

Peripheral Mechanisms II: The Pharmacology of Peripherally Active Antitussive Drugs

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Contents

1	Introduction	156
2	Mechanisms of Hypertussive States	157
2.1	Peripheral Sensitization	157
2.2	Central Sensitization	158
3	Role of Sensory Nerves in the Cough Reflex	159
3.1	A δ -Fibres	159
3.2	C-Fibres	160
3.3	Slowly Adapting Stretch Receptors	162
4	Antitussive Drugs	162
4.1	Sodium Channel Blockers	162
4.2	Tachykinin Receptor Antagonists	164
4.3	NOP Receptor Agonists	165
4.4	Cannabinoids	166
4.5	Drugs Targeting Transient Receptor Potential Channels	167
4.6	Ion Channel Modulators	169
4.7	Leukotriene Receptor Antagonists	169
4.8	Bradykinin Antagonists	170
4.9	Opioids	170
4.10	Sigma Receptor Ligands	171
4.11	GABA Receptor Ligands	171
5	Challenges to the Development of Novel Antitussive Drugs	172
6	Conclusion	176
	References	176

Abstract Cough is an indispensable defensive reflex. Although generally beneficial, it is also a common symptom of diseases such as asthma, chronic obstructive pulmonary disease, upper respiratory tract infections, idiopathic pulmonary fibrosis and lung cancer. Cough remains a major unmet medical need and although the centrally acting opioids have remained the antitussive of choice for decades, they have

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155

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 review, the pathophysiological mechanisms of cough and the development of novel antitussive drugs are reviewed.

1 Introduction

Cough is a reflex mechanism protecting the airways by ejecting obstructive or harmful substances. The afferent component of the reflex involves vagal sensory nerves with bodies in the jugular or nodose ganglia and terminals within the airway wall, activated by a combination of chemical and/or mechanical stimuli. Up to five subtypes of sensory airway afferents have been characterized (Canning 2006), all synapsing in the nucleus tractus solitarius (nTS) of the brainstem, from where second-order neurones project to the medullary respiratory pattern generator to initiate cough. Whilst acute cough (lasting a few weeks) is not a serious clinical problem, it is the most common respiratory ailment for which patients seek medical help and around \$1 billion is spent per annum in the USA on cough remedies (McGarvey and Morice 2006). Chronic cough (persisting for more than 8 weeks) is a serious debilitating condition estimated to affect some 14% of the population (Cullinan 1992). It can be a symptom of both pulmonary conditions, such as asthma (Dicpinigaitis 2006b), chronic obstructive pulmonary disease (COPD) (Braman 2006), idiopathic pulmonary fibrosis (Hope-Gill et al. 2003), upper-airway cough syndrome (postnasal drip) (Pratter 2006) and lung cancer (Kvale 2006), and extrapulmonary conditions, such as gastro-oesophageal reflux (Irwin 2006). It has an adverse effect on quality of life, being associated with complications ranging from frequent retching through incontinence and insomnia to social embarrassment (French et al. 1998, 2004, 2005). Treatment of the underlying disease often resolves chronic cough (Morice et al. 2004; Pratter et al. 2006), but this can take several months, during which time effective antitussive treatment would be desirable. Furthermore, there remains a significant cohort (~40% of patients) (O'Connell et al. 1994) in which either the underlying cause is known but is irreversible or there is no identifiable underlying cause. In these individuals, relief from chronic cough depends upon effective antitussive drug treatment. Available drugs are of either limited effectiveness (Schroeder and Fahey 2002, 2004) or have problematic side effects and consequently there is a pressing need for safer, more effective agents (Dicpinigaitis 2004; Morice and Geppetti 2004; Reynolds et al. 2004).

Current antitussives are broadly divided according to their site of action as either central or peripheral, although many act to some extent at both locations. Centrally acting antitussives act within the central nervous system (CNS) to suppress central cough pathways and comprise the majority of currently used drugs. However, opioids, which are gold standard antitussive agents, suffer from numerous

unwanted side effects, including sedation, constipation and drug dependence. There is therefore a clear and unmet need for the development of novel drugs which target airway afferent nerves directly and/or that target the processes that give rise to central sensitization of the cough reflex, possibly at the level of the nTS.

