



HAL
open science

Are there clinical features of a sensitized cough reflex?

L. Mcgarvey, P. Mckeagney, L. Polley, J. Macmahon, R.W. Costello

► **To cite this version:**

L. Mcgarvey, P. Mckeagney, L. Polley, J. Macmahon, R.W. Costello. Are there clinical features of a sensitized cough reflex?. *Pulmonary Pharmacology & Therapeutics*, 2009, 22 (2), pp.59. 10.1016/j.pupt.2008.11.003 . hal-00516732

HAL Id: hal-00516732

<https://hal.science/hal-00516732>

Submitted on 11 Sep 2010

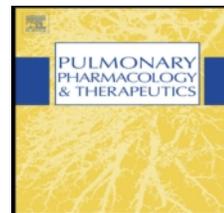
HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Accepted Manuscript

Title: Are there clinical features of a sensitized cough reflex?

Authors: L. McGarvey, P. McKeagney, L. Polley, J. MacMahon, R.W. Costello



PII: S1094-5539(08)00110-7

DOI: [10.1016/j.pupt.2008.11.003](https://doi.org/10.1016/j.pupt.2008.11.003)

Reference: YPUPT 878

To appear in: *Pulmonary Pharmacology & Therapeutics*

Received Date: 19 September 2008

Revised Date: 4 November 2008

Accepted Date: 4 November 2008

Please cite this article as: McGarvey L., McKeagney P., Polley L., MacMahon J., Costello R.W. Are there clinical features of a sensitized cough reflex?, *Pulmonary Pharmacology & Therapeutics* (2008), doi: [10.1016/j.pupt.2008.11.003](https://doi.org/10.1016/j.pupt.2008.11.003)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

PP 08-132, accepted

Are there clinical features of a sensitized cough reflex?

McGarvey L^{1,2}, McKeagney P¹, Polley L^{1,2}, MacMahon J¹, Costello RW³.

¹Regional Respiratory Centre, Belfast City Hospital, ²Department of Medicine, The Queen's University of Belfast, N Ireland, ³Department of Medicine, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland

Corresponding Author:

Dr Lorcan McGarvey

Consultant Physician and Senior Lecturer in Respiratory Medicine

The Queen's University of Belfast

The Royal Group Hospitals

Belfast, N Ireland

Email l.mcgarvey@qub.ac.uk

Telephone +44 (0) 2890 632680

Fax +44 (0) 2890 329899

Key words: sensory hyperresponsiveness, hyperreactivity, cough reflex, receptor

Abstract

Cough reflex hypersensitization is a key feature in patients with troublesome cough. The clinical consequence of this hypersensitive state is typified by bouts of coughing often triggered by low threshold stimuli encountered by the patient during normal daily activities including exposure to aerosols, scents and odours, a change in air temperature and when talking or laughing. These features are often perceived by cough patients to be the most disruptive aspect of their condition and undoubtedly contribute to impaired quality of life. Patients with troublesome cough may describe a range of additional symptoms and sensations including an 'urge to cough' or the feeling of an 'itch' at the back of the throat, or a choking sensation and occasionally chest pain or breathlessness. It is uncertain if these features arise due to the processes responsible for cough reflex sensitisation or as a direct consequence of the underlying cough aetiology. In an attempt to understand the clinical features of a sensitized cough reflex, the spectrum of symptoms typically described by cough patients will be reviewed and possible underlying mechanisms considered. Since an intact cough reflex is crucial to airway protection, anti-tussive treatment that attenuates the hypersensitive cough state rather than abolishing the cough reflex completely would be preferable. Identifying such agents remains a clinical, scientific and pharmacological challenge.

ACCEPTED

1. Introduction

Coughing is an important and appropriate response to noxious stimuli. However, in many acute and chronic respiratory disease states, a cough may develop which is troublesome, seems purposeless and is refractory to medication. While most focus has correctly centred on the investigation and treatment of cough as a specific complaint [1, 2] there is increasing recognition that cough patients report a range of additional sensations including an ‘urge to cough’, the feeling of an ‘itch’ or ‘lump’ at the back of the throat, a choking feeling and occasionally chest discomfort and breathlessness. These patients also complain that bouts of coughing are triggered by relatively innocuous stimuli frequently encountered during normal daily routine such as exposure to aerosols, scents and odours, a change in air temperature or when talking or laughing. This airway sensory hyperreactivity (SHR) is often what disturb patients most about their condition and appears to be of sufficient importance to impact on health status[3]. In the development of the two most widely used cough quality of life questionnaires items most frequently perceived as important by cough patients included statements such as; ‘exposure to paint or fumes made me cough’[4] and ‘I can no longer sing, for example, in church’[5].

Very little is known regarding the pathophysiology of SHR but in this article we consider the evidence that it may arise as a direct consequence of the neuroinflammatory events considered mechanistically important in cough.

2. Clinical features of cough

The act of coughing may cause a variety of musculoskeletal (chest wall pain), cardiovascular (syncope) and neurological (headache) symptoms which arise as a consequence of the cough intensity or a direct and profound effect of vagal stimulation. Some of the reasons why patients seek medical attention for cough include insomnia, a feeling of exhaustion, concern of serious underlying illness and self-consciousness from repeated coughing in public[6, 7]. This information tells us more about the physical impact and cognitive perception of problem coughing but nothing about its aetiology or the mechanisms responsible. Current management guidelines emphasise the importance of taking a careful history from the cough patient at the time of clinical presentation[2]. This usually identifies a range of symptom characteristics of which some, such as the abrupt onset of cough with eating or worsening cough in the workplace may be diagnostically helpful. More typically the history identifies a range of less specific aggravating features such as change in air temperature or exposure to scents and smells[8]. Until fairly recently there has been little focus on the typical irritants

