

The pharmacology of cough

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Cough is an indispensable defensive reflex. Although generally beneficial, cough is also a common symptom of diseases such as asthma, chronic obstructive pulmonary disease (COPD) and lung cancer. Cough remains a major unmet medical need and, although the centrally acting opioids have remained the antitussive drug of choice for decades, such opioids possess many unwanted side-effects. However, new research into the behaviour of airway sensory nerves has provided greater insight into the mechanisms of cough and new avenues for the discovery of novel non-opioid antitussive drugs. In this article, the pathophysiological mechanisms of cough and the implications of this research for the development of novel antitussive drugs will be discussed. A poster depicting the pharmacology of cough is available online and in print as supplementary material to this article.

Cough is a normal protective reflex that is responsible for keeping the airways free of obstruction and harmful substances. However, cough is also the most common symptom for which medical advice is sought. Consequently, and despite a recent study suggesting that over-the-counter antitussive drugs possess little clinically relevant efficacy [1], such antitussives are among the most widely used drugs in the world. Of course, this wide usage probably reflects the many patients who self-medicate for acute cough associated with transient upper respiratory tract infections ('colds'). However, the more serious medical problem is chronic cough, which can be a symptom of other more serious respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD) and lung cancer. In addition, chronic cough can be a symptom of various extra-pulmonary conditions such as post-nasal drip (PND), gastro-oesophageal reflux (GOR) or even ear and heart disorders [2]. Cough is also a side-effect of certain medications (e.g. angiotensin-converting enzyme inhibitors).

The causes of cough are obviously diverse but the common link between them all is the activation of subsets of airway sensory nerves. Diseases of the respiratory system can lead to activation of sensory nerves at the level of the airway lumen following the release of inflammatory mediators, increased mucus secretion or damage to the airway epithelium. Disorders of other organs that have neurons carried in the vagus (i.e. the oesophagus or the heart) probably interact with airway neurons in higher neuronal centres to elicit the cough reflex [3].

Appropriate treatment of many diseases that have cough as a symptom often leads to improvement or abolition of cough. However, when the aetiology of cough is not established or when cough persists despite treatment of the disease, specific antitussive therapy is indicated [4].

Current antitussive drugs are divided broadly according to their site of action as either central or peripheral, although many antitussives act to some extent at both locations. Centrally acting antitussives act within the CNS to suppress the central cough pathway and comprise the majority of currently used antitussives. However, many of these drugs, including the opioids, which have been the antitussives of choice for decades, are limited by their many side-effects. Peripherally acting antitussives generally inhibit the responsiveness of airway nerve subtypes that evoke cough, although these drugs are not used widely. However, as a better understanding of the cough pathway emerges, many new antitussives are being developed to act peripherally to avoid unwanted CNS effects.

Sensory nerves and the cough reflex

The cough reflex is known to include a 'hard wiring' circuit (Figure 1). The stimuli that initiate the cough reflex stimulate sensory nerve fibres that have been divided broadly into three main groups: A δ -fibres, C-fibres and slowly adapting stretch receptors (SARs). These fibres have been differentiated based on their neurochemistry, anatomical location, conduction velocity, physiochemical sensitivity and adaptation to lung inflation (Table 1).

