Lung (2014) 192:459–465
DOI 10.1007/s00408-014-9581-x

REVIEW

Update: The Search for the Human Cough Receptor

Lorcan McGarvey

Received: 14 January 2014 / Accepted: 29 March 2014 / Published online: 26 April 2014

Abstract Despite the best efforts of basic and applied science, the identity of the human "cough receptor" remains elusive. The attraction of identifying a single "catch all" cough receptor is obvious, although such an objective is unlikely to be realised given the concept of "cough hypersensitivity," which is now considered the most clinically relevant description of what underlies problem coughing. One means of progressing this area is to join the thinking and experimental effort of basic science and clinical research in an effective manner. Some of the best examples of cooperative and translational research over the years together with an update on the most recent work will be discussed in this article.

Keywords Cough · Receptor · Human · Review

Introduction

The cough reflex has evolved primarily to protect the airway from noxious stimuli and is activated by a range of mechanical, thermal, and chemical stimuli [1]. There is evidence from animal and human studies for the existence of both mechano-sensing and chemo-sensing airway cough receptors [2, 3]. Much of what we currently know has emerged from experimental models involving the mechanical probing and chemical stimulation of rodent airways and from observing human subjects inhale tussive stimuli, such as capsaicin or citric acid. Whereas the limitations of using animals (especially anaesthetised) to faithfully model human cough are recognised [4] and the value of inhalation cough challenge testing to reflect clinical cough has been questioned [5], both have helped to advance what we currently know about the human cough receptor. However, there are important knowledge gaps and resolving these will help to advance the treatment options not only for patients with acute and chronic cough but for those with common respiratory diseases, including chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and lung cancer where cough often is a disabling and intractable problem. The key therapeutic objective in the management of cough is to "reset" the hypersensitive cough reflex while maintaining its protective role. Ideally, the identification of a peripheral cough receptor or one located centrally that could be modulated in a very selective fashion would overcome the "off-target" effects that limit existing treatment options. Using recent advances in basic science and clinical research techniques significant progress has been made in understanding mechanisms of peripheral and central cough reflex sensitisation. How these findings relate to clinical cough and associated sensations, such as "urge to cough" are currently being determined. The purpose of this article is to provide a brief overview of some of the important "cough receptor" literature of the past 60 years together with comment on how this has helped our understanding and management of human cough.

The Early Work in Search of Cough Receptors

In the original studies of the early 1950s conducted by Widdicombe [6–8], it was observed that both mechanical probing and chemical irritation of the airways of both

L. McGarvey (✉)
Centre for Infection and Immunity, Queens University Belfast, Health Sciences Building, Lisburn Road, Belfast BT9 7BL, Northern Ireland
e-mail: l.mcgarvey@qub.ac.uk