and noxious stimuli which aggravate cough. Inhaling cold air provokes a number of respiratory symptoms including cough[9] and is regarded as a causative factor in the high prevalence of asthma seen in cross country skiers[10]. It has been proposed that cold air may directly sensitize 'cold' thermoreceptors[11]. Noxious heat is known to activate certain receptors although the *in vitro* thresholds are approximately 43°C suggesting that such receptors may be inactive at normal body temperatures[12]. However these receptors exhibit dynamic thresholds for activation that could be significantly lowered in the inflammatory conditions present in airway diseases such as asthma, COPD or cough syndromes. A more complete discussion on thermosensors and their activation will follow below. Talking, laughing and singing also appear to trigger bouts of coughing in patients with chronic cough although the mechanism is uncertain. It may arise from the activation of mechanosensitive receptors by the movement of air drawn through the airway during a fit of laughing or while talking or singing. While a number of studies have reported that laughing is strongly associated with exacerbations of asthma[13,14] there is no current literature on laugh-induced coughing. Possible mechanisms responsible include sudden changes in lung and chest wall mechanics during laughter[15] or in relation to the specific type of humorous stimulation involved and its processing with the cortex (John Widdicombe, personal communication). Further discussion of this topic is outside the scope of this article. For the purpose of this review we have considered three broad categories of noxious stimuli which seem to commonly bother cough patients;

- i) Change in air temperature (thermoactivation)
- ii) Exposure to aerosols, scents and odours (chemoactivation)
- iii) Inhaling of volumes of air into the bronchial tree during laughing, talking or singing (mechanooactivation).

While this categorisation is likely to represent an over-simplification it is intended to serve as a practical outline of the airway sensory hyperreactivity that we consider important in patients with cough.

3. How common is airway sensory hyperreactivity (SHR)?

Millqvist et al. first proposed the term airway sensory hyperreactivity (SHR) to define a syndrome of self reported odour intolerance combined with heightened sensitivity to inhaled capsaicin[16]. An accurate estimate of the prevalence of SHR in the general population is

difficult due to a lack of consistency in its definition. The range of terms commonly used and interchanged include; airway symptoms from chemicals (ASC) [17], multiple chemical sensitivity (MCS) syndrome[18] and the symptoms attributed to low level exposure to chemical and physical hazards in nonindustrial indoor environments called ‘sick-building syndrome’[19]. Furthermore there are no validated objective methods to measure or detect this condition. A number of population based studies have suggested that sensitivity to chemicals is a common problem with reported estimates ranging from 6-18%[20,21]. A number of studies designed to determine the prevalence of odour intolerance or self-reported illness from chemical odours in the general healthy population have reported prevalence rates of 33% and 66% respectively with predominance amongst female study participants[22,23]. Using a combination of the Chemical Sensitivity Scale for Sensory Hyperreactivity (CSS-SH) score and a positive capsaicin inhalation test to define SHR, Johansson *et al* reported the prevalence to be 6.3% in a group of randomly selected individuals from a large general population based study[24]. Airway sensory hyperreactivity, in particular chemosensitivity is of importance in the workplace and can lead to early exit from employment. In one study of irritant-exposed glass bottle workers the term ‘cough and airway irritancy’ was used to describe this group who were found not to have occupational asthma but had increased cough reflex sensitivity compared with healthy control workers[25]. In another example, workers in a chilli pepper factory who continuously exposed to capsaicin reported chronic cough and demonstrated heightened cough reflex sensitivity[26]. A recent review of irritant-induced cough provides a useful overview of this topic[27].

In the clinical setting, the existing literature on the prevalence of SHR reflects the experience of one centre and has focused on patients reporting a range of ‘asthma-like’ symptoms including coughers[28] and atopic individuals[17]. A recent longitudinal follow up of SHR patients over 5 years using repeat quality of life questionnaires and cough reflex sensitivity testing has suggested this syndrome persists unchanged over time[29]. While the existing literature provides important information on the extent of the problem, the definition of SHR, as currently exists, fails to include the non-chemical noxious stimuli that are important aggravants of cough.

4. Prevalence of SHR in a specialist cough clinic

For the purpose of this brief overview, we have provided some preliminary information on the prevalence and characteristics of airway SHR in patients referred to a specialist cough clinic. As alluded to above we have considered chemical, thermal and mechanical stimuli as

the important noxious stimuli that trigger bouts of coughing. We conducted a retrospective review of 135 consecutive patients referred to a specialist cough clinic. We defined airway sensory hyperreactivity (SHR) positive individuals as those who reported aggravation or triggering of cough in the presence of one or more of the following; change in air temperature (thermoactivation), exposure to aerosols, scents, odours (chemoactivation), and/or during talking, laughing or singing (mechanoactivation). The demographics of the study population are presented in table 1. We identified SHR in 85 (63%) of cough patients. There were significantly more females in the SHR positive group ($p=0.001$) although no other features including age, cough duration, cough aetiology, atopic status or bronchial hyperreactivity to methacholine reliably distinguished SHR positive from SHR negative cough patients. These preliminary results have identified airway sensory hyperreactivity as a common problem for cough patients and we suggest that amelioration should be a key aim of any new anti-tussive treatment. A more complete understanding of the mechanisms responsible for airway SHR in cough patients is required.

