Published in final edited form as:
Pulm Pharmacol Ther. 2007 ; 20(4): 396–401. doi:10.1016/j.pupt.2006.12.003.

ENCODING OF THE COUGH REFLEX

Brendan J. Canning
Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Baltimore, Maryland, 21224, USA

Abstract

Coughing can be both voluntarily induced and involuntarily initiated by activation of vagal afferent nerves innervating the airways and lungs. Centrally, cough is regulated at the level of the brainstem through integration of vagal afferent nerve input by relay neurones in the nucleus tractus solitarius (nTS). Projections to and from the nTS add further complexity to cough regulation, as do the profound influences of psychological and social factors known to regulate cough. Peripherally, both neuronal and non-neuronal elements in the airways regulate the excitability of the vagal afferent nerve terminals regulating cough. These multiple levels of integration and encoding of the cough reflex may render this defensive respiratory response highly susceptible to modulation both by disease processes and through therapeutic intervention.

Keywords

NMDA; ouabain; nTS; capsaicin

1. Introduction

Coughing is one of several visceral reflexes that are both voluntarily and involuntarily regulated. Unlike smooth muscle tone, peristalsis, heart rate, cardiac contractility and a host of other processes regulated by visceral reflexes, coughing is not evoked with continuous, graded output nor withdrawn in similar fashion. Rather, there are subthreshold stimuli that almost certainly activate airway sensory nerves but not sufficiently to evoke cough or even the urge to cough, threshold stimuli producing an urge to cough, and then coughing with various degrees of force and repetition depending on stimulus, the perceived irritation, the psychological state and the social situation of the individual. The number and force of coughs is also under conscious control, but in ways not yet adequately quantified or described [1–3]. These convergent influences of the intensity and nature of the tussive stimuli, psychosocial factors, the perception of airways irritation and the resulting urge to cough produce a reflex ripe with potential for integration, amplification and inhibition. Separate but related to central encoding of the cough reflex are the mechanisms regulating the responsiveness of the vagal afferent nerve endings in the airways and lungs. The discontinuous nature of the cough reflex when initiated with just threshold or subthreshold stimuli suggests that the number of active units, the average frequency of activation (impulses/sec) and/or the duration of activation of the afferent nerves regulating cough all contribute to the encoding of this defensive reflex. We

Brendan J. Canning, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Baltimore, Maryland, 21224, USA, Phone: 410-550-2156, Fax: 410-550-2130, E-mail: E-mail: bjc@jhmi.edu.

speculate that alterations in the transduction and encoding of cough can produce either excessive coughing that adversely impacts quality of life (as in asthma and gastro-oesophageal reflux disease) or the infrequent or inadequate coughing of other diseases (including neuromuscular disorders, peripheral neuropathies and central nervous disorders) that render patients susceptible to pulmonary infections and pneumonia. Aspects of the central and peripheral mechanisms regulating the encoding and transduction of cough are briefly reviewed.

2. Encoding of the cough reflex

Coughing is initiated by activation of one or several subtypes of vagal afferent nerves innervating the airways and lungs [4]. In humans, an urge to cough and/or a perception of airway irritation precedes the coughing evoked by tussive stimuli [5]. A similar subthreshold effect can be demonstrated experimentally in anesthetized animals, whereby a subthreshold stimulus (e.g. chemical, electrical) produces alterations in respiratory pattern or rate without coughing (Fig. 1). When stimulation reaches threshold, coughing occurs. This pattern implies that the number of afferent nerves activated and/or the intensity of their activation (impulses/s, duration of activation) may both determine the threshold for cough. Non-neuronal factors regulating responsiveness to chemical and/or mechanical stimuli include the concentration (or force) and duration of challenge, the rate of clearance of the stimulant (through mucociliary transport and/or mucosal blood flow), the integrity of the epithelial barrier, and the rate of inactivation of the stimulus (e.g. neutralization of acid, restoration of tonicity, metabolism of autacoids) [6–8] (Fig. 2). Responsiveness of the nerve terminal also likely plays an important role in the transduction of cough. Bronchopulmonary C-fibres can be sensitized directly and indirectly by a variety of stimuli including prostanoids, histamine, acid, adenosine and protease activated receptor (PAR) stimulation [9–13]. Upon sensitization, C-fibres are rendered hyperresponsive to subsequent challenges, manifesting as an increased sensitivity and/or an increased duration and intensity of activation. This may also result in an increased cough response [14] (Fig 3). Mechanistically, sensitization has been attributed to effects on TRPV1 channel gating and recruitment of TTX-insensitive Na+-channels. Allergen challenge and mediators associated with the allergic response may also sensitize the vagal afferent nerves that regulate cough [15–20].