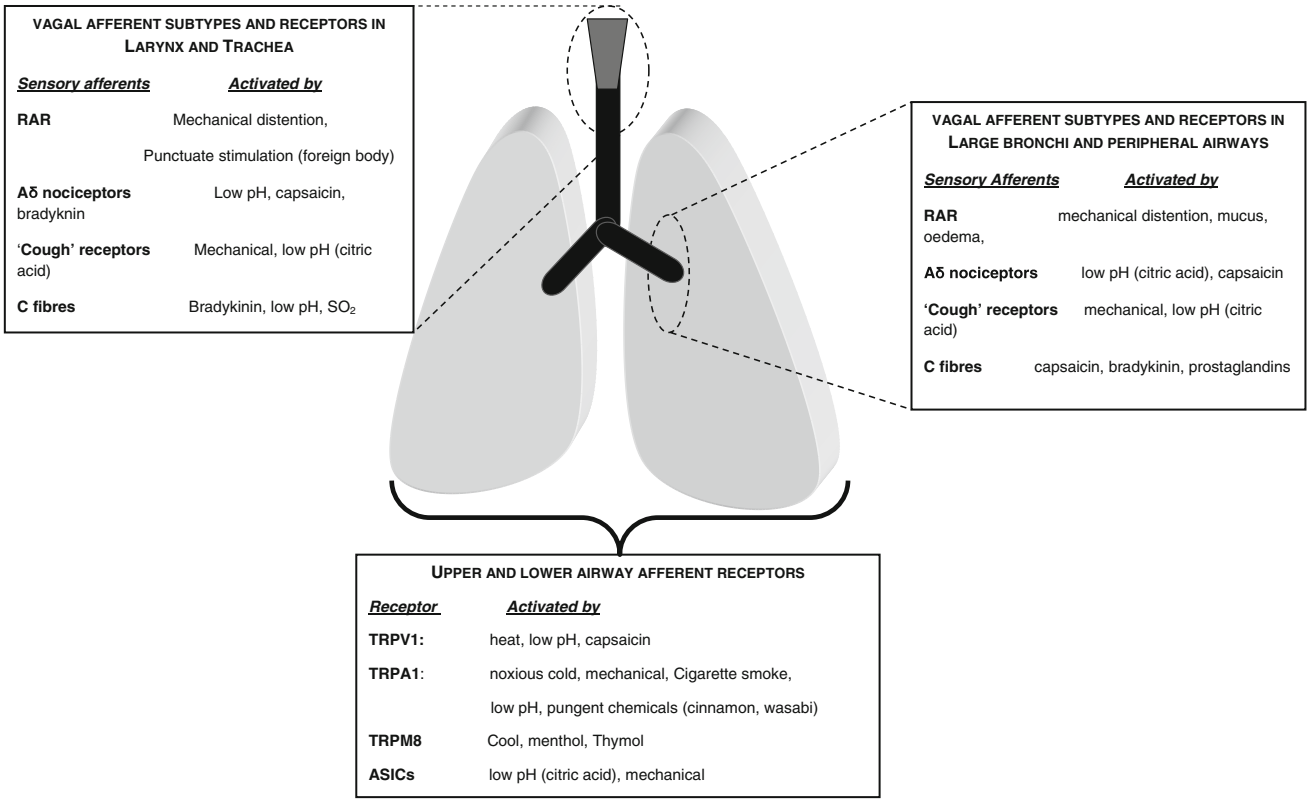

Fig. 1 A schematic of upper and lower airway vagal sensory afferents and receptors with putative role in cough. *RAR* rapidly adapting receptor, *TRPA1* transient receptor potential A1, *TRPV1* transient receptor potential vanilloid 1, *TRPM8* transient receptor potential M8

spontaneously breathing and anaesthetised cats readily evoked cough. Coughing (described as an inspiratory effort followed by expiration) was observed on mechanical stimulation, an effect that could be abolished with vagotomy. The most sensitive area identified for mechanically eliciting cough was the larynx followed by the tracheal bifurcation and distal portion of the trachea. These observations provided important clues about where mechanosensitive "cough receptors" were located. The mechanical distension and volume change that occurred following inflation of air into the trachea and larger airways also was noted to induce coughing. In addition, chemical stimulation evoked coughing, although in some cases only "expiration"-type efforts were observed. Unlike mechanically induced coughing, a chemically induced cough could not be readily abolished following vagotomy. It also was noted that repeated stimulation with sulphur dioxide induced chemical but not mechanical cough receptor refractoriness. Interestingly, a more vigorous response to chemical activation was noted when the stimulus was delivered to more distal airways compared with the trachea and the larger more proximal airways. To summarise these findings, it was apparent that cough could be elicited by the mechanical and chemical stimulation of two quite distinct receptors located on vagal nerves and distributed in the larynx, trachea, and throughout the bronchial tree (Fig. 1). Furthermore, the notion that the mechanosensitive cough receptors that appeared to be located proximally where they could be readily activated was entirely consistent with their assumed physiological role in airway protection. It was also tempting to speculate that chemosensitive receptors might be responsible for the cough associated with disease processes in the smaller more distal airways [9]. Although the majority of research at this time focused on the peripheral afferent and efferent components of the cough reflex, some attention was devoted to the central nervous system and its role in modulating the cough response [10]. May and Widdicombe studied the effect of opiates, which were known to act centrally, on cough reflex responses. They observed that opiates inhibited both chemically and mechanically induced cough and concluded that opiates exerted their antitussive effect via a central rather than peripheral mechanism [10]. The pioneering work of Widdicombe and colleagues [11–16] at this time provided a clear direction of travel for subsequent researchers to study the peripheral [2, 17] and central [18–26] mechanisms associated with coughing more completely.