2 Mechanisms of Hypertussive States

In chronic, hypertussive cough states, normally innocuous stimuli that would not normally initiate a response, evoke cough (Bonham et al. 2004). There are clear parallels here with alterations during chronic pain states, characterized by hyperalgesia and allodynia. The mechanisms underlying such alterations have been well studied (Ji and Woolf 2001; Melzack et al. 2001; Woolf and Salter 2000) and can be subdivided into 'peripheral' and 'central' sensitization.

2.1 Peripheral Sensitization

Peripheral sensitization involves hyperexcitability of sensory neurones due to, for example, changes in voltage-gated sodium channel properties (Lai et al. 2004). Under inflammatory or disease conditions, many pathological changes can occur around and within sensory nerve fibres, leading to increased excitability as well as phenotypic changes in receptor and neurotransmitter expression. For instance, airway mechanosensitive A δ -fibres do not contain neuropeptides under physiological conditions, but following viral and/or allergen challenge begin to synthesize neuropeptides (Carr et al. 2002; Myers et al. 2002). In addition, the excitability of airway A δ -fibres and nTS neurones can be increased by antigen stimulation of the lungs of sensitized animals (Chen et al. 2001; Udem et al. 2002). Similarly, chronic exposure of guinea pigs to sidestream tobacco smoke augments pulmonary C-fibre responses to capsaicin and to lung hyperinflation (Mutoh et al. 1999, 2000). In addition, allergic airway inflammation has been reported to increase neuropeptide expression (substance P, neurokinin A and calcitonin gene related peptide, CGRP) in sensory neurones originating in the guinea pig airway (Fischer and Hoffmann 1996; Myers et al. 2002). Together, these experimental studies suggested that sensory nerve plasticity can occur during inflammatory insults to the lung.

This view is also supported by clinical studies which have reported an increase in the number of TRPV1 immunopositive neurones (Groneberg et al. 2004) and the density of neuropeptide immunoreactive nerves (Lee et al. 2003; O'Connell et al. 1995) in the airways of individuals with chronic cough syndromes. This plasticity of the sensory neurones mediating cough provides a plausible mechanism leading to the hypertussive state, or 'sensitization'. The mechanisms contributing to the sensitization of airway nerves may be a more rational target for antitussive drug development rather than the 'hard-wired' cough reflex since it is generally

accepted that inhibition of cough per se is probably of limited clinical benefit as this protective mechanism is of critical importance for clearing unwanted airway secretions.

2.2 Central Sensitization

In pain pathways, central sensitization involves enhanced efficiency of excitatory synaptic transmission pathways within the CNS, notably in the dorsal horn of the spinal cord at the synapse between the sensory nociceptor fibres and second-order relay neurones (Ji et al. 2003). It has been suggested that central sensitization in the cough reflex loop might also underlie hypertussive states (Bonham et al. 2004, 2006a, b), but to date, there are few data confirming this.

In the spinal cord, central sensitization manifests itself as increased postsynaptic excitability of second-order relay neurones following a period of high-intensity stimulation of nociceptor afferents (Melzack et al. 2001; Woolf and Salter 2000). The relay neurones normally have a high threshold, responding only to the high-intensity stimulation associated with the 'pain' response (Woolf and King 1989). Following central sensitization, the threshold is lowered such that normally innocuous stimuli now activate the relay neurones (Cook et al. 1987; Woolf and King 1990; Woolf and Wall 1986). The primary neurotransmitter at the synapse is glutamate, acting postsynaptically on both ionotropic (*N*-methyl-D-aspartate, NMDA; and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate, AMPA) receptors and metabotropic receptors (Andresen and Yang 1995; Chen et al. 1999; Drewe et al. 1990; Fortin and Champagnat 1993; Mifflin and Felder 1990; Smith et al. 1998; Wang and Bradley 1995), whilst γ -aminobutyric acid (GABA) acting on both GABA_A and GABA_B receptors mediates inhibitory synaptic responses (Brooks et al. 1992; Smith et al. 1998; Wang and Bradley 1995). There is also evidence that substance P is released (Colin et al. 2002; Duggan et al. 1990) and acts on neurokinin 1 (NK₁) receptors to cause postsynaptic excitation and presynaptic modulation of glutamate and GABA release (Bailey et al. 2004; Sekizawa et al. 2003) thereby modulating the responsiveness of the postsynaptic cells.