5. The cough reflex, cough receptors and airway sensory hyperreactivity

5.1 The cough reflex

The protective (physiological) cough response to a noxious stimulus is likely to be elicited by direct activation of receptors on afferent sensory airway nerves with very little involvement from non-neuronal cells. The precise type of afferent sensory nerve responsible for cough in humans is unknown but there are a number of candidates; rapidly adapting receptors (RARs) located on A δ -type nerves (chemo and mechanosensitive), small nonmyelinated C-fibres (chemosensitive) and a specific sodium ATPase receptor[30]. Following stimulation and activation, the nerve cells depolarize, generating an action potential (nerve impulse) which propagates along the vagus nerve to a region in the brain stem believed to be the nucleus tractus solitarius (NTS)[31]. Here, the sensory information undergoes processing, following which efferent fibres relay to the laryngeal structures and thoraco-abdominal musculature responsible for coughing. The cerebral cortex also exerts considerable influence over these processes and is considered responsible for cognitive responses to cough stimuli including the decision to suppress or elicit a cough following the sensation of an 'urge-to-cough'[32]. Some of the neurophysiological events associated with the 'urge-to-cough' have been investigated in man using functional positron emission tomography[33].

5.2 Airway cough receptors

Most of the information concerning the likely receptors (nociceptors) involved in cough (physiological and pathological) has come from work with capsaicin (8-methyl-*n*-vanillyl-6-nomamide), the chemical extract from hot chilli peppers which readily evokes cough in humans and animals[34,35][36]. Capsaicin is believed to activate the transient receptor potential vanilloid 1 (TRPV1) channel which is one of the transient receptor potential (TRP) family of ion channels. TRPV1 is a non-selective, cation channel with a preference for calcium and with extensive neuronal and non-neuronal distribution throughout many organ systems including the lung. Increased expression of TRPV1 receptors has been demonstrated in the airways of humans, including patients with chronic cough[37,38]. In addition to chemoactivation (by capsaicin), the receptor is directly activated by acidification (protons) and noxious temperatures[12]. There are important parallels with TRPV1 activation and other chronic disease states associated with abnormal sensory responses. In a TRPV1-homozygous-null (knockout) mouse model, thermal hypersensitivity failed to develop following hind-paw injection of a pro-inflammatory agent[39]. TRPV1 expression is also increased in A- δ fibres during nerve-injury induced thermal hyperalgesia[40] and in diabetic neuropathy[41].

Within this large TRP superfamily, a number of additional cation channels exist which are likely to be of importance in the cough response to a broad range of noxious stimuli. Among these, there has been interest in the cold-responsive TRP channels, TRPA1 and TRPM8. The vagal sensory nerves innervating the airways of mice are known to express TRPA1[42] and functional TRPM8 receptors have been demonstrated on human bronchial epithelium[43] providing some support for the role of these ion channels in sensing and responding to changes in the ambient temperature. Another receptor which is responsive to acidification is the acid-sensing ion channel (ASIC). It belongs to the ENaC/DEG (epithelial amiloride-sensitive Na⁺ channel and degenerin) family of ion channels. The ASIC family comprises four different genes encoding seven isoforms which are widely expressed in neurons of both the central and peripheral nervous system but also in non-neuronal sites including lung epithelial cells (ASIC3)[44]. The ASIC receptors appear to have a functional role in a variety of nociceptive responses including cough[45]. The ASICs and the TRP family of receptors may represent promising targets for novel anti-tussive therapy.

5.3 The cough reflex in disease

It is generally accepted that the cough reflex is hypersensitive in all respiratory diseases (acute or chronic) where cough is a prominent symptom. This statement is strongly supported

in the literature with evidence of cough reflex hypersensitivity across a range of respiratory diseases including acute viral cough[46][47], asthma and chronic obstructive pulmonary disease[48][49], bronchiectasis[50] and idiopathic pulmonary fibrosis[51]. The cough reflex is also heightened in extra-pulmonary diseases associated with cough such as gastro-oesophageal reflux disease[52] and rhinosinusitis[8]. It is important to appreciate that the cough reflex is in dynamic state of activation and a number of exogenous and endogenous factors may alter the degree of sensitization. The most obvious example is the change in cough reflex sensitivity following an upper respiratory tract infection. After a viral infection, the cough reflex becomes hyperreactive and remains in this activated state for a variable period of time (typically no more than 2-3 weeks while the patient is symptomatic[53]) following which the hyperreactivity diminishes and the cough reflex responsiveness returns to its baseline state[46]. However, in some circumstances this hypersensitized state persists long after the initial triggering event leading to a chronic cough state (Fig. 1). It is unclear if this arises due to direct viral damage of the peripheral sensory nerves or virus-induced changes in central processing of the sensory signal. Irrespective of the exact mechanism, the clinical consequences for the patient are an abnormal sensory response to various chemical, thermal and mechanical stimuli. The neuro-inflammatory mechanisms considered responsible for these abnormally sensitive states may offer important insights into cough and airway SHR.

6. Inflammation, cough reflex sensitisation and airway sensory hyperreactivity

Cough reflex sensitization may occur peripherally and/or centrally[54,55]. As the central processes involved are outside the scope of this review, our intention is to focus on the airway inflammatory events likely to be responsible for the sensitization of cough receptors. Acute and chronic cough are both associated with airway inflammation. Acute viral infection induces lower airway inflammation[56] which may persist long after the infection has resolved[57]. Inflammatory changes including damaged bronchial epithelial, basement membrane thickening and a chronic inflammatory (mainly lymphocytic) infiltrate have been demonstrated in bronchial biopsies from patients with chronic cough[58]. Eosinophils, mast cells and their respective mediators have been detected in both airway lavage samples and induced sputum from chronic coughers[59-61].