Further Characterisation of the Afferent Cough Receptors

There has been considerable debate about the precise vagal afferent subtype responsible for coughing [27]. Vagal afferent nerve fibres are distinguished not just by their response to specific irritant stimuli but by their site of origin (arising either from the nodose or jugular ganglia), their site of termination in the airway, and a number of physiological properties, including conduction velocity, neuropeptide content, and extent of myelination. Using this information, two functional subtypes of afferent nerve fibres are recognised, which have been termed Aδ and C fibres, respectively. Aδ fibres can be further categorised into rapidly adapting receptors (RARs) and slow conducting fibres or slowly adapting receptors, SARs [28]. Using this information, Canning et al. [2] were able to demonstrate in an anaesthetized guinea-pig model that within the laryngeal and tracheal portions of the airway, cough was regulated by Aδ fibres arising from the nodose ganglion. They identified a particular subset of these afferent neurones (with no characteristic features of either RARs or SARs) but which were exquisitely sensitive to mechanical and acid stimulation but insensitive to chemical (capsaicin) activation and which they considered essential for cough reflex regulation [2]. They proposed the role of capsaicin sensitive C fibres to be less relevant to direct activation of cough but did recognise their role in regulating cough. In particular, the observation that capsaicin induced cough in conscious animals (and humans) but not anaesthetized animals suggested that consciousness plays a part in C-fibre-dependent cough. C-fibres therefore may be responsible for the "urge" or sensation of the "need to cough" rather than the "protective" reflex cough response to an inhaled foreign body. As an extension to their earlier work, Canning and colleagues [18] reported the selective expression of a sodium pump isozyme on the terminals of the Aδ fibres. They proposed that this isozyme, the alpha-3 subunit of the Na/K ATP'ase, was integral to cough regulation and a potential target for cough therapy [18]. Work is ongoing to further develop this exciting observation.

Activation of a single receptor on airway sensory nerves is in isolation insufficient to induce a cough. Following receptor activation a nonpropagated action potential called a "generator potential" is produced, which if of sufficient magnitude activates a voltage-gated Na channel. This in turn evokes an action potential that is conducted along the neural axon centrally and ultimately leading to a cough [29]. The effect of blocking Na channels as a treatment for cough will be discussed later in this article.

Human Airway Challenge with Tussive Agents

Bickerman first reported the tussive effects of inhaled citric acid in healthy human subjects almost 50 years ago [30]. A few years later in a series of experiments designed to study the irritant airway responses in patients with obstructive airways disease, Simonsson et al. [31] observed coughing in response to a range of physical and chemical irritants, including aerosols of citric acid, histamine and charcoal dust and cold (−20 °C) air inhalation. The coughing observed with each stimulus occurred within seconds of inhalation and could be blocked by atropine, which was consistent with the view that cough reflex activation occurred through stimulation of receptors present on airway vagal afferents. In this study, Simonsson and colleagues suggested that the patients with airway disease (they had studied asthmatic subjects and chronic bronchitic patients) had sensitized cough receptors. In addition to cough, many of the patients reported additional symptoms, including a "tickle" sensation in the throat and the feeling of an urge or desire to cough. Although the precise identity of the human cough receptor could not be established from these experiments, it did confirm that cough could be activated by a range of distinct irritants and introduced for the first time the idea that in airway disease cough receptors appeared to be sensitized. This concept of cough hypersensitivity is now widely considered as central to the understanding of persistent cough and the symptom profile and trigger factors typically described by patients [31–33]. The mechanism of cough reflex sensitisation is not fully understood, but activation of both peripheral and central neuronal processes is likely to be important. Comprehensive programmes of research developed to address central mechanisms are ongoing [26, 34–36], but more detailed discussion of these is outside the scope of this article. Some of the experimental work undertaken to elucidate the peripheral events will now be discussed.

Airway inflammation and tissue acidosis are both consistent features in acute and chronic pulmonary diseases associated with cough. Acid aerosols are known to provoke cough in a dose-dependent manner in both healthy subjects [37, 38], in patients with chronic cough [39] and other respiratory conditions, such as COPD [40]. These observations suggest an important role for protons in the activation of cough receptors. Further information about the identity of such a receptor was provided by Fox et al. [41] who demonstrated that acid activation of C-fibre afferents from guinea pig trachea could be inhibited by capsazepine, which at the time was considered a capsaicin receptor antagonist. This receptor was subsequently cloned and identified as transient receptor potential vanilloid 1 (TRPV1), a member of the TRP family of ion channels [42]. It became apparent that additional receptors were likely to be responsible for acid-induced neural activation, because acid was observed to activate non-TRPV1-expressing airway vagal afferents [43]. Using a stepwise reduction in the pH of perfusing buffer, Gu and Lee [17]

noted that responses could not be blocked by capsazepine but were attenuated by amiloride a known blocker of the acid sensing ion channel (ASIC). Whereas there is some evidence that ASIC channels are involved in rhinitis [44], little attention has been given to their role in clinical cough. By way of contrast, the TRPV1 receptor, which has been studied extensively, is now considered together with number of other members of the TRP channel family as promising therapeutic target for cough.

Evidence for TRP Channels as the Human Cough Receptors?

