and TRPA1) present in TRPV1-sensitive neurons might also theoretically contribute to the cough response [3]. However, this role has been corroborated only for TRPA1 by experimental evidence [40,41].

Modulation of TRPV1, TRPA1 and their putative endogenous stimulants in the airways

Although TRPA1 was originally cloned in human lung fibroblasts [42], and has been reported to be present in airway epithelial cells [43], functional TRPV1 and TRPA1 channels have only been described in sensory nerve terminals. Accordingly, the description herein is

limited to the neuronal function of these two channels. Of relevance is the observation that, under inflammatory conditions, the TRPV1 receptor is activated and the expression of several mRNAs and proteins are upregulated, including nerve growth factor (NGF) [44], bradykinin [44,45], protease-activated receptor 2 (PAR2) agonist peptides [46,47] or prostanoids [45,48]. All of these mediators or receptors have been proposed to play a role in the mechanism of asthma and other airway inflammatory diseases. In addition, exogenous stimuli may also cause TRPV1 sensitization, thereby potentiating channel-mediated responses. For example, ethanol reduces the threshold temperature for TRPV1 activation from ~~42°~~ [1] to 34°C [49], consequently resulting in the stimulation of neuronal TRPV1 at normal body temperatures. In the airways, this effect of ethanol results in the complete induction of the repertoire of neurogenic inflammatory responses [35], including cough [50]. These findings may explain the still poorly understood clinical entity defined as ethanol-induced asthma [51], and are consistent with the recent report that inhalation of ethanol in patients with sensory hyper-reactivity (SHR), but not in healthy individuals, increased the cough response to capsaicin [52].

Various pollutants have been demonstrated to activate or sensitize TRPV1-mediated responses, including those evoked by subacute exposure to sulfur dioxide [53] or the malodorous gas and endogenous mediator hydrogen sulfide [54,55]. The eicosanoid 20-hydroxy-eicosatetraenoic acid (20-HETE), a product of cytochrome P450 ω-hydroxylase, is another endogenous mediator that has emerged as a potential TRPV1 agonist with a bronchoconstrictor action [56]. Furthermore, TRPV1-positive nerve fibers, but not protein gene product 9.5 (~~Pgp 9.5~~)-positive nerve fibers (~~Pgp 9.5~~ is a non-specific marker that labels all nerve fibers), were increased in airway epithelium from patients with chronic cough, and this increase correlated with an enhanced tussive response to capsaicin [57]. While individual endogenous agonist levels may be insufficient to activate TRPV1, the combination of different stimuli (eg, low extracellular pH, anandamide, *N*-arachidonoyl dopamine or various eicosanoids) with the contribution of sensitizing pathways (eg, the bradykinin pathway) might lead to channel activation [58]. However, there is no evidence that endogenous activators of TRPV1 alone or in combination may reach the concentrations required for TRPV1 activation at sites of inflammation. Accordingly, the role of TRPV1 antagonists in the treatment of inflammatory diseases and chronic cough requires further investigation.

TRPA1 is also present in airway sensory nerves, and is co-expressed with TRPV1 [24]. Studies undertaken in the past several years have demonstrated that TRPA1 acts as a sensor of oxidative and nitrative stress, and can be activated by a variety of byproducts of reactive oxygen species (ROS). These ROS molecules not only include the metabolites of plasma membrane phospholipids, 4-hydroxy-2-nonenal (HNE) and acrolein, but also hydrogen peroxide, nitrolenic acid, cyclopentenone prostaglandins and isoprostanes [58-60]. TRPA1 activity is upregulated by PAR2 activation via a phospholipase C (PLC)- and phosphatidylinositol 4,5-bisphosphate (PIP_2)-dependent pathway [61], or by the bradykinin B_2 receptor via PLC- and protein kinase A (PKA)-dependent pathways [62]. Thus, the observation that HNE is present in millimolar concentrations in the lungs of patients with COPD [63] emphasizes the possibility that one or more of the putative endogenous TRPA1 agonists are encountered at sites of inflammation or tissue injury in concentrations exceeding those required for the activation of neuronal TRPA1.