There is considerable evidence to support the notion that airway inflammation influences neural function and in so doing may sensitize the cough reflex. Guinea pigs exposed to sulphur dioxide (SO₂), an environmental pollutant known to induce airway inflammation,

exhibit an enhanced cough response to capsaicin which can be blocked by the anti-inflammatory agent dexamethasone[62]. Allergic inflammation has been shown to induce expression of neuropeptides in neurones that would not typically express these inflammatory proteins[63]. This 'phenotypic switch' underlines the powerful influence of inflammation on neural function. However the precise mechanism and the specific inflammatory cells and mediators responsible are not well understood. Several inflammatory cells and mediators have been implicated in the activation and sensitization of nociceptors. The peripheral termini of sensory nerves express receptors for a number of mediators implicated in sensitization and activation of nociceptors including histamine, tryptase, tumour necrosis factor (TNF)- α , interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8), bradykinin and prostaglandin E₂ (PGE₂). Many of these pro-inflammatory proteins are known to induce and maintain neural sensitization in other chronic inflammatory diseases such as arthritis. Their release from a variety of airway cells including the bronchial epithelium, neutrophils, macrophages and mast cells suggests an important role for non-neuronal airway cells in cough reflex sensitization.

Mast cells release histamine and tryptase, both of which have been detected in the airways of cough patients[59,60]. In an experimental model of itch, tryptase is known to activate the proteinase activated receptor (PAR-2) located on the C-fibre nerve terminal, releasing substance P which in turn sensitises the mast cell to release TNF α which is known to sensitize nociceptor function[64]. Neuropeptides such as substance P and neurokinin A are elevated in the airways of asthmatic patients with cough[65] and airway levels of calcitonin-gene-related peptide (CGRP) are positively correlated with capsaicin cough reflex sensitivity[66].

Eosinophils are also a potential source of inflammatory mediators which may modify cough. We have previously shown that eosinophils selectively localise to airway nerves of humans[67]. Once localised to airway nerves eosinophils we have shown that adhesion to airway nerves promotes the release of eosinophil granule proteins[68]. Further in vitro studies have shown that eosinophil granule proteins sensitise rat vagal pulmonary sensory neurons thereby promoting cough[69]

Both bradykinin and PGE₂ inhalation is known to sensitise the cough reflex [70]. Bradykinin acts on B1/B2 receptors on the nociceptor terminal and via the protein kinase C (PKC) pathway (phosphorylation) sensitizes TRPV1 channels[71]. Prostanoids such as PGE₂ can also indirectly sensitise the TRPV1 receptor via PKC activation[72].

Nerve growth factor (NGF) is an important mediator stored and released by a number of cells, either resident or recruited to the airway. As the bronchial epithelium is the first point of contact for noxious stimuli to the airway, these cells are an important source of inflammatory mediators including NGF. Increased neurotrophin levels including NGF have been demonstrated in the airways of patients with pulmonary fibrosis and increased capsaicin cough sensitivity[51]. The high affinity NGF receptor (tyrosine kinase receptor TrKA) is expressed on nociceptors and its activation leads to sensitization of the TRPV1 receptor[73]. In addition, NGF can modulate the expression of nociceptor genes including TRPV1 and substance P by transport of NGF-TrKA to the nucleus providing a mechanism for chronic nerve sensitization[74,75]. Following capsaicin challenge, patients with airway sensory hyperreactivity to scents and chemicals, had significantly greater increases in nasal lavage NGF levels than healthy controls[76]. A schematic of some of the mechanisms proposed above has been provided in Fig. 2. They each represent a means of cough reflex sensitization and as such potential targets for new treatments.

7. Conclusions

There is an increased appreciation of the range of symptoms that disturb patients with acute and chronic cough. One of the most important, occurring in two-thirds of patients with chronic cough, is the bouts of coughing provoked by relatively innocuous airborne stimuli such as aerosols, scents and cold air. In the last few years, there have been significant advances in the understanding of mechanisms responsible for abnormal sensory responses such as chronic pain and itch. Much of this knowledge is directly relevant to our understanding of the abnormal airway sensory hyperresponsiveness and cough reflex hyperreactivity common in respiratory disease. Almost certainly the airway neuro-inflammatory events triggered by a variety of chemical, thermal, mechanical and infective aggravants damage airway sensory nerves and are responsible for sensitization of nociceptors. Treatment aimed at ‘resetting’ this cough reflex sensitization to baseline or pre-disease levels is a key therapeutic objective.

References

- [1] Morice AH, Fontana GA, Sovijarvi AR, et al. (2004) The diagnosis and management of chronic cough. *Eur Respir J* 24:481-492
- [2] Morice AH, McGarvey L, Pavord I, British Thoracic Society Cough Guideline Group (2006) Recommendations for the management of cough in adults. *Thorax* 61 Suppl 1:i1-24
- [3] French CL, Irwin RS, Curley FJ, Krikorian CJ (1998) Impact of chronic cough on quality of life. *Arch Intern Med* 158:1657-1661
- [4] Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID (2003) Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 58:339-343
- [5] French CT, Irwin RS, Fletcher KE, Adams TM (2002) Evaluation of a cough-specific quality-of-life questionnaire. *Chest* 121:1123-1131
- [6] Irwin RS, Rosen MJ, Braman SS (1977) Cough. A comprehensive review. *Arch Intern Med* 137:1186-1191
- [7] Irwin RS, Curley FJ (1991) The treatment of cough. A comprehensive review. *Chest* 99:1477-1484
- [8] McGarvey LP, Heaney LG, Lawson JT, et al. (1998) Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. *Thorax* 53:738-743
- [9] Cho YS, Park SY, Lee CK, et al. (2003) Enhanced cough response to hyperpnea with cold air challenge in chronic cough patients showing increased cough sensitivity to inhaled capsaicin. *Allergy* 58:486-491
- [10] Larsson K, Ohlsen P, Larsson L, Malmberg P, Rydstrom PO, Ulriksen H (1993) High prevalence of asthma in cross country skiers. *BMJ* 307:1326-1329
- [11] Xing H, Ling JX, Chen M, et al. (2008) TRPM8 mechanism of autonomic nerve response to cold in respiratory airway. *Mol Pain* 4:22
- [12] Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D (1997) The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 389:816-824
- [13] Liangas G, Morton JR, Henry RL (2003) Mirth-triggered asthma: is laughter really the best medicine? *Pediatr Pulmonol* 36:107-112
- [14] Liangas G, Yates DH, Wu D, Henry RL, Thomas PS (2004) Laughter-associated asthma. *J Asthma* 41:217-221
- [15] Filippelli M, Pellegrino R, Iandelli I, et al. (2001) Respiratory dynamics during laughter. *J Appl Physiol* 90:1441-1446