The exact mechanism responsible for the hypersensitive cough response is unknown, but upregulation of receptors responsible for sensing chemical and physical stimuli is one such possibility. Members of the TRP channel family, which are expressed on many cell types, including airway sensory nerves [45, 46], have the capacity to detect noxious physical and chemical stimuli and therefore represent potential candidate receptors. A number of TRP channel gene polymorphisms have recently been found to be associated with asthma [47], COPD [48], and cough [49]. Several TRP channels, in particular TRP channel, subfamily vanilloid, member 1 (TRPV1) [42], TRP channel melastatin member 8 (TRPM8) [50], TRP channel, subfamily A, member 1 (TRPA1) [51], which are directly activated by chemical, thermal, and mechanical stimuli, are of particular interest.

TRPV1 and TRPA1 in particular have now acquired an established role in the understanding of cough. Capsaicin, which directly activates the TRPV1 receptor, has been widely used both in the clinical assessment of cough reflex sensitivity and in human and animal research. In patients with chronic cough, TRPV1 is overexpressed in airway sensory neurones compared with healthy controls [46]. Recently, functional TRPV1 channels (sensitive to acid and capsaicin stimulation) have been expressed in the human airway epithelium and are overexpressed in the airways of severe asthmatics [52]. It is now apparent that TRPV1 is a polymodal receptor, which can be activated not only directly by factors, including noxious heat (>42 °C), capsaicin, and low pH, but indirectly by the binding of proinflammatory mediators to G protein coupled receptors on the cell membrane, which initiate intracellular signalling cascades, the net effect of which is to modify the TRPV1 channel sensitivity by lowering its activation threshold. The list of inflammatory proteins associated with this sensitisation of the TRPV1 channel is long and includes bradykinin, BK [53], nerve growth factor [54], and adenosine triphosphate (ATP) [55] together with many other proinflammatory cytokines [56]. These findings provide insight into how inflammation and tissue acidosis associated with acute and chronic respiratory disease can activate and sensitise cough receptors and may help to identify novel anti-inflammatory strategies, which may be effective to treat cough. Recent, experimental evidence shows that activation of the TRPA1 channel can cause coughing in both animals and human subjects [51]. TRPA1 also has been identified as a mediator of irritant responses evoked by certain pungent foods, such as wasabi, garlic, and cinnamon, and by volatile irritants, such as acrolein and crotonaldehyde, both of which are common chemical constituents in cigarette smoke [57]. TRPA1 and TRPV1 are known to be coexpressed in sensory neurones in rodent airways [58], and like TRPV1, the TRPA1 channel can be sensitised via the indirect action of inflammatory substances, including BK and PGE2 [59].

Menthol, which is an agonist of the cold sensing channel TRPM8, is a constituent in many over-the-counter (OTC) cough therapies. When menthol is applied as a nasal vapour (but interestingly not when delivered to the lower airway), it has been shown to inhibit cough responses to inhaled citric acid in guinea pigs. The researchers concluded that the cough suppression observed with menthol was mediated primarily by a nasal reflex [60]. Thymol, another cooling agent that also is found in many OTC cough treatments, is an agonist of the TRPV3 receptor. Both thymol and menthol when applied nasally have been shown to reduce capsaicin-induced cough responses in healthy volunteers [61]. These findings raise the possibility that targeting TRP channels on nasal trigeminal afferents may prove effective in modulating the cough response. This may be of particular relevance as rhinovirus, the most frequent cause of the common cold, can infect human neuronal cells and upregulate the expression of TRP channels [62].

Current Experience of Treatments Directed at the 'Cough Receptors'

TRP channels represent important target candidates for the development of novel drugs for the treatment for cough. The antitussive potential of TRPV1 antagonists appeared promising at least in animal models with one such compound inhibiting capsaicin-induced cough in guinea pigs with similar efficacy to codeine [63]. This provided preclinical support for the development of a TRPV1 antagonist for cough; however, further progress of this molecule was halted because of marked hyperthermia observed in the early clinical studies [64]. The results of a recent phase II clinical study of another TRPV1 antagonist for the treatment of cough has been disappointing [65]. In contrast TRPA1 antagonists have been shown to have no effect on

temperature regulation or pain sensation and may represent a more suitable alternative [66]. TRPA1 antagonists have recently entered clinical trials for the treatment of cough and the results are awaited [67]. There are case reports of lignocaine, a nonselective blocker of voltage-gated Na channels, being used for the treatment of refractory cough [68]. However, any efficacy is significantly limited by loss of airway protection and cardiotoxicity [69]. The use of more selective inhibition of Na channels may prove more promising. A number of voltage-gated Na channel isoforms are expressed in sensory neurons [70] and one in particular (Nav 1.7) seems to have a key role in the regulation of cough [71]. The selective blockade this channel may prove to be an effective strategy for the treatment of cough.