In contrast to the sensitizing effects on the cough reflex mediated by the various autacoids and stimuli listed above, therapeutic agents that limit afferent nerve excitation at the level of the nerve terminals may *inhibit* coughing or at least normalize cough thresholds and coughing intensities. Beta-adrenoceptor agonists and anticholinergics, for example, are unlikely to act directly at the sensory nerve terminals to inhibit coughing, but by promoting clearance or preventing mucus secretion and/or bronchospasm, they may minimize the stimulus produced by tussive agents [6,21]. At afferent nerve terminals, local anaesthetics can block action potential formation entirely or may reduce the duration of activation and peak action potential frequencies evoked by tussive stimuli, resulting in an inhibition of cough. Mexiletine, for example, is a local anaesthetic that blocks both TTX-sensitive and –insensitive Na^+-channels. At concentrations =100 μM, mexilitine does not prevent airway afferent nerve activation by mechanical stimulation or by acid and does not overtly shift thresholds for activation or prevent electrically evoked activation of airway vagal afferent nerves. Nevertheless, mexilitine reduces the duration and frequency of action potentials produced by any given threshold mechanical or acidic stimulus and when administered topically to the tracheal mucosa nearly abolishes coughing in anaesthetized guinea pigs evoked by tracheal challenge with citric acid [22] (Fig. 4). We have also found that a subset of mechanically sensitive afferents innervating the larynx, trachea, and mainstem bronchi expresse a unique isozyme of the Na+-K+-ATPase, the sodium pump, which is critical for restoring Na+ gradients particularly during high frequency nerve stimulation. In a subset of vagal afferents innervating the guinea pig trachea which we found were essential in regulating the cough reflex, inhibition of the sodium pump with ouabain

reduces peak action potential frequencies attained following mechanical or acid stimulation *in vitro* and nearly abolishes coughing evoked by acid *in vivo* [4]. A similar effect on afferent nerve terminal excitability has been proposed to explain the antitussive effects of the BK channel opener NS1619 and the peptide transmitter nociceptin [23–26].

3. Integration of afferent nerve input and regulation of cough

Afferent nerve input arising from the airways and lungs is integrated centrally primarily in the nucleus tractus solitarius (nTS). Central projections to and from the nTS add further complexity to airway reflex regulation [27]. Interventions or projections that act in the nTS to alter synaptic efficacy can either enhance or inhibit coughing. It seems likely that the coughing associated with gastro-oesophageal reflux disease and/or upper airways disease (allergic rhinitis, sinusitis) is due in part to parallel, convergent afferent inputs that exaggerate airway reflexes including cough [7,28,29]. Direct stimulation of nasal or oesophageal afferent nerves in animals or in human subjects does not evoke coughing, but enhances cough responsiveness to subsequent airway challenges [30–32]. This sensitization of the cough reflex can be mimicked by central activation of nociceptive (capsaicin-sensitive) afferent nerve terminals or by nTS microinjection of substance P [28]. The enhanced coughing associated with cigarette smoke exposure has been attributed to a neuropeptide-dependent sensitization of the cough reflex in the nTS [33–35].

Centrally acting antitussive agents have proved efficacy in both human subjects and in animals. The most dramatic illustration of the effectiveness of centrally acting antitussives is the observation that general anaesthesia can completely prevent coughing evoked by capsaicin and bradykinin (Fig. 5), two potent and effective tussive agents in awake humans and animals that have been consistently ineffective at evoking cough in anaesthetized cats, dogs and guinea pigs [36–40]. General anaesthesia does not prevent airway afferent nerve activation or other airway reflexes and fails also to prevent coughing evoked by mechanical or acid stimulation of the airways, and yet completely prevents capsaicin and bradykinin evoked coughing [7,39]. Very deep general anaesthesia prevents coughing altogether. In addition to implying the existence of at least two pathways and/or mechanisms for cough (capsaicin-sensitive and insensitive pathways, that are highly sensitive or less sensitive to general anaesthesia, respectively), this selective effect of general anaesthesia on capsaicin and bradykinin evoked cough highlights the potential for more selective centrally-acting antitussive agents. Other antitussive agents acting at least in part centrally include the GABAB receptor agonist baclofen, codeine and other opioid receptor agonists, tachykinin receptor antagonists and perhaps dextromethorphan [41–45].

Progress in identifying novel centrally acting antitussives has been hampered somewhat by a limited knowledge of central termination sites of the afferent nerves regulating cough and by extension, a poor understanding of the pharmacology of these first central synapses. Using microinjection and tracing techniques in guinea pigs, we have identified a discrete location in the nTS that seems to be the primary site of termination for the tracheal and laryngeal afferent nerves regulating cough in guinea pigs [7,40]. Microinjecting a combination of NMDA and nonNMDA glutamate receptor antagonists bilaterally into this location nearly abolishes coughing evoked by citric acid and by mechanical and electrical stimulation of the tracheal and laryngeal mucosa. Importantly, respiratory reflexes evoked by C-fibre stimulation (laryngeal capsaicin, right atrial injection of bradykinin) or by rapidly adapting receptor activation (right atrial injection of histamine) are essentially unaffected by the glutamate receptor antagonists microinjected into this location. Microinjecting these antagonists at identical concentrations and volumes in adjacent locations 0.5–2mm rostral, caudal, lateral or medial to the sites of cough receptor termination has no effect on subsequently evoked coughing. Importantly, NMDA receptor antagonism alone appears to be very effective at

preventing cough and yet has little or no demonstrable effects on basal respiratory rate or pattern. This effect of NMDA receptor antagonism may relate to the modulatory role of this receptor subtype in regulating high frequency synaptic inputs at central synapses and may have important implications for drug discovery [46,47].