- [16] Millqvist E, Bende M, Lowhagen O (1998) Sensory hyperreactivity--a possible mechanism underlying cough and asthma-like symptoms. *Allergy* 53:1208-1212
- [17] Millqvist E, Johansson A, Bende M (2004) Relationship of airway symptoms from chemicals to capsaicin cough sensitivity in atopic subjects. *Clin Exp Allergy* 34:619-623
- [18] Cullen MR (1987) Multiple chemical sensitivities: summary and directions for future investigators. *Occup Med* 2:801-804
- [19] Redlich CA, Sparer J, Cullen MR (1997) Sick-building syndrome. *Lancet* 349:1013-1016
- [20] Meggs WJ, Dunn KA, Bloch RM, Goodman PE, Davidoff AL (1996) Prevalence and nature of allergy and chemical sensitivity in a general population. *Arch Environ Health* 51:275-282
- [21] Kreutzer R, Neutra RR, Lashuay N (1999) Prevalence of people reporting sensitivities to chemicals in a population-based survey. *Am J Epidemiol* 150:1-12
- [22] Johansson A, Bramerson A, Millqvist E, Nordin S, Bende M (2005) Prevalence and risk factors for self-reported odour intolerance: the Skovde population-based study. *Int Arch Occup Environ Health* 78:559-564
- [23] Bell IR, Schwartz GE, Peterson JM, Amend D (1993) Self-reported illness from chemical odors in young adults without clinical syndromes or occupational exposures. *Arch Environ Health* 48:6-13
- [24] Johansson A, Millqvist E, Nordin S, Bende M (2006) Relationship between self-reported odor intolerance and sensitivity to inhaled capsaicin: proposed definition of airway sensory hyperreactivity and estimation of its prevalence. *Chest* 129:1623-1628
- [25] Gordon SB, Curran AD, Fishwick D, Morice AH, Howard P (1998) Respiratory symptoms among glass bottle workers--cough and airways irritancy syndrome? *Occup Med (Lond)* 48:455-459
- [26] Blanc P, Liu D, Juarez C, Boushey HA (1991) Cough in hot pepper workers. *Chest* 99:27-32
- [27] Brooks SM (2008) Irritant-induced chronic cough: irritant-induced TRPpathy. *Lung* 186 Suppl 1:S88-93
- [28] Millqvist E (2000) Cough provocation with capsaicin is an objective way to test sensory hyperreactivity in patients with asthma-like symptoms. *Allergy* 55:546-550
- [29] Ternesten-Hasseus E, Lowhagen O, Millqvist E (2007) Quality of life and capsaicin sensitivity in patients with airway symptoms induced by chemicals and scents: a longitudinal study. *Environ Health Perspect* 115:425-429
- [30] Canning BJ (2006) Anatomy and neurophysiology of the cough reflex: ACCP evidence-based clinical practice guidelines. *Chest* 129:33S-47S

- [31] Shannon R, Baekey DM, Morris KF, Nuding SC, Segers LS, Lindsey BG (2004) Production of reflex cough by brainstem respiratory networks. *Pulm Pharmacol Ther* 17:369-376
- [32] Davenport PW (2008) Urge-to-cough: what can it teach us about cough? *Lung* 186 Suppl 1:S107-11
- [33] Mazzone SB, McLennan L, McGovern AE, Egan GF, Farrell MJ (2007) Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. *Am J Respir Crit Care Med* 176:327-332
- [34] Dicipinigaitis PV (2003) Short- and long-term reproducibility of capsaicin cough challenge testing. *Pulm Pharmacol Ther* 16:61-65
- [35] Morice AH, Fontana GA, Belvisi MG, et al. (2007) ERS guidelines on the assessment of cough. *Eur Respir J* 29:1256-1276
- [36] McLeod RL, Correll CC, Jia Y, Anthes JC (2008) TRPV1 antagonists as potential antitussive agents. *Lung* 186 Suppl 1:S59-65
- [37] Groneberg DA, Niimi A, Dinh QT, et al. (2004) Increased expression of transient receptor potential vanilloid-1 in airway nerves of chronic cough. *Am J Respir Crit Care Med* 170:1276-1280
- [38] Mitchell JE, Campbell AP, New NE, et al. (2005) Expression and characterization of the intracellular vanilloid receptor (TRPV1) in bronchi from patients with chronic cough. *Exp Lung Res* 31:295-306
- [39] Caterina MJ, Leffler A, Malmberg AB, et al. (2000) Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* 288:306-313
- [40] Rashid MH, Inoue M, Kondo S, Kawashima T, Bakoshi S, Ueda H (2003) Novel expression of vanilloid receptor 1 on capsaicin-insensitive fibers accounts for the analgesic effect of capsaicin cream in neuropathic pain. *J Pharmacol Exp Ther* 304:940-948
- [41] Rashid MH, Inoue M, Bakoshi S, Ueda H (2003) Increased expression of vanilloid receptor 1 on myelinated primary afferent neurons contributes to the antihyperalgesic effect of capsaicin cream in diabetic neuropathic pain in mice. *J Pharmacol Exp Ther* 306:709-717
- [42] Nassenstein C, Kwong K, Taylor-Clark T, et al. (2008) Expression and function of the ion channel TRPA1 in vagal afferent nerves innervating mouse lungs. *J Physiol* 586:1595-1604
- [43] Sabnis AS, Reilly CA, Veranth JM, Yost GS (2008) Increased transcription of cytokine genes in human lung epithelial cells through activation of a TRPM8 variant by cold temperatures. *Am J Physiol Lung Cell Mol Physiol* 295:L194-200
- [44] Su X, Li Q, Shrestha K, et al. (2006) Interregulation of proton-gated Na(+) channel 3 and cystic fibrosis transmembrane conductance regulator. *J Biol Chem* 281:36960-36968
- [45] Kollarik M, Ru F, Udem BJ (2007) Acid-sensitive vagal sensory pathways and cough. *Pulm Pharmacol Ther* 20:402-411