Conclusions

The rapid progress in experimental technology has added pace to the progress of cough research and helped to shape thinking on disease mechanisms [72]. However, to date, the initial excitement around a number of potential candidate molecules, most notably the TRPV1 channel, has been offset by disappointing results from early-phase proof-of-concept trials. Newer, TRPV1 antagonists with preclinical and early-phase clinical evidence suggesting cleaner safety profiles have been described [73]. This receptor and a number of other TRP channels remain attractive therapeutic targets for cough.

Finally, it is worth remembering that we are not alone and there is a lot to learn from the experience of researchers and clinicians in other therapeutic areas in particular pain. Change in the existing strategy for discovery science is required if optimal therapeutic target selection is to be achieved. There is broad recognition that no single researcher or company is likely to achieve this alone, hence the importance of cooperative precompetitive effort [74]. The challenges associated with identifying the correct cough receptor and developing effective treatments are enormous but so too are the rewards.

Conflict of interest None.

References

1. Mazzone SB (2005) An overview of the sensory receptors regulating cough. Cough 4(1):2
2. Canning BJ, Mazzone SB, Meeker SN, Mori N, Reynolds SM, Undem BJ (2004) Identification of the tracheal and laryngeal afferent neurones mediating cough in anaesthetized guinea-pigs. J Physiol 557(Pt 2):543–558
3. McGarvey L, McKeagney P, Polley L, MacMahon J, Costello RW (2009) Are there clinical features of a sensitized cough reflex? Pulm Pharmacol Ther 22(2):59–64
4. Canning BJ (2008) The cough reflex in animals: relevance to human cough research. Lung 186(Suppl 1):S23–S28
5. McGarvey LP (2004) Cough. 6: Which investigations are most useful in the diagnosis of chronic cough? Thorax 59(4):342–346
6. Widdicombe JG (1952) Rapidly adapting mechanoreceptors in the trachea of the cat. J Physiol 118(2):46P–47P
7. Widdicombe JG (1954) Respiratory reflexes from the trachea and bronchi of the cat. J Physiol 123(1):55–70
8. Widdicombe JG (1954) Respiratory reflexes excited by inflation of the lungs. J Physiol 123(1):105–115
9. Hansson L, Wollmer P, Dahlbäck M, Karlsson JA (1992) Regional sensitivity of human airways to capsaicin-induced cough. Am Rev Respir Dis 145(5):1191–1195
10. May AJ, Widdicombe JG (1954) Depression of the cough reflex by pentobarbitone and some opium derivatives. Br J Pharmacol Chemother 9(3):335–340
11. Ivanco I, Korpas J (1954) Contribution to the laryngeal and tracheal cough. Bratisl Lek Listy 34(12):1391–1396
12. Sant'Ambrogio G, Widdicombe JG (1965) Respiratory reflexes acting on the diaphragm and inspiratory intercostal muscle of the rabbit. J Physiol 180(4):766–779
13. Tomori Z, Widdicombe JG (1969) Muscular, bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. J Physiol 200(1):25–49
14. Hanácek J, Widdicombe JG, Korpás J (1981) Effect of SO_2 inhalation on the cough reflex in rabbits. Ceskoslov Fysiol 30(3):243–245
15. Korpas J, Widdicombe JG (1983) Defensive respiratory reflexes in ferrets. Respiration 44(2):128–135
16. Tatar M, Webber SE, Widdicombe JG (1988) Lung C-fibre receptor activation and defensive reflexes in anaesthetized cats. J Physiol 402:411–420
17. Gu Q, Lee LY (2006) Characterization of acid signaling in rat vagal pulmonary sensory neurons. Am J Physiol Lung Cell Mol Physiol 291(1):L58–L65
18. Mazzone SB, Reynolds SM, Mori N, Kollarik M, Farmer DG, Myers AC, Canning BJ (2009) Selective expression of a sodium pump isozyme by cough receptors and evidence for its essential role in regulating cough. J Neurosci 29(43):13662–13671
19. Mutoh T, Joad JP, Bonham AC (2000) Chronic passive cigarette smoke exposure augments bronchopulmonary C-fibre inputs to nucleus tractus solitarii neurones and reflex output in young guinea-pigs. J Physiol 523(Pt 1):223–233
20. Bonham AC, Sekizawa S, Chen CY, Joad JP (2006) Plasticity of brainstem mechanisms of cough. Respir Physiol Neurobiol 152(3):312–319
21. Bolser DC, Aziz SM, DeGennaro FC, Kreutner W, Egan RW, Siegel MI, Chapman RW (1993) Antitussive effects of GABAB agonists in the cat and guinea-pig. Br J Pharmacol 110(1):491–495
22. Bolser DC, DeGennaro FC, O'Reilly S, Chapman RW, Kreutner W, Egan RW, Hey JA (1994) Peripheral and central sites of action of GABA-B agonists to inhibit the cough reflex in the cat and guinea pig. Br J Pharmacol 113(4):1344–1348
23. Bolser DC, Hey JA, Chapman RW (1999) Influence of central antitussive drugs on the cough motor pattern. J Appl Physiol (1985) 86(3):1017–1024
24. Lavorini F, Fontana GA, Pantaleo T, Geri P, Piumelli R, Pistolesi M, Widdicombe J (2007) Fog-induced cough with impaired respiratory sensation in congenital central hypoventilation syndrome. Am J Respir Crit Care Med 176(8):825–832
25. Mazzone SB, Cole LJ, Ando A, Egan GF, Farrell MJ (2011) Investigation of the neural control of cough and cough