Sneezing, cough and TRPV1

Sneezing and cough produced by TRPV1 agonists is well described in humans [64]. Several studies suggest that inflammation specifically enhances the reflex response mediated by the capsaicin (TRPV1) receptor. For example, the reduced threshold for capsaicin-evoked cough in a large series of inflammatory airway diseases, including asthma, cough-variant asthma, interstitial lung disease (ILD), rhinitis and COPD [65,66], highlights the importance of TRPV1 as a marker of airway inflammation. Capsaicin (TRPV1)-evoked cough has been demonstrated to be insensitive to bronchodilators [31]. In addition, patients with upper respiratory tract infections (URTIs) demonstrated a selective potentiation of their sensitivity to cough by inhaled capsaicin [67]. Patients treated with angiotensin-converting enzyme inhibitors who developed a dry, persistent cough also exhibited an increased and selective sensitivity to cough in response to capsaicin [68]. However, in patients with cough induced by asthma, gastroesophageal reflux disease (GERD), or rhinitis-specific treatment of the underlying disease, the capsaicin response was diminished [69]. Collectively, these findings support the intriguing hypothesis that TRPV1 antagonists may be effective medicines for the treatment of chronic cough.

Repeated topical application of capsaicin results in transient sensory nerve function impairment [70,71] and diminished pain perception from the skin area affected by a painful condition [72]. Although a topical route of administration, which is ideal for the treatment of skin conditions, does not appear feasible in the lower airways because of the intrinsic irritant potential of capsaicin, this route of administration has been exploited successfully in the nasal mucosa, which contains a dense sensory innervation network in both rodents and humans [73]. Indeed, pain, sneezing and nasal secretion are produced by topical capsaicin administered to the noses of both rodents and humans [74,75].

Following a pioneering study demonstrating the feasibility of human nasal mucosa desensitization after repeated topical capsaicin applications [75], the beneficial effects of this treatment were reported in patients with perennial rhinitis, variably defined as either vasomotor

rhinitis [76,77] or chronic rhinitis [78]. An augmented pain response to capsaicin suggests that sensory nerve hyper-responsiveness may characterize allergic airway diseases. Mechanistic studies have suggested a role for sensory nerve activation in models of asthma [79] and allergic rhinitis [80]. However, a recent meta-analysis collected insufficient data to assess the use of capsaicin for allergic rhinitis in clinical practice [81].

Cigarette smoke, oxidative stress, mechanosensation and TRPA1

Sensory nerves and neurogenic inflammation contribute to acute inflammatory and defensive responses in a variety of models of airway disease. For example, cigarette smoke is the major causative agent of COPD. A seminal study by Lundberg and Saria demonstrated that the early inflammatory response to cigarette smoke inhalation is mediated entirely by a neurogenic mechanism [82]. However, a subsequent study clarified that the response was independent of TRPV1 [8]. Only after 25 years of research, and by selectively stimulating the TRPA1 channel co-expressed with TRPV1 on sensory nerve endings, were the two major α,β-unsaturated aldehydes (ie, crotonaldehyde and acrolein) contained in cigarette smoke demonstrated to be responsible for the bronchoconstriction [24], plasma extravasation [82] and neutrophil accumulation [83] resulting from cigarette smoke in rodent airways. Neurogenic inflammation has also been implicated in various acute responses caused by antigen challenge in rabbits [84] and guinea pigs [85,86]. In addition, asthma-like symptoms, including cough, wheezing, chest tightness and dyspnea, have been reported to occur after accidental exposure to a broad series of environmental irritants or industrial pollutants. These symptoms, labeled as irritant-induced asthma [87], reactive airways dysfunction syndrome [88] or occupational asthma [89], may outlast the short-lived exposure to the irritant molecule by months or years [87]. Several of these substances, including chlorine gas and ROS [90], acrolein [24,58], nitric oxide via nitro-oleic acid formation [91], isocyanates [92] and toluene diisocyanate [93], have been identified as TRPA1 stimulants.

In the allergic response in airways, the contribution of TRPV1 ~~to~~ is unknown, although preliminary observations appear to negate the involvement of this receptor [23]. However, a recent study demonstrated that TRPA1-null mice do not develop hyper-reactivity to methacholine, and have reduced levels of cytokines and other markers of allergic inflammation compared with their wild-type littermates, suggesting that TRPA1 and its putative endogenous ligands are major contributors of allergic reactions [23]. An additional emerging role of TRPA1 in cough has been proposed by two recent studies [40,41]. Exogenous or endogenous TRPA1 agonists and cigarette smoke (which contains large amounts of TRPA1 agonists) caused coughing in guinea pigs and humans. Thus, in addition to TRPV1, TRPA1 may be considered as a major target for the development of antitussive medicines.