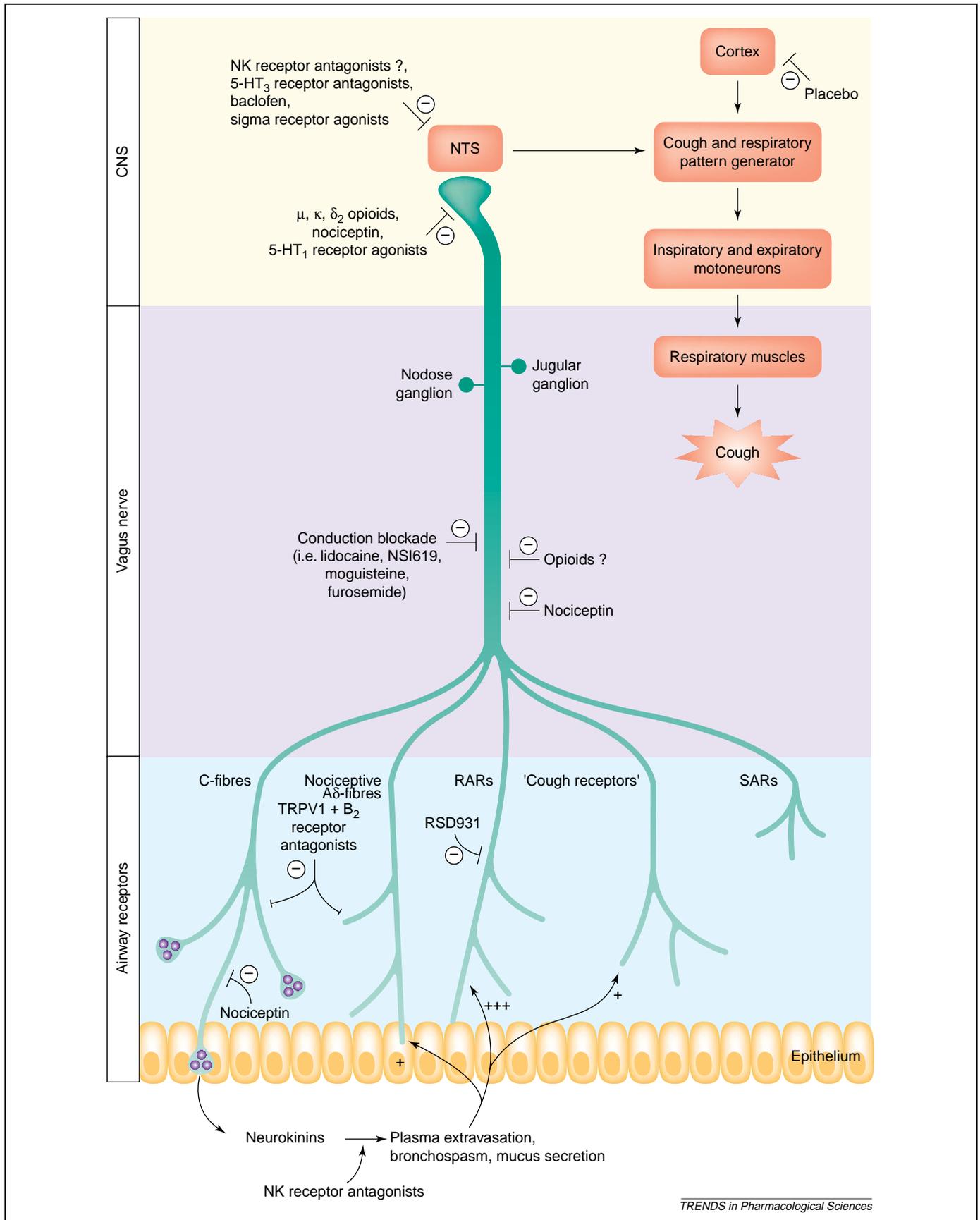
A δ -fibres

Rapidly adapting receptors (RARs) are myelinated A δ -fibres that are thought to terminate within or slightly beneath the epithelium throughout the intrapulmonary airways and respond to changes in airway mechanics to regulate normal breathing [5]. These fibres fire in response to most tussive stimuli and it is likely that their stimulation is of primary importance in the elicitation of the cough reflex [6]. In general, their activity is increased by mechanical stimuli such as mucus secretion or oedema but they are insensitive to many chemical stimuli that provoke cough, including bradykinin and capsaicin [7]. However, in the guinea-pig, at least, the variability in mechanical and chemical sensitivities of RARs is sufficient to believe there might be as many as three subdivisions: RAR-like, nociceptive and polymodal A δ -fibres [3].

The RAR-like fibres are very responsive to mechanical stimulation, unresponsive to direct chemical stimuli such as bradykinin and capsaicin and have their cell bodies in

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Figure 1. The cough reflex and sites of action of some antitussive agents. Airway sensory nerves [e.g. C-fibres, nociceptive A δ -fibres, rapidly adapting receptors (RARs), polymodal A δ -fibres ('cough receptors') and slowly adapting stretch receptors (SARs)] activated in response to a pro-tussive stimulus travel through the vagus nerve to the medulla, where they terminate in the nucleus tractus solitarius (NTS). Second-order neurons relay the message to the respiratory pattern generator, which modifies the activity of the inspiratory and expiratory motoneurons and leads to cough. Antitussives can act peripherally at the level of the airway receptors or on nerve conduction. They can also act centrally, both pre- and post-synaptically.