suppression in humans using functional brain imaging. J Neurosci 31(8):2948–2958
26. Mazzone SB, McGovern AE, Yang SK, Woo A, Phipps S, Ando A, Leech J, Farrell MJ (2013) Sensorimotor circuitry involved in the higher brain control of coughing. Cough 9(1):7. doi:10.1186/1745-9974-9-7
27. Widdicombe JG (1995) Neurophysiology of the cough reflex. Eur Respir J 8(7):1193–1202
28. Spina D, Page CP (2013) Regulating cough through modulation of sensory nerve function in the airways. Pulm Pharmacol Ther 26(5):486–490
29. Carr MJ (2013) Regulation of cough and action potentials by voltage-gated Na channels. Pulm Pharmacol Ther 26(5):508–509
30. Bickerman HA, Barach AL (1954) The experimental production of cough in human subjects induced by citric acid aerosols; preliminary studies on the evaluation of antitussive agents. Am J Med Sci 228(2):156–163
31. Simonsson BG, Jacobs FM, Nadel JA (1967) Role of autonomic nervous system and the cough reflex in the increased responsiveness of airways in patients with obstructive airway disease. J Clin Investig 46(11):1812–1818
32. Davenport PW (2008) Urge-to-cough: what can it teach us about cough? Lung 186(Suppl 1):S107–S111
33. Morice AH, McGarvey LP, Dicpinigaitis PV (2012) Cough hypersensitivity syndrome is an important clinical concept: a pro/con debate. Lung 190(1):3–9
34. Davenport PW (2009) Clinical cough I: the urge-to-cough: a respiratory sensation. Handb Exp Pharmacol 187:263–276
35. Bolser DC (2009) Central mechanisms II: pharmacology of brainstem pathways. Handb Exp Pharmacol 187:203–217
36. Smith JA, Hilton EC, Saulsberry L, Canning BJ (2012) Antitussive effects of memantine in guinea pigs. Chest 141(4):996–1002
37. Lowry RH, Wood AM, Higenbottam TW (1988) Effects of pH and osmolarity on aerosol-induced cough in normal volunteers. Clin Sci (Lond) 74(4):373–376
38. Wong CH, Matai R, Morice AH (1999) Cough induced by low pH. Respir Med 93(1):58–61
39. Kastelik JA, Thompson RH, Aziz I, Ojoo JC, Redington AE, Morice AH (2002) Sex-related differences in cough reflex sensitivity in patients with chronic cough. Am J Respir Crit Care Med 166(7):961–964
40. Wong CH, Morice AH (1999) Cough threshold in patients with chronic obstructive pulmonary disease. Thorax 54(1):62–64
41. Fox AJ, Urban L, Barnes PJ, Dray A (1995) Effects of capsazepine against capsaicin- and proton-evoked excitation of single airway C-fibres and vagus nerve from the guinea-pig. Neuroscience 67(3):741–752
42. 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(6653):816–824
43. Kollarik M, Undem BJ (2004) Activation of bronchopulmonary vagal afferent nerves with bradykinin, acid and vanilloid receptor agonists in wild-type and TRPV1−/− mice. J Physiol 555(Pt 1):115–123
44. Khoo SG, Al-Alawi M, Walsh MT, Hannigan K, Glynn S, Thornton M, McQuaid S, Wang Y, Hamilton PW, Verriere V, Gleich GJ, Harvey BJ, Costello RW, McGarvey LP (2012) Eosinophil peroxidase induces the expression and function of acid-sensing ion channel-3 in allergic rhinitis: in vitro evidence in cultured epithelial cells. Clin Exp Allergy 42(7):1028–1039
45. Bessac BF, Jordt S-E (2008) Breathtaking TRP channels: TRPA1 and TRPV1 in airway chemosensation and reflex control. Physiology 23:360–370
46. Groneberg DA, Niimi A, Dinh QT, Cosio B, Hew M, Fischer A, Chung KF (2004) Increased expression of transient receptor potential vanilloid-1 in airway nerves of chronic cough. Am J Respir Crit Care Med 170:1276–1280