4. Conclusions

Coughing can be both enhanced and inhibited through central and peripheral mechanisms. Peripherally, the pattern of afferent nerve discharge, the duration of activation, and the number of units active all likely determine the intensity of the cough response. Altering these parameters by targeting the ion channels regulating these aspects of afferent nerve discharge may account for the antitussive actions of peripherally acting agents. Centrally acting antitussive agents effectively limit the amount of afferent input encoded into coughing either by reducing relay neurone excitability or by reducing afferent transmitter release. Coughing can also be modified by parallel afferent inputs that may enhance the cough reflex (as in upper airways disease and gastro-oesophageal reflux disease) or inhibit coughing (as shown with bronchopulmonary C-fibre activation and perhaps with slowly adapting stretch receptor activation).

References

1. Hutchings HA, Morris S, Eccles R, Jawad MS. Voluntary suppression of cough induced by inhalation of capsaicin in healthy volunteers. Respir Med 1993;87:379–82. [PubMed: 8209058]
2. Pinto A, Yanai M, Sekizawa K, Aikawa T, Sasaki H. Conditioned enhancement of cough response in awake guinea pigs. Int Arch Allergy Immunol 1995;108:95–8. [PubMed: 7647591]
3. Lee PC, Jawad MS, Hull JD, West WH, Shaw K, Eccles R. The antitussive effect of placebo treatment on cough associated with acute upper respiratory infection. Psychosom Med 2005;67:314–7. [PubMed: 15784799]
4. Canning BJ, Mori N, Mazzone SB. Vagal afferent nerves regulating the cough reflex. Respir Physiol Neurobiol 2006;152:223–42. [PubMed: 16740418]
5. Davenport PW, Bolser DC, Vickroy T, Berry R, Martin AD, Hey JA, Danzig M. The effect of codeine on the urge-to-cough response to inhaled capsaicin. Pulm Pharmacol Therap. 2007this Issue, in press
6. Canning BJ. Interactions between vagal afferent nerve subtypes mediating cough. Pulm Pharmacol Ther 2002;15:187–92. [PubMed: 12099762]
7. Canning BJ, Farmer DG, Mori N. Mechanistic studies of acid-evoked coughing in anesthetized guinea pigs. Am J Physiol Regul Integr Comp Physiol 2006;291:R454–63. [PubMed: 16914432]
8. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129(1 Suppl):169–73S. [PubMed: 16424428]
9. Lee L-Y, Shuei Lin Y, Gu Q, Chung E, Ho CY. Functional morphology and physiological properties of bronchopulmonary C-fiber afferents. Anat Rec A Discov Mol Cell Evol Biol 2003;270:17–24. [PubMed: 12494486]
10. Xu F, Gu QH, Zhou T, Lee L-Y. Acute hypoxia prolongs the apnea induced by right atrial injection of capsaicin. J Appl Physiol 2003;94:1446–54. [PubMed: 12482767]
11. Lin RL, Gu Q, Lin YS, Lee L-Y. Stimulatory effect of CO2 on vagal bronchopulmonary C-fiber afferents during airway inflammation. J Appl Physiol 2005;99:1704–11. [PubMed: 15994240]
12. Kwong K, Lee L-Y. Prostaglandin E2 potentiates a TTX-resistant sodium current in rat capsaicin-sensitive vagal pulmonary sensory neurones. J Physiol 2005;564:437–50. [PubMed: 15705651]
13. Gu Q, Lee L-Y. Hypersensitivity of pulmonary chemosensitive neurons induced by activation of protease-activated receptor-2 in rats. J Physiol 2006;574:867–76. [PubMed: 16709636]
14. Gatti R, Andre E, Amadesi S, Dinh TQ, Fischer A, Bunnett NW, Harrison S, Geppetti P, Trevisani M. Protease-activated receptor-2 activation exaggerates TRPV1-mediated cough in guinea pigs. J Appl Physiol 2006;101:506–11. [PubMed: 16627674]

