

TRP channels and temperature in airway disease—clinical significance

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Abbreviations: COPD, chronic obstructive pulmonary disease; EID, exercise induced dyspnea; e-NANC, non-adrenergic non-cholinergic; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential melastin 8; TRPV1, transient receptor potential vanilloid 1.

Temperatures above and below what is generally regarded as “comfortable” for the human being have long been known to induce various airway symptoms, especially in combination with exercise in cold climate with temperatures below 0°C, which is naturally since exercise is followed by enhanced ventilation and thus greater amounts of inhaled cold air. The aim was to highlight the knowledge we have today on symptoms from the airways (here also including the eyes) arisen from various temperatures; the mechanisms, the pathophysiology and their clinical significance. The most common eye and airway conditions related to temperature changes are dry eye disease, rhinitis, laryngeal dysfunction, asthma, chronic obstructive pulmonary disease and chronic cough. Transient receptor potential (TRP) ion channels are probably involved in all temperature induced airway symptoms but via different pathways, which are now beginning to be mapped out. In asthma, the most persuasive hypothesis today is that cold-induced asthmatic bronchoconstriction is induced by dehydration of the airway mucosa, from which it follows that provocations with osmotic stimuli like hypertonic saline and mannitol can be used as a surrogate for exercise provocation as well as dry air inhalation. In chronic unexplained cough there seems to be a direct influence of cold air on the TRP ion channels followed by coughing and increased cough sensitivity to inhaled capsaicin. Revelations in the last decades of the ability of several airway TRP ion channels to sense and react to ambient air temperature have opened new windows for the understanding of the pathogenesis in a diversity of airway reactions appearing in many common respiratory diseases.

Introduction

The transient receptor potential (TRP) ion channels are the sensors giving the human being vital information on environmental temperature, and thereby the possibility to react with alarm to both noxious heat and cold, and to escape from them. Beyond these essential and necessary functions, temperature stimulation of TRP channels may contribute to unwanted reactions and symptoms.¹ For the airways, there are few reports of negative influences of temperature above normal ambient degrees, although noxious heat is likely to be followed by airway injury. Luckily, human beings are seldom in contact with ambient air temperature in the noxious range. On the other hand, the first identified TRP channel, the transient receptor ion channel vanilloid 1 (TRPV1), is triggered by noxious heat, capsaicin and low pH.² Capsaicin has for decades been used in airway research to provoke cough, as when inhaled, it is

considered to mirror the airway sensory nerve reactivity. Somewhat to the contrary, inhalation of cold air has long been known to provoke various airway symptoms, especially in combination with exercise, which is logical, since exercise is followed by increased respiratory rate and thus greater amounts of inhaled cold air. TRP channels are widely expressed in the airways,^{3–5} and the growing knowledge of the role of these receptors in sensing and reacting to environmental stimuli is followed by greater focus on these channels as targets for respiratory disease.^{6–10} It seems likely that the transient receptor potential melastin 8 (TRPM8) and the transient receptor potential ankyrin 1 (TRPA1), known to react to low temperature, are involved in airway symptoms induced by cold air. However, TRP channels belonging to the vanilloid (V) group, like those sensing osmotic stimuli (TRPV3 and TRPV4) and the before mentioned TRPV1 (also known to function as “integrator” of a wide field of sensory stimuli) may influence

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Table 1. Relation between TRP ion channels, airway symptoms and temperature

TRP ion channels	Airway symptoms	Temperature °C	Related stimuli
TRPV1	Cough, rhinitis and dyspnea induced from “noxious” stimuli	≥42°	Capsaicin pH ≤ 5.9 “Noxious” stimuli Ethanol Vanilloides Pain
TRPV3 TRPV4 TRPM8 TRPM4	Asthma, cough, dry eyes Inhalation of menthol <i>reduces</i> cough	22–40° 8–22°	Osmolarity Mechanical stimuli “Cool” stimuli Menthol
TRPA1	Asthma, cough, laryngeal obstruction, rhinitis	<8° and below	Mustard oil Garlic “Noxious” stimuli? Pain

temperature induced airway symptoms.¹¹ There are a number of recognized airway diseases and symptoms related to cold temperature, and these may affect both the upper and lower airways and may include the eyes. **Table 1** gives an overview of TRP channels and temperatures related to various airway symptoms.