Table 1. Differentiation of the various sensory nerve receptors thought to be involved in cough, based on a selection of relevant physiological properties^{a,b}

Physiological property	C-fibres	A δ -fibres			SARs
		Nociceptive	'Cough' receptors	RARs	
Ganglia		Jugular		Nodose	
Conduction velocity			Slow		Fast
Involved in the control of regular breathing			No		Yes
Sensitivity to mechanical stimuli		Low		High	
Chemosensitivity: acid			Yes	Probably	No
Chemosensitivity: capsaicin, bradykinin		Yes		No	
Expresses sensory neurokinins	Yes		When sensitized?		No

^aNot all of these receptors have been identified in species other than guinea-pigs.

^bAbbreviations: RARs, rapidly adapting receptors; SARs, slowly adapting receptors.

the nodose ganglia [8,9]. By comparison, nociceptive A δ -fibres are sensitive to capsaicin and bradykinin, are 15 times less responsive to mechanical stimulation and have their cell bodies in the jugular ganglia.

Polymodal A δ -fibres ('cough receptors') have been identified only recently [10]. These fibres are similar to RAR-like fibres because they originate in the nodose ganglia, are activated by mechanical stimulation and acid but are unresponsive to capsaicin, bradykinin, smooth muscle contraction or stretching of the airways. Severing these nerves abolishes the cough response to citric acid and mechanical stimulation in an anaesthetized model of cough in guinea-pigs. It has been proposed that the primary function of these fibres is the elicitation of cough and as such could be regarded as the 'hard-wiring' of the cough reflex [10].

C-fibres

C-fibres have an important role in airway defensive reflexes. They respond to both mechanical (although with a higher threshold than RARs) and chemical stimuli, including sulfur dioxide, capsaicin and bradykinin [7]. In certain species they evoke the peripheral release of sensory neuropeptides via an axon reflex [11]. Neuropeptide-dependent airway smooth muscle contraction, oedema and mucus secretion can activate RARs [12]. However, human airways have very few substance P-containing nerve fibres and at present there is a lack of evidence indicating that these nerves correspond to the terminals of capsaicin-sensitive C-fibres [13,11]. Indeed, human airways only contract modestly in response to capsaicin when compared with guinea-pigs [14], although recently nerves positive for the capsaicin receptor [i.e. transient receptor potential vanilloid 1 (TRPV1)] have been described that do not contain sensory neuropeptides [15], suggesting that capsaicin-mediated effects might be able to occur independently of neuropeptides.

An important role for C-fibres in cough has been proposed because cough can be induced by citric acid, capsaicin and bradykinin, all of which are known to be stimulants of C-fibres in humans and animals [16]. In animal studies, chronic pretreatment with capsaicin to deplete C-fibres of their sensory neuropeptides abolished cough in response to citric acid in conscious animals, without affecting mechanically induced cough [17]. Moreover, cough induced by capsaicin, citric acid, cigarette smoke and bronchospasm in guinea-pigs is inhibited by both centrally and peripherally acting tachykinin receptor

antagonists [18,19] and neutral endopeptidase [20], suggesting a role for neuropeptides, at least in guinea-pigs.

However, there is also evidence suggesting that C-fibres do not evoke cough [10] and might even inhibit cough [21,22]. In several studies where C-fibre stimulants have been administered systemically, mechanically induced cough has been inhibited in various species [21–23]. As described earlier, there is also now evidence that capsaicin might exert its effects via mechanisms other than sensory neuropeptide release [15]. Indeed, TRPV1 receptors have been identified on A δ nociceptive fibres [24], which under normal physiological conditions do not synthesize neuropeptides, but can be activated by capsaicin. Such observations might explain the inability of tachykinin receptor antagonists to modify cough clinically even though they are antitussive in guinea-pigs [25]. Anaesthetized animals fail to cough when capsaicin and bradykinin are applied topically to the lung, but mechanically induced cough can still be evoked [10]. This suggests that C-fibres do not incite cough *per se* but might be involved in the sensitization of the cough reflex. During general anaesthesia cough is inhibited in humans [26], although C-fibres are activated readily and cause profound cardiovascular and respiratory reflexes. Furthermore, RAR-activated cough can be induced in anaesthetized animals [23]. Vagal cooling has been shown to abolish cough while preserving C-fibre dependent reflexes [22], further suggesting that C-fibre activation is not sufficient to cause cough *per se*.