15. Fox AJ, Lalloo UG, Belvisi MG, Bernareggi M, Chung KF, Barnes PJ. Bradykinin- evoked sensitization of airway sensory nerves: a mechanism for ACE-inhibitor cough. Nat Med 1996;2:814–7. [PubMed: 8673930]
16. Riccio MM, Myers AC, Undem BJ. Immunomodulation of afferent neurons in guinea- pig isolated airway. J Physiol 1996;491:499–509. [PubMed: 8866873]
17. Liu Q, Fujimura M, Tachibana H, Myou S, Kasahara K, Yasui M. Characterization of increased cough sensitivity after antigen challenge in guinea pigs. Clin Exp Allergy 2001;31:474–84. [PubMed: 11260161]
18. Xiang A, Uchida Y, Nomura A, Iijima H, Sakamoto T, Ishii Y, Morishima Y, Masuyama K, Zhang M, Hirano K, Sekizawa K. Involvement of thromboxane A(2) in airway mucous cells in asthma-related cough. J Appl Physiol 2002;92:763–70. [PubMed: 11796690]
19. House A, Celly C, Skeans S, Lamca J, Egan RW, Hey JA, Chapman RW. Cough reflex in allergic dogs. Eur J Pharmacol 2004;492:251–8. [PubMed: 15178372]
20. El-Hashim AZ, Amine SA. The role of substance P and bradykinin in the cough reflex and bronchoconstriction in guinea-pigs. Eur J Pharmacol 2005;513:125–33. [PubMed: 15878717]
21. Karlsson JA, Fuller RW. Pharmacological regulation of the cough reflex--from experimental models to antitussive effects in man. Pulm Pharmacol Ther 1999;12:215–28. [PubMed: 10500001]
22. Carr MJ. Influence of mexiletine on action potential discharge and conduction in nodose Adelta afferent neurons innervating guinea pig isolated trachea. Pulm Pharmacol Ther 2006;19:258–63. [PubMed: 16139534]
23. Fox AJ, Barnes PJ, Venkatesan P, Belvisi MG. Activation of large conductance potassium channels inhibits the afferent and efferent function of airway sensory nerves in the guinea pig. J Clin Invest 1997;99:513–9. [PubMed: 9022086]
24. Bolser DC, McLeod RL, Tulshian DB, Hey JA. Antitussive action of nociceptin in the cat. Eur J Pharmacol 2001;430:107–11. [PubMed: 11698070]
25. McLeod RL, Parra LE, Mutter JC, Erickson CH, Carey GJ, Tulshian DB, Fawzi AB, Smith Torhan A, Egan RW, Cuss FM, Hey JA. Nociceptin inhibits cough in the guinea-pig by activation of ORL (1) receptors. Br J Pharmacol 2001;132:1175–8. [PubMed: 11250866]
26. Lee MG, Undem BJ, Brown C, Carr MJ. Effect of nociceptin in acid-evoked cough and airway sensory nerve activation in guinea pigs. Am J Respir Crit Care Med 2006;173:271–5. [PubMed: 16239621]
27. Kubin L, Alheid GF, Zuperku EJ, McCrimmon DR. Central pathways of pulmonary and lower airway vagal afferents. J Appl Physiol 2006;101:618–27. [PubMed: 16645192]
28. Mazzone SB, Mori N, Canning BJ. Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea-pigs. J Physiol 2005;569:559–73. [PubMed: 16051625]
29. Hanacek J, Tatar M, Widdicombe J. Regulation of cough by secondary sensory inputs. Respir Physiol Neurobiol 2006;152:282–97. [PubMed: 16584927]
30. Ing AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 1994;149:160–7. [PubMed: 8111576]
31. Wu DN, Yamauchi K, Kobayashi H, Tanifuji Y, Kato C, Suzuki K, Inoue H. Effects of esophageal acid perfusion on cough responsiveness in patients with bronchial asthma. Chest 2002;122:505–9. [PubMed: 12171823]
32. Plevkova J, Kollarik M, Brozmanova M, Revallo M, Varechova S, Tatar M. Modulation of experimentally-induced cough by stimulation of nasal mucosa in cats and guinea pigs. Respir Physiol Neurobiol 2004;142:225–35. [PubMed: 15450482]
33. Karlsson JA, Zackrisson C, Lundberg JM. Hyperresponsiveness to tussive stimuli in cigarette smoke-exposed guinea-pigs: a role for capsaicin-sensitive, calcitonin gene- related peptide-containing nerves. Acta Physiol Scand 1991;141:445–54. [PubMed: 1877346]
34. Kwong K, Wu ZX, Kashon ML, Krajnak KM, Wise PM, Lee L-Y. Chronic smoking enhances tachykinin synthesis and airway responsiveness in guinea pigs. Am J Respir Cell Mol Biol 2001;25:299–305. [PubMed: 11588007]
35. Joad JP, Munch PA, Bric JM, Evans SJ, Pinkerton KE, Chen CY, Bonham AC. Passive smoke effects on cough and airways in young guinea pigs: role of brainstem substance P. Am J Respir Crit Care Med 2004;169:499–504. [PubMed: 14644932]