Upper Airways and Eyes

Dry eye disease

There is a close connection between the responses to environmental airborne stimuli affecting the eyes and to those affecting the upper airways; an example of this connection is the allergic reactions labeled as rhino-conjunctivitis. Expression of TRPV isotypes 1, 2, and 3 were detected in human corneal endothelial cells,¹² and also TRPM8 has been identified in the eyes as a cold- and menthol-activated ion channel in peripheral sensory neurons, where it plays an important role in cold temperature detection.¹³ Dry eye disease is a multifactorial disorder affecting the composition and volume of tears. It causes ocular surface dryness, cooling, and hyperosmolarity and may lead to corneal epithelium damage and reduced visual performance. Recent findings indicate that elevations of tear osmolarity found in this disease predominantly excite cold thermoreceptors, indicating that dryness sensations experienced by these patients can be due to an augmented activity of corneal cold thermoreceptors.¹⁴

Rhinitis

It is common knowledge that the nose may be runny in cold weather and that such problems increase with aging.¹⁵ TRPV1 is widely expressed in the nasal mucosa, suggesting that capsaicin can directly influence the epithelial secretory and other functions via TRPV1, followed by activation of the sensory neurons.³ In both allergic and non-allergic rhinitis a non-specific nasal hyperreactivity can be diagnosed with cold dry air provocations.^{16,17} Such findings have given rise to hopes of targeting TRPV1 in the development of new therapeutic agents,⁶ though in a clinical trial a TRPV1 inhibitor

did not prevent cold dry air-elicited symptoms in non-allergic rhinitis.¹⁸ Other studies report TRPV1 overexpression in patients with idiopathic rhinitis, and topical capsaicin treatment reduced nasal hyperreactivity and nasal symptoms, the capsaicin action interpreted as ablating the TRPV1 nociceptive signaling pathway in the nasal mucosa.^{19,20} The TRPM8, known to be triggered by cold temperatures, is abundant in the nasal sub-epithelium²¹ and in idiopathic rhinitis Van Gerven et al found reduced expression of TRPM8, after capsaicin treatment, a finding that may have contributed to improvement of nasal hyperreactivity.¹⁹

Laryngeal dysfunction

Reports of respiratory difficulties caused by exercise-induced laryngeal obstructions are increasing in frequency.²² Laryngeal obstruction like vocal cord dysfunction, often occurring in young women, especially elite athletes, can masquerade as asthma and also coexist with asthma.²³ Since both these conditions are characterized by exercise-induced dyspnea (EID), differential diagnosis is problematic and may be followed by incorrect information and medication. Non-specific stimuli like cold and dry air are known to be among the most common triggers in the newly established laryngeal hypersensitivity syndrome.^{24,25} Studies of the expression of TRP channels in the human larynx are sparse, but at least in rat, TRPV1 seems to play an important role in the nociception of the laryngeal innervation,²⁶ and it is logical to hypothesize that the laryngeal reaction to exercise and cold air is dependent on TRP signaling.

Lower Airways

Asthma

Bronchial asthma as a disease is characterized by an underlying inflammation that in recent decades has been the main target for pharmacological treatment and the focus of intensive research activity.^{27,28} However, the link between the inflammatory cascade of asthma, causing bronchial hyperreactivity, and the axon

reflex of bronchoconstriction remains unclear.²⁹ Increasing evidence points to a potential role for members of the TRP family of cation channels on airway sensory non-adrenergic non-cholinergic (e-NANC) nerves in the development of bronchial hyperactivity and several features of asthmatic disease.^{27,30,31} The nature of the neurotransmitters involved in e-NANC bronchodilation and bronchoconstriction is still under debate, but the most likely candidates are vasoactive intestinal peptide and nitric oxide.²⁹