47. Cantero-Recasens G, Gonzalez JR, Fandos C, Duran E, Smit LA, Kauffmann F, Antó JM, Valverde MA (2010) Loss-of-function of transient receptor potential vanilloid 1 (TRPV1) genetic variant is associated with lower risk of active childhood asthma. J Biol Chem 285:27532–27535
48. Zhu G, Gulsvik A, Bakke P, Ghatta S, Anderson W, Lomas DA, Silverman EK, Pillai SG (2009) Association of TRPV4 gene polymorphisms with chronic obstructive pulmonary disease. Hum Mol Genet 18:2053–2062
49. Smit LA, Kogevinas M, Anto JM, Bouzigon E, Gonzalez JR, Le Moual N et al (2012) Transient receptor potential genes, smoking, occupational exposures and cough in adults. Respir Res 13(1):26
50. Sabnis AS, Shadid M, Yost GS, Reilly CA (2008) Human lung epithelial cells express a functional cold-sensing TRPM8 variant. Am J Respir Cell Mol Biol 39:466–474
51. Birrell MA, Belvisi MG, Grace M, Sadofsky L, Faruqi S, Hele DJ, Maher SA, Freund-Michel V, Morice AH (2009) TRPA1 agonists evoke coughing in guinea-pig and human volunteers. Am J Respir Crit Care Med 180:1042–1047
52. McGarvey LP, Butler CA, Stokesberry S, Polley L, McQuaid S, Abdullah H, Ashraf S, McGahon MK, Curtis TM, Arron J, Choy D, Warke TJ, Bradding P, Ennis M, Zholos A, Costello RW, Heaney LG (2013) Increased expression of bronchial epithelial transient receptor potential vanilloid 1 channels in patients with severe asthma. J Allergy Clin Immunol. doi:10.1016/j.jaci.2013.09.016
53. Tang HB, Inoue A, Oshita K, Nakata Y (2004) Sensitization of vanilloid receptor 1 induced by bradykinin via the activation of second messenger signaling cascades in rat primary afferent neurons. Eur J Pharmacol 498(1–3):37–43
54. 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(4):689–700
55. Hsieh YL, Chiang H, Lue JH, Hsieh ST (2012) P2X3-mediated peripheral sensitization of neuropathic pain in resiniferatoxin-induced neuropathy. Exp Neurol 235(1):316–325
56. Zhang N, Inan S, Cowan A, Sun R, Wang JM, Rogers TJ, Caterina M, Oppenheim JJ (2005) A proinflammatory chemokine, CCL3, sensitizes the heat- and capsaicin-gated ion channel TRPV1. Proc Natl Acad Sci USA 102(12):4536–4541
57. Andrè E, Campi B, Materazzi S, Trevisani M, Amadesi S, Massi D, Creminon C, Vaksman N, Nassini R, Civelli M, Baraldi PG, Poole DP, Bunnett NW, Geppetti P, Patacchini R (2008) Cigarette smoke-induced neurogenic inflammation is mediated by alpha, beta-unsaturated aldehydes and the TRPA1 receptor in rodents. J Clin Investig 118(7):2574–2582
58. Taylor-Clark TE, Ghatta S, Bettner W, Undem BJ (2009) Nitrooleic acid, an endogenous product of nitrative stress, activates nociceptive sensory nerves via the direct activation of TRPA1. Mol Pharmacol 75(4):820–829
59. Grace M, Birrell MA, Dubuis E, Maher SA, Belvisi MG (2012) Transient receptor potential channels mediate the tussive response to prostaglandin E2 and bradykinin. Thorax 67(10):891–900
60. Plevkova J, Kollarik M, Poliacek I, Brozmanova M, Surdenikova L, Tatar M, Mori N, Canning BJ (1985) The role of trigeminal nasal TRPM8-expressing afferent neurons in the antitussive effects of menthol. J Appl Physiol 115(2):268–274
61. Gavliakova S, Biringerova Z, Buday T, Brozmanova M, Calkovsky V, Poliacek I, Plevkova J (2013) Antitussive effects of nasal thymol challenges in healthy volunteers. Respir Physiol Neurobiol 187(1):104–107
62. Abdullah H, Heaney LG, Cosby SL, McGarvey LP (2014) Rhinovirus upregulates transient receptor potential channels in a