36. Tatar M, Webber SE, Widdicombe JG. Lung C-fibre receptor activation and defensive reflexes in anaesthetized cats. J Physiol 1988;402:411–20. [PubMed: 3236245]
37. Choudry NB, Fuller RW, Pride NB. Sensitivity of the human cough reflex: effect of inflammatory mediators prostaglandin E2, bradykinin, and histamine. Am Rev Respir Dis 1989;140:137–41. [PubMed: 2751160]
38. Karlsson JA, Sant'Ambrogio FB, Forsberg K, Palecek F, Mathew OP, Sant'Ambrogio G. Respiratory and cardiovascular effects of inhaled and intravenous bradykinin, PGE2, and PGF2 alpha in dogs. J Appl Physiol 1993;74:2380–6. [PubMed: 8335571]
39. Tatar M, Sant'Ambrogio G, Sant'Ambrogio FB. Laryngeal and tracheobronchial cough in anesthetized dogs. J Appl Physiol 1994;76:2672–9. [PubMed: 7928899]
40. Canning BJ, Mazzone SB, Meeker SN, Mori N, Reynolds SM, Undem BJ. Identification of the tracheal and laryngeal afferent neurones mediating cough in anaesthetized guinea-pigs. J Physiol 2004;557:543–58. [PubMed: 15004208]
41. Bolser DC, DeGennaro FC, O'Reilly S, Chapman RW, Kreutner W, Egan RW, Hey JA. Peripheral and central sites of action of GABA-B agonists to inhibit the cough reflex in the cat and guinea pig. Br J Pharmacol 1994;113:1344–8. [PubMed: 7889290]
42. Bolser DC, DeGennaro FC, O'Reilly S, McLeod RL, Hey JA. Central antitussive activity of the NK1 and NK2 tachykinin receptor antagonists, CP-99,994 and SR 48968, in the guinea-pig and cat. Br J Pharmacol 1997;121:165–70. [PubMed: 9154323]
43. Dicpinigaitis PV, Dobkin JB. Antitussive effect of the GABA-agonist baclofen. Chest 1997;111:996–9. [PubMed: 9106580]
44. Kotzer CJ, Hay DW, Dondio G, Giardina G, Petrillo P, Underwood DC. The antitussive activity of delta-opioid receptor stimulation in guinea pigs. J Pharmacol Exp Ther 2000;292:803–9. [PubMed: 10640321]
45. Brown C, Fezoui M, Selig WM, Schwartz CE, Ellis JL. Antitussive activity of sigma-1 receptor agonists in the guinea-pig. Br J Pharmacol 2004;141:233–40. [PubMed: 14691051]
46. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44:293–9. [PubMed: 1828878]
47. Willis WD. Role of neurotransmitters in sensitization of pain responses. Ann N Y Acad Sci 2001;933:142–56. [PubMed: 12000017]

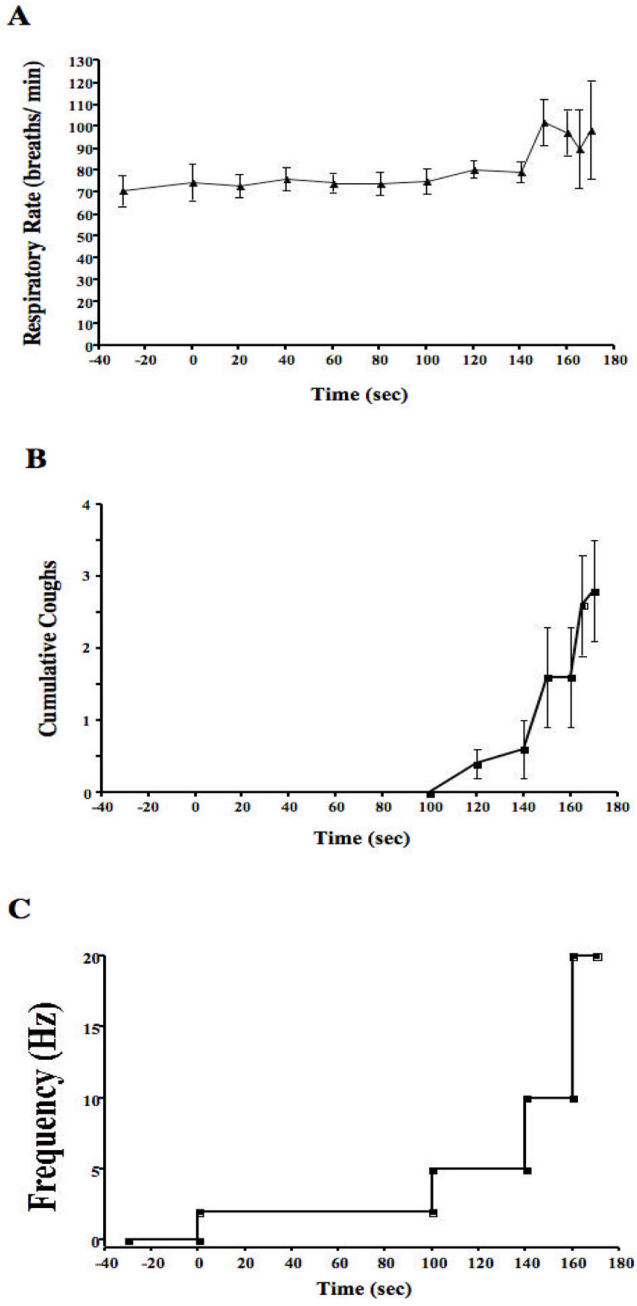

Fig. 1.

Coughing and increased respiratory rate evoked by electrically stimulating the tracheal mucosa of anaesthetized guinea pigs. A custom-built electrode was positioned onto the tracheal mucosa as previously described [40]. Following an equilibration period, four consecutive stimulations consisting of 200 square pulses delivered at 2, 5, 10 and 20 Hz (over consecutive and contiguous time periods of 100, 40, 20 and 10 s, respectively) were delivered while recording A) respiratory rate and B) the cumulative number of coughs evoked. Only when the stimulation frequency reached 20 Hz did all five animals cough (0, 2 and 4 of five animals coughed during stimulation at 2, 5 and 10 Hz, respectively). Respiratory rate increased in all guinea pigs stimulated at 5 Hz Panel C shows the stimulation frequencies and stimulation durations.