SARs

Although SARs also conduct in the 'A' range, unlike the fibres described earlier, SAR activity is not altered by stimuli that evoke cough, and these fibres are not believed to be directly involved in the cough reflex. However, they might facilitate the cough reflex, as shown in cats and rabbits, via interneurons called 'pump cells', which are believed to either permit or augment the cough reflex as a result of RAR activity [27,28].

Central integration

Clearly, many sensory afferent fibre types contribute to or modulate the cough reflex. The integration of their signals occurs at the level of the nucleus tractus solitarius (NTS) found in the dorsal medulla. Here, both pulmonary and extrapulmonary (from other vagally innervated organs) afferent fibres terminate and provide polysynaptic input to second-order neurons [29]. Although subject to substantial cortical control, these second-order neurons

probably alter the activity of the respiratory neurons that are typically responsible for normal breathing to produce cough [30]. Each of the synapses in this 'cough network' is a potential target for centrally acting antitussives.

Sensitization of the cough reflex

Under inflammatory or disease conditions, many pathological changes can occur around and within sensory nerve fibres, leading to increased excitability in addition to phenotypic changes in receptor and neurotransmitter expression. For example, mechanosensitive A δ -fibres do not contain neuropeptides under physiological conditions but following viral and/or allergen challenge they begin to synthesize neuropeptides [31,24]. In addition, the excitability of airway A δ -fibres and NTS neurons can be increased by antigen stimulation [32,33]. This plasticity of the neurons that mediate cough probably 'sensitizes' the cough reflex, leading to heightened responses. This sensitization of airway nerves could be a more rational target for antitussive development rather than the 'hard-wired' cough reflex (Box 1).

Peripherally acting antitussives

Most cough treatments are designed to target the underlying disease pathology, although a range of pharmacological agents are available that target neuronal pathways directly (Figure 1).

Local anaesthetics

Local anaesthetics such as lidocaine, benzonatate and mexiletine are the most consistently effective peripherally acting antitussive drugs used to treat cough that is resistant to other treatments; this confirms the neural basis of cough. However, their effects are transient and their repeated use is associated with tachyphylaxis, making high doses necessary and leading to unwanted side-effects [34]. Their mechanism of action is believed to be through use-dependent inhibition of voltage-gated Na⁺ channels, thereby reducing action potential generation and transmission in afferent nerves. However, mexiletine blocks cough induced by tartaric acid but not by capsaicin [35], suggesting that different tussive stimuli induce cough by pathways that can be differentially regulated by blockade of Na⁺ channels.

RSD931

RSD931 (see [Chemical names](#)) is a quaternary ammonium compound that exhibits antitussive activity in both guinea-pigs and rabbits [36]. Although RSD931 is a weak local anaesthetic, in the rabbit it inhibits spontaneous and histamine-evoked discharges from A δ -fibres and activates pulmonary C-fibres, which is distinctive from lidocaine because lidocaine suppresses all nerve fibres in the airway [36]. Such results suggest that RSD931 is antitussive via an effect on A δ -fibres, independent of local anaesthetic effects. Analogues of RSD931 are currently under investigation as novel peripherally acting antitussives.

Tachykinin receptor antagonists

Tachykinins are a group of peptides, including substance P, neurokinin A (NKA) and neurokinin B (NKB), located

in peripheral endings of capsaicin-sensitive primary afferent neurons (C-fibres). Neuropeptides have been implicated in cough because their release from C-fibres via axon reflex can stimulate RARs to enhance the cough reflex [37]. A central action is also likely because SP and NKA can directly activate cough pathways in the brainstem (termed central sensitization) [38]. Several potent tachykinin receptor antagonists have been developed as antitussive drugs.