Ozone [94], cold air [95] and low pH [96] represent additional examples of agents that cause an early inflammatory response in the airways, with sensory nerve endings contributing to this response. More recently, exposure to hot air was demonstrated to activate TRPV1-dependent bronchoconstriction in guinea pigs [97]. In addition, acid instillation into the airways caused neurogenic inflammation [98] and cough [37], with both responses being sensitive to TRPV1 antagonism. Remarkable decreases from the normal pH level of 7.7 in the exhaled breath condensate obtained from patients with asthma, COPD exacerbations, cystic fibrosis and other diseases have been reported (for a review, see reference [99]). Therefore, an acid-driven and TRPV1-dependent mechanism may be hypothesized to contribute to the local and reflex responses observed in patients with asthma. However, evidence that these changes in pH are sufficient to trigger responses mediated by TRPV1 and neurogenic mechanisms in humans is lacking. Neurogenic inflammation in the respiratory system, ~~via~~ a hitherto unknown neuro-anatomical pathway, is produced by the presence of acid in the esophagus [100]. Moreover, the acidic component of gastroesophageal reflux is considered to be a major causative agent of the inflammatory response associated with GERD-induced asthma, and an association between GERD and asthma has been proposed [101].

Although a genetic study excluded a role of TRPV1 in mechanical hyperalgesia [102], pharmacological data obtained with different TRPV1 antagonists have challenged this proposal [103,104]. Although not supportive of a primary role for TRPA1 in mechanosensation, available data suggest that TRPA1 modulates the excitability of mechanosensitive afferent neurons [104,105]. However, the relevance of these observations, generally obtained at the somatic level, has not been determined at the level of visceral mechanosensation. Therefore, while the hypothesis that TRPV1/TRPA1 activators (eg, low extracellular pH, micromolar concentrations of anandamide or α,β-unsaturated aldehydes) may be sufficient for tonic channel activation under physiological conditions cannot be rejected, this idea has not yet been supported by conclusive experimental evidence. Phasic TRPV1/TRPA1 stimulation by mediators generated during inflammatory circumstances may be a more plausible explanation.

Conclusion

Neurogenic inflammation is regarded as a self-limiting primary defensive mechanism. From an historical perspective, peptidergic somatosensory neurons may be considered to be the major component of the nocifensor system [106]. An example of the protective

function of neurogenic inflammation is provided by pharmacological and genetic evidence that activation of lung TRPV1 receptors reduces bronchial hyper-reactivity in endotoxin-induced airway inflammation [107]. However, if triggering factors are produced continuously, neurogenic inflammation may cause exaggerated and self-perpetuating detrimental effects that could contribute to the mechanism of airway inflammatory diseases. In this scenario, the roles of TRPV1 and, more recently, TRPA1 are emerging. Support for the hypothesis that TRPV1 and TRPA1 play a role in airway inflammatory disease is provided by chronic cough, which may result from conditions such as asthma. The established role of TRPV1 in the exaggerated cough response observed in a variety of inflammatory airway diseases, and the novel identification of TRPA1 as a sensor of oxidative and nitrative stress and as a powerful cough mediator, indicate these two channels are suitable targets for antitussive and, perhaps, anti-inflammatory drugs. Various TRPV1 antagonists have undergone clinical development, including for inflammatory pain [108]; thus clinical testing in other indications may soon be possible. In contrast, although the first drug targeting TRPA1, HC-030031 (Hydra Biosciences Inc/ Cubist Pharmaceuticals Inc), has been reported [109], the design and development of potent and selective TRPA1 antagonists is still at an early stage. However, on the basis of pathophysiological findings obtained regarding the putative endogenous ligands of the TRPA1 channel and their role in models of airway diseases, this channel is anticipated to exert a primary role in airway disease; thus, antagonists of both TRPV1 and TRPA1 may represent innovative therapeutics for respiratory diseases.

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