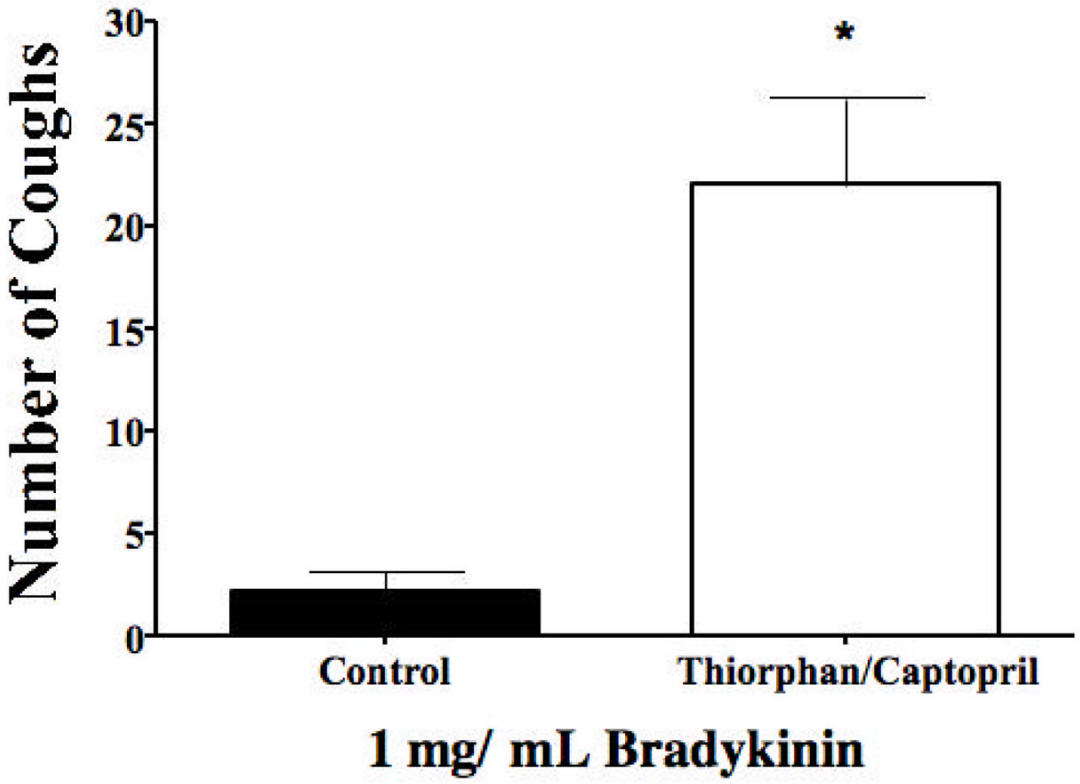

Fig. 2.

Potentiation of bradykinin evoked coughing in conscious guinea pigs following pretreatment with the peptidase inhibitors captopril and thiorphan. Both compounds (0.1 mM) were delivered via aerosol to guinea pigs for 5 min prior to bradykinin challenge. Control animals were similarly pretreated with the vehicle for captopril and thiorphan (saline). Bradykinin challenges were given over 10 min and the total number of coughs evoked was recorded. In the absence of the peptidase inhibitors, the concentration of bradykinin required to evoke coughing was =5 mg/ml. Each bar represents the mean±sem of five experiments.