Several mechanisms have been reported to contribute to the increase in synaptic efficacy (Ji et al. 2003; Ji and Woolf 2001; Malcangio and Lessmann 2003; Park and Vasko 2005). Relatively low frequency (~5 Hz) stimulation of nociceptors can cause 'windup' whereby successive stimuli cause increasing degrees of postsynaptic depolarization owing to removal of the voltage-dependent magnesium block of NMDA receptors. Windup is short-lived, dissipating on removal of the synaptic input, but the calcium entry associated with NMDA receptor activation, allied to that through voltage-gated channels, activates intracellular signalling cascades that lead to longer-lasting changes in the expression and function of receptors and ion channels (Caudle et al. 2005; Gao et al. 2005; Guo et al. 2002; Ji et al. 1999; Pezet et al. 2005; Suzuki et al. 2005; Yang et al. 2004; Zou et al. 2000).

There is good evidence to suggest that a similar scenario might operate in the nTS following stimulation of airway afferent nerves during an inflammatory insult

to the airways. Insults that can induce a hypertussive state produce changes in the presynaptic inputs to the nTS, but whether they also produce postsynaptic changes indicative of central sensitization is less clear. This view is supported by various experimental findings. The increased C-fibre responsiveness to capsaicin in guinea pigs exposed to tobacco smoke is paralleled by increased firing of nTS relay neurones (Bonham et al. 2001; Mutoh et al. 2000); extended allergen exposure and episodic exposure to ozone can also cause an increase in excitability of primate nTS neurones (Chen et al. 2001, 2003). Furthermore, the intracerebroventricular administration of neurokinin antagonists inhibited the ability of airway C-fibre stimulation to increase the sensitivity of the cough response to mechanical irritation of the airway mucosa (Mazzone et al. 2005). The release of sensory neuropeptides centrally into the brainstem might facilitate synaptic input from mechanosensitive afferent nerves in the lung that are involved in cough.

Clearly many sensory afferent fibre types contribute to or modulate the cough reflex. The integration of their signals occurs at the level of the 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 neurones (Jordan 2001). Although subject to substantial cortical control, these second-order neurones likely alter the activity of the respiratory neurones typically responsible for normal breathing to produce cough (Pantaleo et al. 2002). Each of the synapses in this 'cough centre' is a potential pharmacological target for centrally acting antitussives.

3 Role of Sensory Nerves in the Cough Reflex

The cough reflex is known to include a 'hard-wiring' circuit as recently proposed (Canning et al. 2004; Canning 2006). The stimuli initiating the cough reflex stimulate sensory nerve fibres that have been broadly divided into three main groups: A δ -fibres, C-fibres and slowly adapting stretch receptors (SARs). These fibres have been differentiated on the basis of their neurochemistry, anatomical location, conduction velocity, physiochemical sensitivity and adaptation to lung inflation (Canning et al. 2004; Canning 2006; Reynolds et al. 2004).

3.1 A δ -Fibres

Rapidly adapting receptors (RARs) 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 (Widdicombe 2003). These fibres are sensitive to most tussive stimuli and it is likely their stimulation is of primary importance in the elicitation of the cough reflex (Widdicombe 2003). 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 (Lee et al. 2001). However, in the guinea pig at least, the variability in mechanical and chemical sensitivities of A δ -fibres is sufficient to believe there may be as many as three subdivisions: RAR-like, nociceptive and polymodal A δ -fibres (Mazzone 2005).