- [46] O'Connell F, Thomas VE, Studham JM, Pride NB, Fuller RW (1996) Capsaicin cough sensitivity increases during upper respiratory infection. *Respir Med* 90:279-286
- [47] Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA (1976) Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis* 113:131-139
- [48] Doherty MJ, Mister R, Pearson MG, Calverley PM (2000) Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. *Thorax* 55:643-649
- [49] Wong CH, Morice AH (1999) Cough threshold in patients with chronic obstructive pulmonary disease. *Thorax* 54:62-64
- [50] Torrego A, Haque RA, Nguyen LT, et al. (2006) Capsaicin cough sensitivity in bronchiectasis. *Thorax* 61:706-709
- [51] Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK (2003) A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 168:995-1002
- [52] Ferrari M, Olivieri M, Sembenini C, et al. (1995) Tussive effect of capsaicin in patients with gastroesophageal reflux without cough. *Am J Respir Crit Care Med* 151:557-561
- [53] Curley FJ, Irwin RS, Pratter MR, et al. (1988) Cough and the common cold. *Am Rev Respir Dis* 138:305-311
- [54] Carr MJ, Lee LY (2006) Plasticity of peripheral mechanisms of cough. *Respir Physiol Neurobiol* 152:298-311
- [55] Bonham AC, Sekizawa SI, Joad JP (2004) Plasticity of central mechanisms for cough. *Pulm Pharmacol Ther* 17:453-7; discussion 469-70
- [56] Fraenkel DJ, Bardin PG, Sanderson G, Lampe F, Johnston SL, Holgate ST (1995) Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. *Am J Respir Crit Care Med* 151:879-886
- [57] Heino M, Juntunen-Backman K, Leijala M, Rapola J, Laitinen LA (1990) Bronchial epithelial inflammation in children with chronic cough after early lower respiratory tract illness. *Am Rev Respir Dis* 141:428-432
- [58] Boulet LP, Milot J, Boutet M, St Georges F, Laviolette M (1994) Airway inflammation in nonasthmatic subjects with chronic cough. *Am J Respir Crit Care Med* 149:482-489
- [59] McGarvey LP, Forsythe P, Heaney LG, MacMahon J, Ennis M (1999) Bronchoalveolar lavage findings in patients with chronic nonproductive cough. *Eur Respir J* 13:59-65
- [60] Birring SS, Parker D, Brightling CE, Bradding P, Wardlaw AJ, Pavord ID (2004) Induced sputum inflammatory mediator concentrations in chronic cough. *Am J Respir Crit Care Med* 169:15-19
- [61] Brightling CE, Symon FA, Birring SS, Bradding P, Wardlaw AJ, Pavord ID (2003) Comparison of airway immunopathology of eosinophilic bronchitis and asthma. *Thorax* 58:528-532

- [62] McLeod RL, Fernandez X, Correll CC, et al. (2006) TRPV1 antagonists attenuate antigen-provoked cough in ovalbumin sensitized guinea pigs. *Cough* 2:10
- [63] Myers AC, Kajekar R, Undem BJ (2002) Allergic inflammation-induced neuropeptide production in rapidly adapting afferent nerves in guinea pig airways. *Am J Physiol Lung Cell Mol Physiol* 282:L775-81
- [64] Steinhoff M, Vergnolle N, Young SH, et al. (2000) Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 6:151-158
- [65] Patterson RN, Johnston BT, Ardill JE, Heaney LG, McGarvey LP (2007) Increased tachykinin levels in induced sputum from asthmatic and cough patients with acid reflux. *Thorax* 62:491-495
- [66] Chang AB, Gibson PG, Ardill J, McGarvey LP (2007) Calcitonin gene-related peptide relates to cough sensitivity in children with chronic cough. *Eur Respir J* 30:66-72
- [67] Costello RW, Schofield BH, Kephart GM, Gleich GJ, Jacoby DB, Fryer AD (1997) Localization of eosinophils to airway nerves and effect on nerve M2 muscarinic receptor function. *Am J Physiol Lung Cell Mol Physiol* 273:L93-L103
- [68] Kingham PJ, McLean WG, Sawatzky DA, Walsh M-T, Costello RW (2002) Adhesion-dependent interactions between eosinophils and cholinergic nerves. *Am J Physiol Lung Cell Mol Physiol* 282:L1229-L1238
- [69] Qihai Gu, Michelle E. Wiggers, Gerald J. Gleich, and Lu-Yuan Lee Sensitization of isolated rat vagal pulmonary sensory neurons by eosinophil-derived cationic proteins (2008) *Am J Physiol Lung Cell Mol Physiol* 294: L544 - L552
- [70] Choudry NB, Fuller RW, Pride NB (1989) Sensitivity of the human cough reflex: effect of inflammatory mediators prostaglandin E2, bradykinin, and histamine. *Am Rev Respir Dis* 140:137-141
- [71] Sikand P, Premkumar LS (2007) Potentiation of glutamatergic synaptic transmission by protein kinase C-mediated sensitization of TRPV1 at the first sensory synapse. *J Physiol* 581:631-647
- [72] Kwong K, Lee LY (2005) Prostaglandin E2 potentiates a TTX-resistant sodium current in rat capsaicin-sensitive vagal pulmonary sensory neurones. *J Physiol* 564:437-450
- [73] Zhu W, Oxford GS (2007) Phosphoinositide-3-kinase and mitogen activated protein kinase signaling pathways mediate acute NGF sensitization of TRPV1. *Mol Cell Neurosci* 34:689-700
- [74] Zhang X, Huang J, McNaughton PA (2005) NGF rapidly increases membrane expression of TRPV1 heat-gated ion channels. *EMBO J* 24:4211-4223
- [75] Yang XD, Liu Z, Liu HX, Wang LH, Ma CH, Li ZZ (2007) Regulatory effect of nerve growth factor on release of substance P in cultured dorsal root ganglion neurons of rat. *Neurosci Bull* 23:215-220