EID due to bronchoconstriction is regarded as a cardinal feature of asthma and is a measure of bronchial hyperactivity, as most asthmatic patients develop breathing problems after physical exertion, especially in a cold temperature.²⁷ A number of different mechanisms have been suggested as potential causes of cold air- and hyperventilation-provoked airflow limitation.^{32,33} The most persuasive hypothesis today is that cold-induced asthmatic bronchoconstriction depends on dehydration of the airway mucosa, from which it follows that provocations with osmotic stimuli like hypertonic saline and mannitol can be used as a surrogate for exercise provocation as well as dry air inhalation.³⁴ Cold air is by definition dry and the dehydration of the airways following exercise and hyperventilation, especially in cold climate, results in release of mediators followed by bronchoconstriction. The likely source of these mediators is the mast cell, but the exact mechanism by which dehydration and hyperosmolarity trigger the mast cell is not known. Alterations in the osmolarity of the media surrounding the cell will lead to changes in cell volume as water (and solute) leaves or enters the cell to maintain osmotic balance. Accumulating evidence indicates that osmotic activation of some TRP channels may occur via one of 2 mechanisms: (1) swelling-induced activation whose downstream metabolites then activate TRP channels, or (2) post-synaptic density protein supporting proteins such as ezrin/radixin/moesin that act as the mediators between some TRP channels and F-actin cytoskeleton.³⁵ On the other hand, some studies support a reflex mechanism from the upper to the lower airways with quickly induced bronchoconstriction after nasal cold air stimulation,³⁶ and cold air provocations of the face in healthy subjects and asthmatics have been shown to induce decreased of lung function.³⁴ These studies were performed before the identification of TRPV1, and the authors hypothesized vagal and trigeminal reflexes to be the underlying mechanism. The role of the cold sensitive TRPM8 channel in the normal and diseased airway is relatively unexplored, but the findings of TRPM8 channels in a subset of nasal trigeminal afferent neurons that do not coincidentally express TRPA1 or TRPV1 indicate the possibility of a reflex initiated from the nose.³⁷

Some studies have found increased capsaicin cough sensitivity in asthma patients,^{38,39} while others have failed to detect this phenomenon,^{40–43} and the cough sensitivity seemed to “normalize” when the asthmatic inflammation was treated with inhaled corticosteroids. Further, a recent study reported overexpression of TRPV1 in asthma, especially in patients with a severe condition.⁴⁴

Chronic Obstructive Pulmonary Disease (COPD)

It is a common clinical experience that patients with COPD complain of airway symptoms provoked by environmental factors like cold temperature, although few studies can confirm such connections.⁴⁵ In contrast to asthma, COPD is characterized by airflow limitation that is not fully reversible and is usually progressive, comprising a heterogeneous group of airway diseases and types of inflammation. Cough reflex sensitivity to capsaicin in patients with COPD has been recorded in only a few studies with small groups of patients and was reported to be normal or increased,^{39,46,47} and so far, only sparse reports have focused on TRP channels in COPD disease, though the interest seems rising.^{8,10} One study suggests that TRPA1 is involved in the neurogenic inflammation in COPD and contributes to the progression of the disease.⁴⁸

Chronic cough

Coughing is a common clinical problem and is followed by reduced quality of life.^{49–51} When it persists for more than 2 months, it is regarded as chronic, though the definition of “chronic cough” varies in the literature.⁵² In a cross-sectional, population-based epidemiologic study the overall prevalence of self-reported chronic cough was 6.3%, and cold air sensitivity was related to cough with statistical significance.⁵³ The pathophysiology behind coughing is fairly well understood in a number of conditions, but it is not always possible to attribute a persistent cough to an airway disorder or any other medical disorder. Cough can be a sign of many disorders, but there remains a group of patients with no obvious explanation for their coughing; these patients are often described as presenting with chronic idiopathic cough.^{54,55}

A subgroup of patients with airway complaints who report cough and other airway symptoms from environmental irritants and cold air have increased capsaicin cough sensitivity levels.⁴¹ As this capsaicin-induced cough can be blocked by inhaled lidocaine, it has been suggested that sensory nerves are involved in the pathophysiology.⁵⁶ Consequently, previously was proposed a mechanism to increase sensitivity of the afferent sensory nerves in such patients and further suggesting using the term sensory hyper-reactivity (SHR) to identify this mechanism.⁵⁷ The prevalence of SHR, often misdiagnosed as asthma or allergy, is estimated to be 6% in the Swedish population.⁵⁸ The meeting with SHR patients is often problematic for the physician and the risk for wrong diagnosis and medication is evident. **Figure 1** illustrates the airway reaction in asthmatic hyperresponsiveness with wheeze and bronchial narrowing and in SHR where the airway symptoms can be compared to hyperalgesia or neuropathic pain. In many chronic cough patients where the cough is labeled idiopathic or unexplained, there is a history of sensitivity to environmental irritants such as chemicals and perfumed products as well as increased capsaicin cough sensitivity.^{51,59}