The RAR-like A δ -fibres are very responsive to mechanical stimulation, unresponsive to direct chemical stimuli like bradykinin and capsaicin, and have their cell bodies in the nodose ganglia (Hunter and Udem 1999; Riccio et al. 1996). By comparison, nociceptive A δ -fibres are sensitive to capsaicin and bradykinin, are 15 times less responsive to mechanical stimulation, have their cell bodies in the jugular ganglia and are mainly carried in the superior laryngeal nerve. The role of RARs as primary initiators of cough has been disputed following a number of observations (Mazzone and McGovern 2007). For example, cough sensitivity in healthy subjects is not altered by bronchoconstrictor agents which would be expected to activate RARs (Fujimura et al. 1996); exogenous administration of neuropeptides which would be anticipated to activate RARs indirectly owing to a combination of bronchoconstriction, mucus secretion and oedema was ineffective at evoking cough in healthy subjects, although cough to this stimulus is observed in patients with inflamed lungs (Hope-Gill et al. 2003; Sekizawa et al. 1996); and sensory nerve activation and, by extension, release of sensory neuropeptides failed to initiate cough following indirect activation of RARs in anaesthetized guinea pigs (Canning et al. 2004; Mazzone et al. 2005). It seems likely that activation of RARs resulting in cough may be of greater relevance in disease. Nonetheless, these inconsistencies have led investigators to further probe the role of A δ -fibres in cough.

Only recently have the polymodal A δ -fibres been identified. These fibres are similar to RAR-like fibres in that 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. Interestingly, the conduction velocity of these polymodal A δ -fibres is much slower than the conduction velocity of RARs or SARs and is much faster than that of C-fibres. Furthermore, severing the recurrent laryngeal nerves which supply innervation to the trachea abolished cough in response to mechanical irritation of the tracheal mucosal surface in guinea pigs (Canning et al. 2004). It has been proposed that the primary function of these fibres is the elicitation of cough and as such they may be regarded as the 'hard-wiring' of the cough reflex (Canning et al. 2004; Mazzone et al. 2005).

3.2 C-Fibres

C-fibres play an important role in airway defensive reflexes. They respond to both mechanical (though with a higher threshold than A δ -fibres) and chemical stimuli, including sulphur dioxide, capsaicin and bradykinin (Lee et al. 2001). In certain species they evoke the peripheral release of neuropeptides such as substance P, neurokinin A and CGRP via an axon reflex which leads to bronchoconstriction and

neurogenic inflammation. Neuropeptide-dependent airway smooth-muscle contraction, oedema and mucus secretion can activate RARs. However, human airways contain 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 (Lundberg et al. 1984). Consistent with this observation, human airways from non-diseased individuals only contract modestly in response to capsaicin when compared with those of guinea pigs (Spina et al. 1998), although TRPV1-positive nerves have been described in the lung which do not contain sensory neuropeptides (Kagaya et al. 2002; Watanabe et al. 2005, 2006), suggesting that capsaicin-mediated effects may be able to occur independently of the release of neuropeptides. Similarly, TRPV1 receptors have been identified on A δ nociceptive fibres (Myers et al. 2002), which under normal physiological conditions do not synthesize neuropeptides, but can be activated by capsaicin. If these fibres were involved in the sensitization of the cough reflex, then this might explain the inability of neurokinin antagonists to modify cough clinically (Fahy et al. 1995). However, it is also likely that changes in C-fibre activity may occur in disease and hence these nerves would be anticipated to play a role in hypertussive states. Indeed, cough sensitivity to capsaicin is heightened in respiratory disease (Hope-Gill et al. 2003; Nakajima et al. 2006; O'Connell et al. 1996; Weinfeld et al. 2002) and the density of TRPV1- and neuropeptide-containing nerves is increased in chronic cough states (Groneberg et al. 2004; Lee et al. 2003; O'Connell et al. 1995).

A critical role for C-fibres in cough has been proposed since this response can be induced by citric acid, capsaicin and bradykinin, all agents known to be stimulants of C-fibres in humans and animals (Karlsson 1996). In animal studies, chronic pretreatment with capsaicin to deplete C-fibres of their sensory neuropeptides abolished cough as a response to citric acid in conscious animals, without affecting mechanically induced cough (Forsberg et al. 1988). It is plausible that high doses of capsaicin might also impair the function of a subpopulation of A δ nociceptive fibres which express TRPV1 (Myers et al. 2002) and therefore might have contributed to the functional impairment to cough in response to citric acid. Furthermore cough induced by capsaicin and citric acid was abolished when animals were pretreated with neurokinin antagonists (Bolser et al. 1997); whilst cough induced by capsaicin, cigarette smoke and bronchospasm in guinea pigs is inhibited with neurokinin antagonists (Yasumitsu et al. 1996) and by promoting degradation of endogenously released neuropeptides following treatment with neutral endopeptidase (Kohrogi et al. 1989), suggesting a role for neuropeptides in this cough response, at least in guinea pigs.