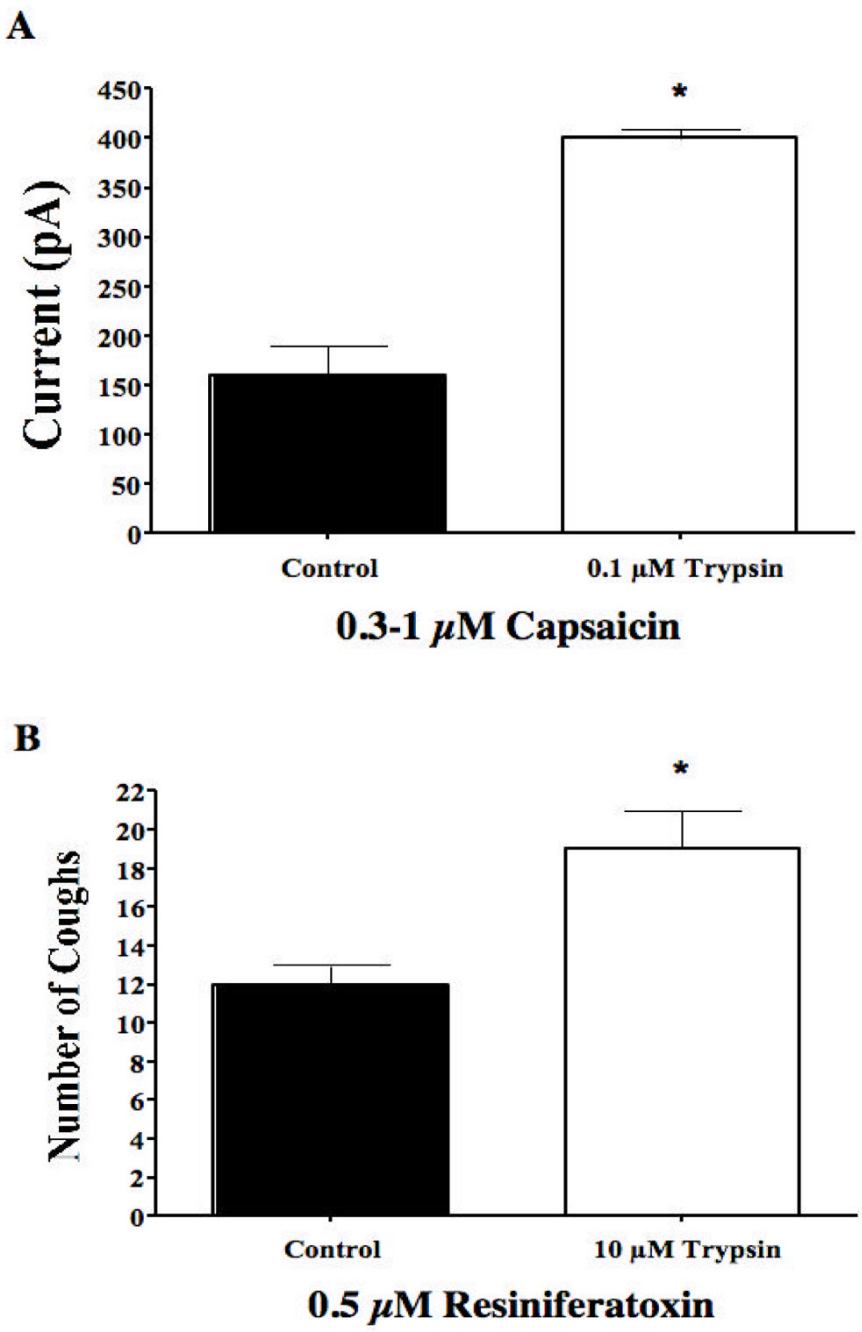

Fig. 3.

Trypsin potentiates TRPV1-dependent A) inward currents in isolated rat bronchopulmonary C-fibres studied using patch clamp techniques and B) coughing in awake guinea pigs. A PAR2 receptor selective agonist mimicked the effects of trypsin. Each bar represents the mean ± sem of at least eight experiments. Data modified from [13,14].