[76] Millqvist E, Ternesten-Hasseus E, Stahl A, Bende M (2005) Changes in levels of nerve growth factor in nasal secretions after capsaicin inhalation in patients with airway symptoms from scents and chemicals. *Environ Health Perspect* 113:849-852

ACCEPTED MANUSCRIPT

	SHR n= 85	No SHR n= 50	Total group n= 135
Sex (F:M)	70 : 15	27 : 23	97 : 38
Age (years)	55±12	51±16	52 ±10
Duration of Cough (months)	60±61	41±53	48±43
Referral source	49	26	75
- Primary care (GP)	32	23	55
- Secondary care			
Preceding URTI? (n)	34	18	52
Yes	32	15	47
No			
BMI*	28±6	28±4	28±4
Smoking status	55	30	85
- Never	18	13	31
- Ex smoker	4	4	8
- Current	70	45	115
Treated cough	15	5	20
Idiopathic cough			

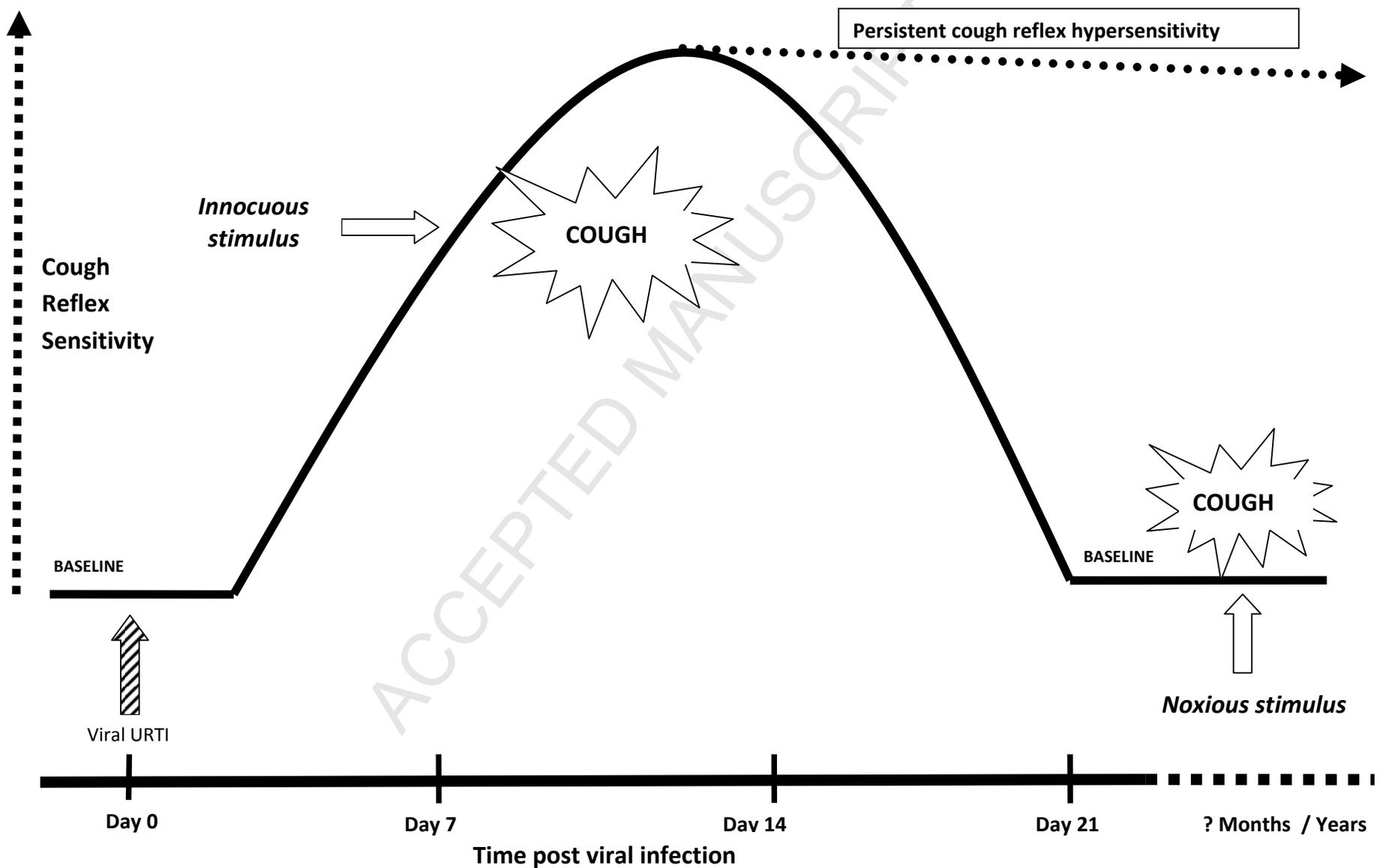
Table 1. Characteristics of cough patients with and without airway sensory hyperresponsiveness

SHR, airway sensory hyperresponsiveness; GP, General Practitioner; BMI, Body Mass Index

Values shown as mean \pm SD unless otherwise stated.