However, there is evidence to show that activation of C-fibres does not evoke cough. Anaesthetized animals failed to cough in response to capsaicin and bradykinin, yet the topical application of citric acid or mechanical irritation of the mucosal surface still evoked a cough response (Canning et al. 2004). This suggested that activation of C-fibres does not incite cough per se. In several studies, the systemic administration of capsaicin actually inhibited cough following mechanical stimulation of the upper airways in anaesthetized animals (Tatar et al. 1988, 1994). In contrast to these findings, the subthreshold stimulation of C-fibres by capsaicin

or bradykinin administered topically to the lung increased cough sensitivity to mechanical irritation of the upper airways (Mazzone et al. 2005) and could therefore help to explain why direct stimulation of these nerves is not necessary to induce cough per se, but is likely to 'sensitize' the cough reflex.

3.3 Slowly Adapting Stretch Receptors

The role of SARs in cough has received very little attention, although they are not believed to be directly involved, as their activity is not altered by stimuli evoking cough. However, experimental evidence in cats and rabbits suggested that SARs may facilitate the cough reflex, via interneurons called 'pump cells', by mechanisms that remain to be established, which either permit or augment the cough reflex due to RAR activity (Shannon et al. 2000).

4 Antitussive Drugs

Most cough treatments are designed to target the underlying disease which can cause cough as a symptom. However, there are a range of drugs available which directly target neuronal pathways (Fig. 1).

4.1 Sodium Channel Blockers

At least nine subtypes of sodium channels have been characterized (Alexander et al. 2007) and of particular interest are the tetrodotoxin-insensitive sodium channels (Nav 1.8, Nav 1.9) expressed on pulmonary C-fibres (Kwong and Lee 2005).

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; however, their effects are transient and their repeated use is associated with tachyphylaxis, making high doses necessary, which can lead to unwanted side effects (Yukioka et al. 1985). Their mechanism of action is believed to be through use-dependent inhibition of voltage-gated sodium channels, thereby reducing action potential generation and transmission in afferent nerves. However, whilst topical administration of lidocaine to the airways has been reported to inhibit cough induced by capsaicin in healthy subjects (Choudry et al. 1990), the orally acting local anaesthetic mexiletine only attenuated cough induced by tartaric acid and not by capsaicin (Fujimura et al. 2000). The explanation for these observations might be explained by pharmacodynamic differences due to the routes of drug administration, although this remains to be determined.

RSD 931 is a quaternary ammonium compound (carcainium chloride) and a structural analogue of lidocaine, that exhibits antitussive activity in both guinea