The tachykinin NK₁ receptor antagonists FK888 and CP99994 inhibited cough induced by tobacco smoke and citric acid in guinea-pigs, and mechanical stimulation of the trachea in anaesthetized cats [18,19]. CP99994 can cross the blood-brain barrier and thus some central activity might account for its effect [18]. However, in a single study of asthmatic subjects CP99994 did not inhibit bronchoconstriction or cough induced by hypertonic saline [25]. Following a similar pattern, NK₁ receptor antagonists attenuated nociceptive responses in animals but failed as analgesics in humans [39]. An NK₂ receptor antagonist (SR48968) suppressed the cough reflex and was more potent than codeine in the guinea-pig [40]. Interestingly, both SR48968 and codeine only partially inhibited the cough reflex when administered by the inhaled route [19,41]. The NK₃ receptor antagonists SR142801 and SB235375 (which has low CNS penetration) inhibited cough induced by citric acid in guinea-pigs and pigs [42,43].

Nociceptin

Nociceptin/orphanin FQ (N/OFQ) is an opioid-like peptide and is the endogenous ligand for the NOP₁ receptor [44]. NOP₁ receptors are distributed widely in the CNS and on airway nerves [45]. Nociceptin has been found to inhibit the release of sensory neuropeptides following depolarization of C-fibres [46] and to inhibit bronchospasm in the guinea-pig [47]. Recently, McLeod *et al.* showed that N/OFQ inhibited cough induced by mechanical stimuli or capsaicin in guinea-pigs and cats [48]. This suggests that NOP₁ receptors are involved in the modulation of the cough reflex and that selective NOP₁ receptor agonists might therefore have potential as novel peripherally acting antitussives, although to date there have been no studies with such drugs in humans.

Vanilloid receptor (TRPV1) antagonists

TRPV1 receptors are localized predominantly in small-diameter afferent neurons in dorsal and vagal sensory ganglia [49]. They are activated by capsaicin, noxious stimuli such as protons and heat, and a range of lipid mediators such as 15-hydroperoxyeicosatetraenoic acid (15-HPETE) [50] and N-arachidonoyl-dopamine (NADA) [51]. Anandamide was described initially as an endogenous activator of cannabinoid receptors, although it has also been shown to activate TRPV1. Consequently, its effect on cough is variable and might depend on the balance between cannabinoid and TRPV1 activity [48,52]. The TRPV1 antagonist capsazepine has been shown to inhibit cough in animal models [53] as has iodo-resiniferatoxin (i-RTX), a TRPV1 antagonist that is 10–100 times more potent than capsazepine [54]. Distilled water-induced cough is not blocked by TRPV1 antagonism [53],

Box 1. Challenges in the development of new antitussives

The development of novel antitussives is a challenging area, not least because of the lack of good predictive models, both clinically and preclinically. For example, it is highly debatable whether capsaicin challenge in healthy volunteers is a good cough model because many drugs that improve pathological cough fail to inhibit capsaicin-induced cough (Table I). Much of the preclinical work has also relied on using capsaicin- or citric acid-induced cough in healthy guinea-pigs and there are many examples of drugs, including 5-HT₃ receptor antagonists, 5-HT₁ receptor agonists, nifedipine, tachykinin NK₁ receptor antagonists and the dopamine D₂-β₂-adrenoceptor antagonist sibenadet, that are antitussive in these preclinical models but do not show antitussive effects in humans [6,73–75].

The value and limitations of animal models of cough have been discussed elsewhere [76]. It would seem sensible to ensure that novel drugs exhibit antitussive activity in at least two species before being tried in humans and perhaps more importantly should exhibit antitussive activity in hypertussive models because the ultimate aim of antitussive therapy in the clinic is to reduce excess cough (sensitization of cough reflexes), rather than inhibiting cough altogether (i.e. the 'hard wiring' cough reflex). Clearly, there is an urgent need to develop more-realistic models of cough preclinically and, equally importantly, to consider the best way of evaluating novel antitussives in early clinical development for proof of concept before entering larger clinical studies.