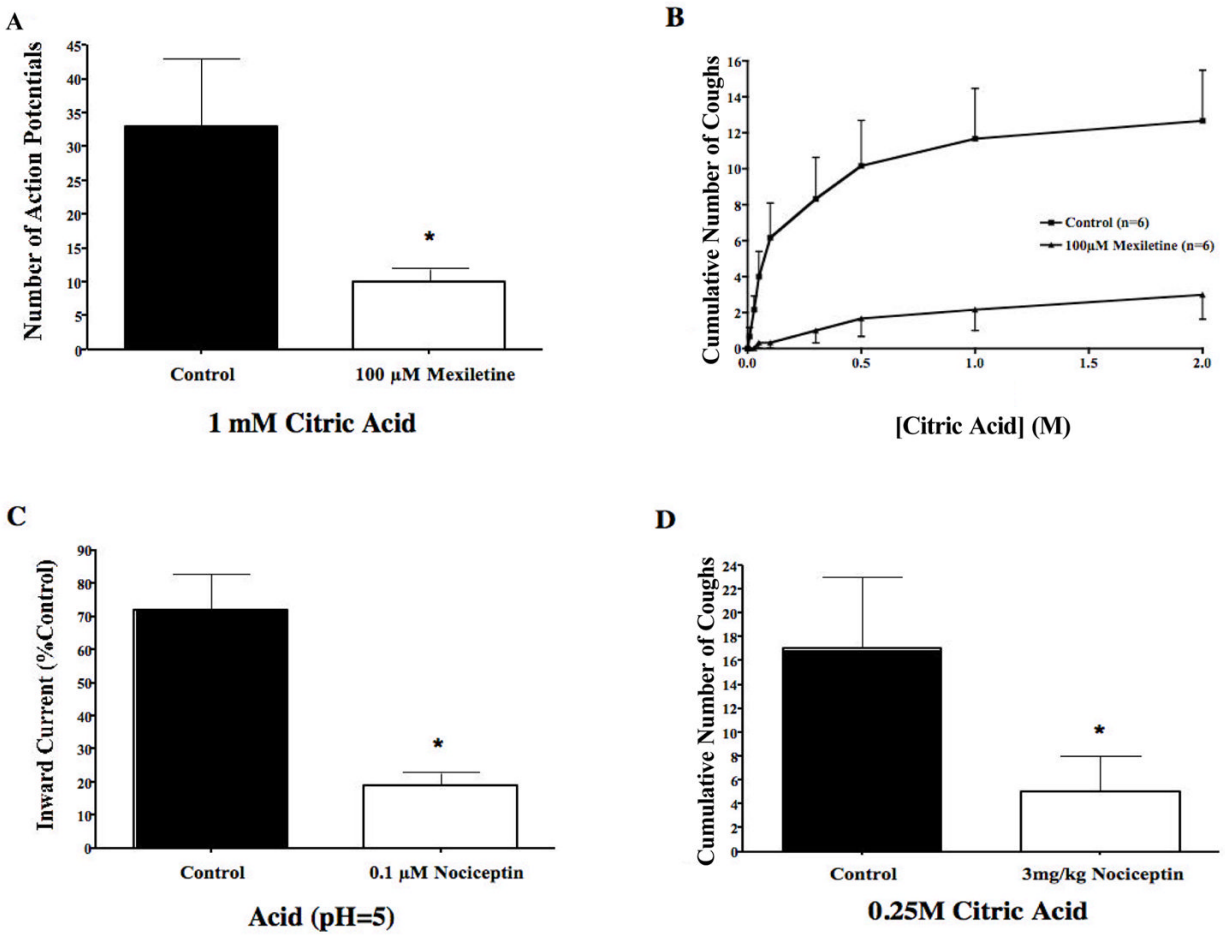

Fig. 4.

Inhibition of airway afferent nerve activation studied *in vitro* (panels A and C) and coughing evoked *in vivo* (panels B and D) in guinea pigs. A) Mexiletine reduces the number of action potentials and the peak frequency of activation evoked by citric acid *in vitro* in studies of nodose ganglia neurones projecting to the guinea pig trachea (n=4). Mexiletine was without effect on threshold sensitivities of these afferents to acid or to mechanical stimulation or their responsiveness to electrical stimulation (data not shown; Figure modified from Carr, 2006). B) Mexiletine markedly inhibits coughing evoked by citric acid, applied topically to the tracheal mucosa of anaesthetized guinea pigs. C) The peptide neurotransmitter nociceptin inhibits the TRPV1-dependent inward currents evoked by acid in isolated airway afferent neurones studied in vitro using patch clamp techniques. Nociceptin was without effect on the TRPV1-independent (amiloride-sensitive) inward currents evoked by acid (data not shown). D) In vivo, nociceptin inhibited citric acid evoked coughing in awake guinea pigs. Data in panels C and D are modified from [26] and are the mean±sem of 5–10 experiments.

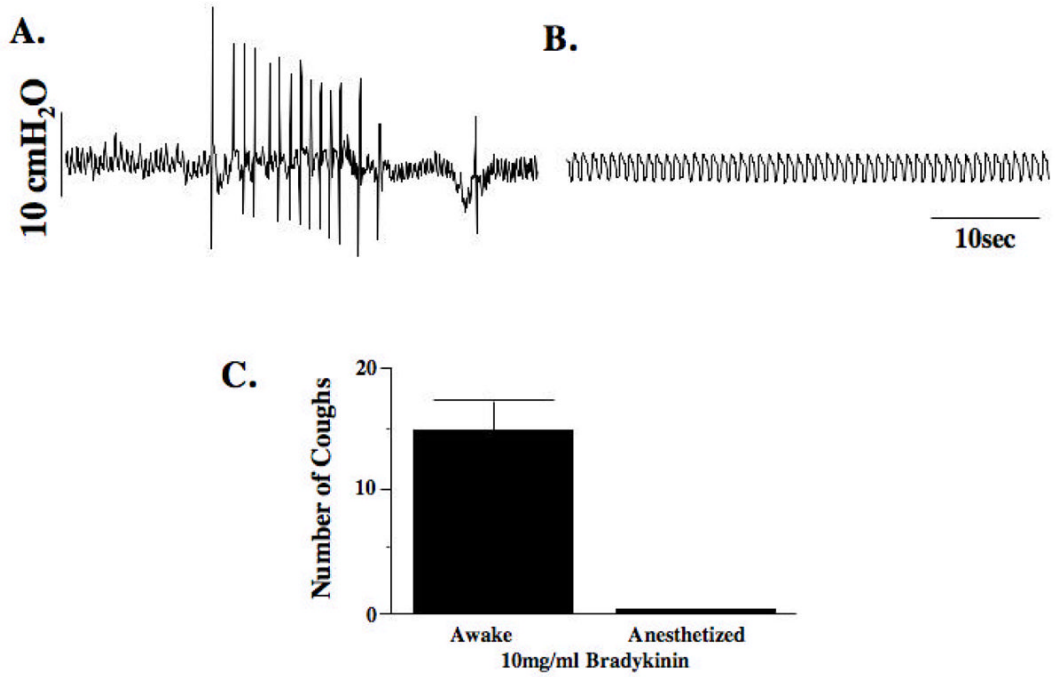

Fig. 5.

General anaesthesia (urethane, 1.5 g/ kg) completely abolishes bradykinin-evoked coughing in guinea pigs (n=5–12). Anaesthetized guinea pigs cough readily in response to electrical or mechanical stimulation of the laryngeal, tracheal or bronchial mucosa or to acid applied topically to the tracheal mucosa (see Figs. 1 and 4; also see [40]). The effects of anesthesia on cough seem to be selective for coughing dependent upon C-fibre activation. Representative traces of the response to bradykinin in awake and anaesthetized guinea pigs are shown in panels A and B respectively. The mean data from these experiments are presented in panel C. Figure reproduced with permission from [40].