* BMI available on n=56

ACCEPTED MANUSCRIPT



Legend to figure 1.

Schematic of proposed changes in cough reflex sensitivity following viral upper respiratory tract infection.

Following a viral infection, the cough reflex becomes hyperreactive and remains in this activated state for a variable period of time (two-three weeks) during which cough may be provoked by innocuous stimuli such as exposure scents, aerosols and changes in air temperature. In the majority of subjects the hyperreactivity diminishes and the cough reflex responsiveness returns to its baseline state. However, in some circumstances this hypersensitized state persists long after the initial triggering event leading to a chronic cough state

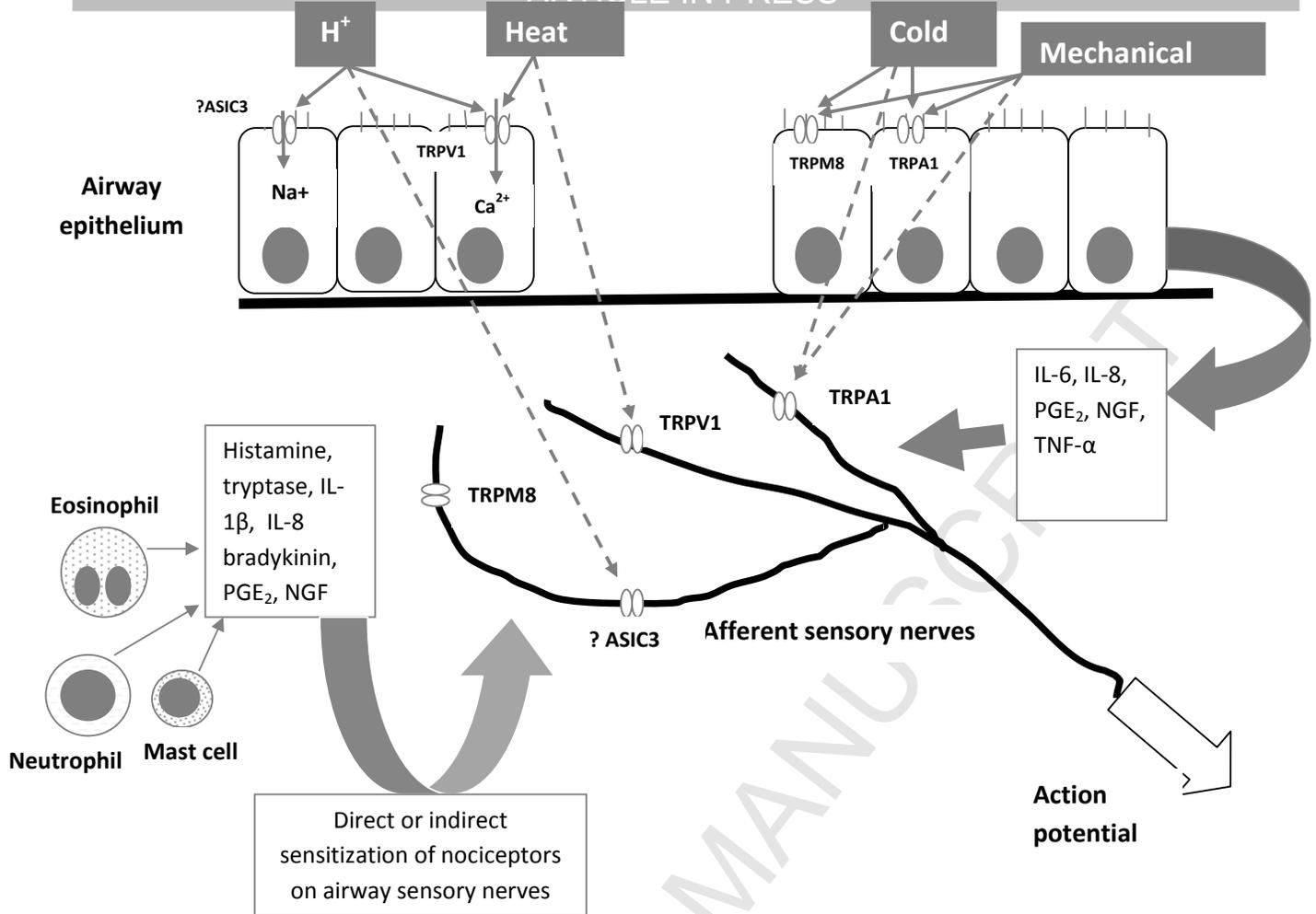


Figure 2. A proposed schematic of the direct and indirect activation of nociceptors on neuronal and non-neuronal cells in the airway by chemical, thermal and mechanical stimuli.

Noxious stimuli such as heat, cold, protons, and mechanical stress may directly activate TRP and ASIC receptors on airway nerves. In addition, inflammatory mediators such as IL-6, IL-8, NGF, TNF- α , PGE₂ and bradykinin released from non-neuronal cells (e.g. bronchial epithelium, mast cells, neutrophils, eosinophils) may directly or indirectly sensitize nerve receptors.

TRP, transient receptor potential; ASIC, acid sensing ion channel; IL-6, interleukin-6; IL-8, interleukin-8; NGF, nerve growth factor; TNF- α , tumour necrosis factor- α ; PGE₂, prostaglandin E₂