Table I. Results of clinical trials investigating the efficacy of selected antitussive compounds against agents used to induce cough and in disease states^a

Class of compound or drug tested	Capsaicin	Low [Cl ⁻]	Citric acid	ACE inhibitor cough	Pathological cough ^d	URTI	Other ^e	Clinical use in cough treatment	Refs
Opioids	±		+		+	–		Gold standard	[1,2,73,77]
Sigma receptor agonists ^f	–		+/-		+	+/-		Yes	[1,4,78–80]
Baclofen	+			+ ^c	+ ^c			Yes	[4]
Caramiphen					+			Yes	[4]
Histamine H ₁ receptor antagonists	–		+		+/-	–		Yes	[1,4,81,82]
Furosemide	–	± ^b						Yes	[58,59]
Glaucine			–		+	+ ^c		Yes	[83–85]
Local anaesthetics	+		+ ^c		+ ^c			Yes	[73,86]
Corticosteroids					+			Primarily anti-asthmatic	[87]
β ₂ -Adrenoceptor agonists	– ^{b,c}		± ^b			+ ^c		Primarily anti-asthmatic	[73]
Cromones	–	+ ^b		+	+	+		Primarily anti-asthmatic	[73,88–91]
Expectorants and mucolytics	–		+			+/-		OTC 'cough remedies'	[1,4,92]
Antimuscarinics	– ^c	+ ^b	± ^b		+				[73,93,94]
5-HT ₁ receptor agonists	–	+							[59]
5-HT ₃ receptor antagonists	–								[73]
Leukotriene receptor antagonists	+ ^b /– ^{b,c}				–				[60,73,95]
Moguisteine						+			[1]
Tachykinin receptor antagonists							+ ^{b,c} /– ^b		[74]
Sibenadet (dopamine D ₂ receptor and β ₂ -adrenoceptor antagonist)					–				[75]

^aAbbreviations and symbols: ACE, angiotensin-converting enzyme; OTC, over the counter; URTI, upper respiratory tract infection; +, significant antitussive effect; –, no significant effect; ±, conflicting data between asthmatics and normal subjects; +/-, conflicting data between studies.

^bAt least one trial was in asthmatic subjects.

^cTrial lacking a placebo control.

^dIncludes cancer, chronic obstructive pulmonary disease, chronic non-productive cough and respiratory disease.

^eIncludes bradykinin-induced and hypertonic saline-induced cough.

^fSome sigma receptor agonists might have other mechanisms of action. See main text for details.

implying that TRPV1 antagonists might not affect defensive cough but could be of potential use under conditions where there is sensitization of the cough reflex via activation of TRPV1-sensitive afferents.

Ion channel openers

NS1619 causes cell hyperpolarization by opening Ca²⁺-activated K⁺ channels (BK_{Ca}), thereby inhibiting citric acid- and bradykinin-induced cough and the generation of action potentials in guinea-pig tracheal Aδ- and

C-fibres [55]. However, clinical studies have not yet been reported with such drugs.

Moguisteine is a peripherally acting antitussive that can act as an ATP-sensitive K⁺ channel opener [56] and in clinical trials reduced the frequency of cough in patients with lung cancer to a similar extent as that produced by codeine [57].

The loop diuretic furosemide might alter the Cl⁻ concentration around airway sensory receptors located near the epithelial surface [58]. In humans, furosemide

Chemical names**BW443C:** Tyr-D.Arg-Gly-Phe (4NO₂).Pro.NH₂**CP99994:** (+), (2*R*,3*R*)-3-(2-methoxybenzyl-amino)-2-phenylpiperidine**FK888:** N(2)-[(4*R*)-4-hydroxy-1-(1-methyl-1*H*-indol-3-yl) carbonyl-L-prolyl]-N-methyl-N-phenylmethyl-3-(2-naphthyl)-L-alaninamide**NS1619:** 1-(2'-hydroxy-5'-trifluoromethylphenyl)-5-trifluoromethyl-2(3 H) benzimidazolone**RSD931:** carcinium chloride**SB235375:** (-)-(S)-N-(α -ethylbenzyl)-3-(carboxymethoxy)-2-phenylquinoline-4-carboxamide**SKF10047:** N-allylnormetazocine**SR142801:** (S)-(N)-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl) piperidin-3-yl) propyl)-4-phenylpiperidin-4-yl)-N-methylacetamide**SR48968:** (+)-N-methyl-[4-(4-acetylamino-4-phenyl piperidino)-2-(3,4-dichloro-phenyl)butyl] benzamide

inhibited cough induced by low [Cl⁻] solutions but not capsaicin. Furosemide also inhibited airway afferent action potential discharge and sensitized SARs. However, intravenous furosemide failed to suppress cough [58] and the antitussive effects of furosemide were less apparent in subjects with mild asthma when compared with healthy subjects [59].