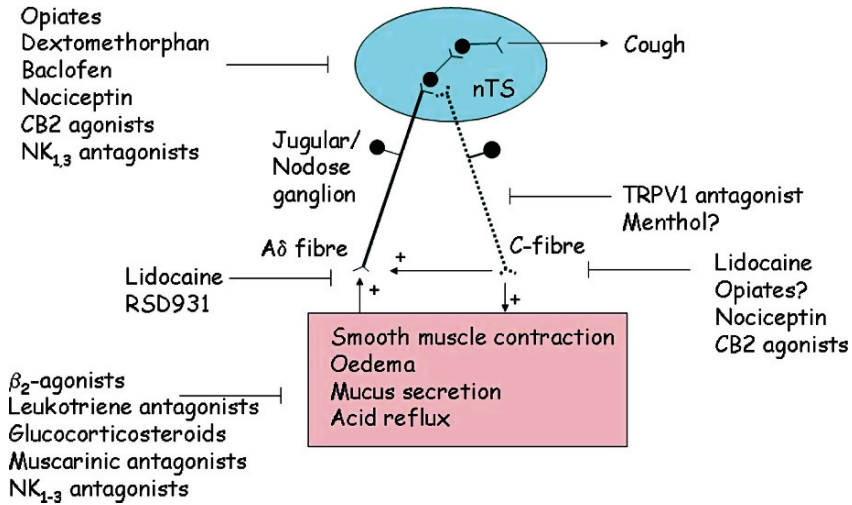


Fig. 1 The cough reflex and sites of action of some antitussive agents. Airway sensory nerves activated in response to a protussive stimulus travel through the vagus nerve to the medulla, where they terminate in the nucleus tractus solitarius (nTS). Second-order neurons relay the message to the respiratory pattern generator, which modifies the activity of the inspiratory and expiratory motor neurons 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 presynaptically and postsynaptically. C-fibres are depicted as playing a role in facilitating nTS activity. The activation of their terminal processes by inflammatory mediators such as 15-hydroperoxyeicosatetraenoic acid, bradykinin, *N*-arachidonoyl dopamine or low pH stimulates C-fibre input into the nTS, thereby facilitating central processing of afferent information received from Aδ-fibres innervating the proximal airways. Also note that the Aδ-fibres shown consist of nociceptive Aδ-fibres, ‘cough’ receptor and rapidly adapting receptors. It is the lattermost subset which can be activated by sensory neuropeptides either directly or indirectly via bronchoconstriction, oedema and mucus secretion

pigs and rabbits (Adcock et al. 2003). Whilst RSD 931 is a weak local anaesthetic, in the rabbit it only inhibited spontaneous and histamine-evoked discharges from Aδ-fibres, whilst modestly activating pulmonary C-fibres, which is distinctive from the effect of lidocaine, which suppressed all nerve fibres in the airway (Adcock et al. 2003). Such results suggest that RSD931 is antitussive via a selective effect on Aδ-fibres independent of local anaesthetic effects. Another structurally related analogue of lidocaine, JMF2-1, has also been described to have anti-inflammatory activity and to be able to inhibit bronchospasm, whilst being 2 orders of magnitude weaker than lidocaine as a Na⁺ channel blocker (da Costa et al. 2007), although it is unclear whether this agent has antitussive activity.

Citric acid is a tussive stimulus that is thought to cause cough by direct activation of a recently described subset of Aδ fibres referred to as ‘cough’ receptors (Canning et al. 2004). The precise molecular target for citric acid on these nerves has not been identified, but pharmacological studies suggested the potential involvement of acid-sensing ion channels (ASICs) (Canning et al. 2006). ASICs are members of the Na⁺ channel superfamily that includes the epithelium Na⁺ channel (ENaC)

and the degenerins (DEG) that support Na^+ conductance in response to lowering of extracellular pH. The activation of these ion channels on afferent nerves either in the oesophagus or following microaspiration of acid into the respiratory tract has been implicated in the cough resulting from gastro-oesophageal reflux (Kollarik et al. 2007). Amiloride is a non-selective inhibitor of ASICs and partially inhibited cough induced by citric acid in an anaesthetized-guinea-pig model (Canning et al. 2006), although an effect on other Na^+ channels in this response cannot be ruled out. These experimental data are also consistent with a report showing the ability of amiloride to suppress cough induced by acetic acid in asthmatic children (Mochizuki et al. 1995), although whether inhibition of ASICs on epithelial cells resulting in changes in local concentration of ions (e.g. chloride) was responsible for this antitussive action remains to be established. The development of subtype-selective ASIC channel blockers will be useful for further investigation of the role of these ion channels in the cough response, and to ascertain their utility as antitussive drugs.

4.2 Tachykinin Receptor Antagonists

Tachykinins are a group of peptides, including substance P, neurokinin A and neurokinin B, which are located in the peripheral endings of capsaicin-sensitive primary afferent neurones (C-fibres). Neuropeptides have been implicated in cough as their release from C-fibres may stimulate RARs either directly, or indirectly as a consequence of airway smooth-muscle contraction and increased vascular permeability leading to mucosal oedema and/or mucus secretion (Widdicombe 1995). Hence, tachykinin antagonists are most likely to act in the peripheral lung to inhibit the actions of endogenously released neuropeptides and thereby ameliorate cough to tussive agents which also stimulate the activation and release of sensory neuropeptides from sensory C-fibres (e.g. citric acid).