The augmented capsaicin sensitivity is a general characterization of chronic cough,⁶⁰ and when, in such patients, capsaicin inhalation was preceded by a standardized exercise provocation in cold air, it was followed by coughing and increased capsaicin

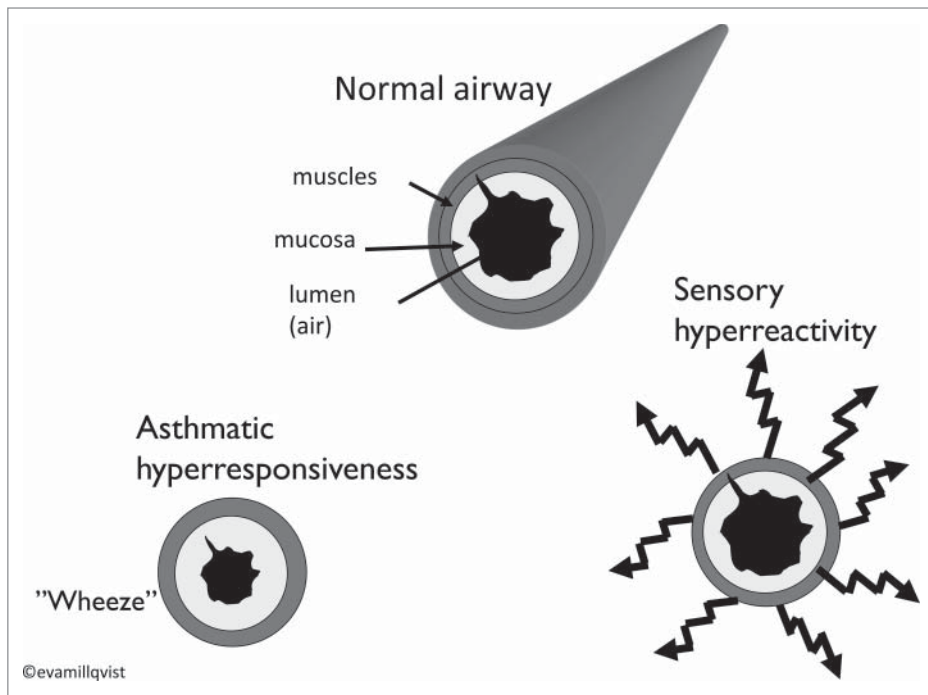


Figure 1. Airway reaction in asthmatic hyperresponsiveness with wheeze and bronchial narrowing and in SHR where the airway symptoms can be compared to hyperalgesia.

cough sensitivity.⁶¹ On the other hand, pre-inhalation of menthol, known to stimulate the cold sensitive receptor TRPM8, reduced cough sensitivity both in healthy subjects and in patients with chronic cough,^{62–64} and when menthol was administered in the nose cough parameters like capsaicin cough sensitivity were significantly modulated while the reactions were opposed following application of a TRPA1 agonist.³⁷ The findings may provide scientific support for the common practice of using menthol as a reliever for variant airway discomfort. The use of menthol in different cigarette brands could be questioned, since it could conceal the natural irritation following smoking.⁶⁵

A new paradigm, the “cough hypersensitivity syndrome,” has recently been developed. It includes both patients with general

cough hypersensitivity toward, for example, cold air, environmental irritants, and those having cough in combination with symptoms that may indicate a reflux disease.^{66,67} In a new report there was a high degree of agreement among opinion leaders to the idea that cough hypersensitivity underlies the etiology of chronic cough in the majority of patients.⁶⁸ Biopsy studies have shown increased expression of TRPV1 in chronic cough patients,^{69,70} and great interest has been focused on the possibility of blocking this receptor, sometimes called the “cough receptor.” Following this pathway, a TRPV1 antagonist was developed, and a recent study reported improvement of capsaicin cough sensitivity, although not in cough symptoms of patients with refractory chronic cough.⁷¹ On the other hand, capsaicin powder taken orally decreased capsaicin cough sensitivity and cough symptoms in chronic cough patients indicating a desensitization of the TRPV1.⁷²

Summary

Revelations in the last decades of the ability of several airway TRP ion channels to sense and react to ambient air temperature have opened new windows for the understating of the pathogenesis in a diversity of airway reactions appearing in many common respiratory diseases. This understanding should lead to development of new drugs targeting cough and other symptoms, which today are followed by reduced health and quality of life.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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