Leukotriene receptor antagonists

Zafirlukast, a cysteinyl leukotriene receptor antagonist, has shown therapeutic efficacy in cough-variant asthma even in patients who are unresponsive to inhaled bronchodilators and corticosteroids [60]. The mechanism of action of zafirlukast in the clinical setting is not fully understood and further investigation is needed to establish whether leukotriene receptor antagonists have wider potential as antitussive drugs.

Bradykinin receptor antagonists

Bradykinin activates C-fibres and can induce coughing in asthmatic subjects [61]. Icatibant (HOE140), a bradykinin B₂ receptor antagonist, inhibited citric acid-induced cough in the guinea-pig [61], suggesting that B₂ receptor antagonists should be evaluated for their antitussive effects in humans.

Centrally acting antitussives**Opiates**

Narcotic opioids such as codeine, morphine and dihydrocodone are all good antitussives primarily via their action at central mu opioid peptide receptors [62]. However, at effective doses they can cause addiction, respiratory depression and nausea. Codeine has a better side-effect profile than the others and is often considered the 'gold standard' in antitussive therapy. Recently, both delta opioid peptide receptor antagonists and agonists have been found to be antitussive in animal models [2]. These conflicting data probably reflect variable selectivity of these drugs for δ_1 and δ_2 receptors [63]. Additionally, antitussive kappa opioid peptide receptor agonists have been reported [63]. Modulation of previously untargeted central opioid receptors appears a promising avenue for antitussive drug development.

Opioid receptors have also been located in the periphery but their ability to exert considerable antitussive action at this level is debatable. Aerosol administration of

a mu opioid was not antitussive in humans challenged with capsaicin [64] and, although the peripherally acting peptide BW443C was antitussive in animal studies [65], there is only limited clinical evidence to support this antitussive effect [66].

Sigma receptors

It is thought that the opioids dextromethorphan and noscapine act on sigma receptors (centrally and peripherally) rather than at classic opioid receptors [67]. The inhibitory effect of noscapine on the B₂ receptor [68] and the activity of dextromethorphan at NMDA receptors [69] might also contribute to their antitussive effects. Some research has been undertaken with newer, more efficacious sigma receptor agonists such as SKF10047 [69].

GABA receptors

GABA is an inhibitory neurotransmitter that is present both centrally and in the periphery. The GABA_B receptor antagonist baclofen has been shown to be antitussive centrally in animal studies and several clinical trials have proven its efficacy as an antitussive drug in humans [4]. An analogue of baclofen that does not cross the blood-brain barrier has also been shown to be antitussive [70], suggesting that peripherally acting GABA receptor agonists might also be useful in the treatment of cough.

Other centrally acting agents

Many effective centrally acting antitussives have not been shown to target any of the above pathways and their mechanisms of action remain to be elucidated. Diphenhydramine, a histamine H₁ receptor antagonist, and caramiphen are both centrally acting antitussives with unknown sites of action [4]. Glucine is another such drug, although α -adrenoceptor and phosphodiesterase E₄ (PDE₄) inhibition could contribute to this effect [71]. This latter effect is of interest because recent studies have shown that the PDE₄ inhibitor cilomilast is not antitussive *per se* but inhibits hypertussive responses in guinea-pigs [72].

Concluding remarks

Our understanding of the reflexes involved in modulating cough and hypertussive responses is increasing but there is still much to learn. Cough remains a relatively poorly studied area of pulmonary research compared with bronchospasm and airways inflammation. There is a clear need to develop a non-opioid antitussive drug that ideally modulates pathological cough reflexes while leaving the normal cough reflex unaltered. Nonetheless, significant progress is being made to develop novel antitussive drugs and the growing recognition of cough as an unmet medical need will hopefully ensure more research into this important symptom.

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Supplementary data

Supplementary data associated with this article can be found at [10.1016/j.tips.2004.09.009](http://dx.doi.org/10.1016/j.tips.2004.09.009)

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