human neuronal cell line: implications for respiratory virus-induced cough reflex sensitivity. Thorax 69(1):46–54
63. Bhattacharya A, Scott BP, Nasser N, Ao H, Maher MP, Dubin AE, Swanson DM, Shankley NP, Wickenden AD, Chaplan SR (2007) Pharmacology and antitussive efficacy of 4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide (JNJ17203212), a transient receptor potential vanilloid 1 antagonist in guinea pigs. J Pharmacol Exp Ther 323(2):665–674
64. Swanson DM, Dubin AE, Shah C, Nasser N, Chang L, Dax SL, Jetter M, Breitenbucher JG, Liu C, Mazur C, Lord B, Gonzales L, Hoey K, Rizzolio M, Bogenstaetter M, Codd EE, Lee DH, Zhang SP, Chaplan SR, Carruthers NI (2005) Identification and biological evaluation of 4-(3-trifluoromethylpyridin-2-yl)piperazine-1-carboxylic acid (5-trifluoromethylpyridin-2-yl)amide, a high affinity TRPV1 (VR1) vanilloid receptor antagonist. J Med Chem 48(6):1857–1872
65. Smith JA, Murdoch RD, Newlands A, Smart K, Khalid S, Kelsall A, Holt K, Dockry R, Woodcock A (2012) The impact of a selective oral TRPV1 antagonist in patients with chronic cough. Thorax 67(Suppl 2):A128
66. Chen J, Joshi SK, DiDomenico S, Perner RJ, Mikusa JP, Gauvin DM, Segreti JA, Han P, Zhang XF, Niforatos W, Bianchi BR, Baker SJ, Zhong C, Simler GH, McDonald HA, Schmidt RG, McGaraughty SP, Chu KL, Faltynek CR, Kort ME, Reilly RM, Kym PR (2011) Selective blockade of TRPA1 channel attenuates pathological pain without altering noxious cold sensation or body temperature regulation. Pain 152(5):1165–1172
67. Preti D, Szallasi A, Patacchini R (2012) TRP channels as therapeutic targets in airway disorders: a patent review. Expert Opin Ther Pat 22(6):663–695
68. Howard P, Cayton RM, Brennan SR, Anderson PB (1977) Lignocaine aerosol and persistent cough. Br J Dis Chest 71(1):19–24
69. Lim KG, Rank MA, Hahn PY, Keogh KA, Morgenthaler TI, Olson EJ (2013) Long-term safety of nebulized lidocaine for adults with difficult-to-control chronic cough: a case series. Chest 143(4):1060–1065
70. Kwong K, Carr MJ, Gibbard A, Savage TJ, Singh K, Jing J, Meeker S, Undem BJ (2008) Voltage-gated sodium channels in nociceptive versus non-nociceptive nodose vagal sensory neurons innervating guinea pig lungs. J Physiol 586(5):1321–1336
71. Muroi Y, Ru F, Chou YL, Carr MJ, Undem BJ, Canning BJ (2013) Selective inhibition of vagal afferent nerve pathways regulating cough using NaV1.7 shRNA silencing in guinea pig nodose ganglia. Am J Physiol Regul Integr Comp Physiol 304(11):R1017–R1023
72. Chung KF, McGarvey L, Mazzone SB (2013) Chronic cough is a neuropathic condition. Lancet Respir Med 19(5):414–422
73. Round P, Priestley A, Robinson J (2011) An investigation of the safety and pharmacokinetics of the novel TRPV1 antagonist XEN-D0501 in healthy subjects. Br J Clin Pharmacol 72(6):921–931
74. Hughes JP, Chessell I, Malamut R, Perkins M, Bačkonja M, Baron R, Farrar JT, Field MJ, Gereau RW, Gilron I, McMahon SB, Porreca F, Rappaport BA, Rice F, Richman LK, Segerdahl M, Seminowicz DA, Watkins LR, Waxman SG, Wiech K, Woolf C (2012) Understanding chronic inflammatory and neuropathic pain. Ann NY Acad Sci 1255:30–44