However, direct stimulation of the 'cough receptor' in anaesthetized guinea pigs by citric acid was unaffected by systemic or topical application of neurokinin antagonists, thereby ruling out a role for the release of sensory neuropeptides into the airways and subsequent modulation of the activity of these $\text{A}\delta$ -fibres (Canning et al. 2006; Mazzone et al. 2005). In contrast, administration of neurokinin antagonists directly into the nTS, whilst not preventing cough per se, did attenuate the sensitization of the cough reflex following local application of capsaicin to the airways (Mazzone et al. 2005). Therefore, a central site of action cannot be entirely ruled out in view of the purported role of brainstem neuropeptides in central sensitization (Mazzone et al. 2005).

A number of potent tachykinin antagonists have been developed as antitussive drugs. The NK_1 antagonists FK 888, CP-99,994 and NKP608 inhibited cough induced by tobacco smoke and citric acid in guinea pigs, and mechanical stimulation of the trachea in anesthetized cats (Bolser et al. 1997; Chapman et al. 2004; El-Hashim et al. 2004; Yasumitsu et al. 1996). CP-99,994 can cross the blood-brain

barrier and interference with neuropeptide transmission within the nTS and/or other regions of the CNS involved in cough may have accounted for the antitussive activity of this drug (Bolser et al. 1997). However, in healthy human subjects CP-99,994 did not inhibit bronchoconstriction or cough induced by hypertonic saline (Fahy et al. 1995), which is consistent with the view that the cough receptor is distinct from nociceptors.

The neurokinin 2 (NK₂) receptor antagonist (SR 48968) suppressed the cough reflex and was more potent than codeine in the guinea pig (Girard et al. 1995). Interestingly both SR48968 and codeine only partially inhibited the cough reflex when administered by the inhaled route (Advenier and EmondsAlt 1996; Yasumitsu et al. 1996), possibly reflecting differences in the concentration of these antagonists at receptor sites following the different routes of administration.

Neurokinin 3 (NK₃) receptors have received very little attention in relation to the cough reflex. Nevertheless the NK₃ receptor antagonist SR142,801 inhibited cough induced by citric acid in guinea pigs and in pigs (Daoui et al. 1998; Moreaux et al. 2000). Another high-binding-affinity, non-peptide NK₃ receptor antagonist, SB 235375 (Giardina et al. 1996), having low CNS penetration, was also effective against cough in the guinea pig (Hay et al. 2002) and could be a useful compound as a novel peripherally acting antitussive drug.

4.3 NOP Receptor Agonists

Nociceptin/orphanin FQ (NOP) is an opioid-like peptide and is the endogenous ligand for the NOP1 receptor (Meunier et al. 1995). NOP1 receptors are G_{i/o}-coupled receptors that mediate presynaptic inhibition of neurotransmitter release (Meis and Pape 2001) and are widely distributed in the CNS and on peripheral airway nerves (Fischer et al. 1998). Nociceptin has been found to inhibit the release of sensory neuropeptides following depolarization of C-fibres (Shah et al. 1998), but interestingly did not prevent neuropeptide release from C-fibre terminal endings following direct activation of TRPV1 (Fischer et al. 1998; Shah et al. 1998). However, the antidromic stimulation of C-fibres by capsaicin is sensitive to nociceptin (Corboz et al. 2000), presumably reflecting a preferential inhibition of the opening of N-type calcium channels induced by this stimulus (Buchan and Adcock 1992).

Nociceptin inhibited cough induced by mechanical stimuli and capsaicin in guinea pigs and cats (McLeod et al. 2002) and induced by citric acid in guinea-pigs (Lee et al. 2006), and the antitussive action of the non-peptide NOP agonist Ro-64-6198 demonstrates the possibility of developing novel drugs free from side effects normally associated with opioid treatment (McLeod et al. 2004). Hence, NOP1 receptors are involved in the modulation of the cough reflex and selective NOP1 agonists may have potential as novel peripherally acting antitussives, although to date there have been no studies with such drugs in humans.

4.4 Cannabinoids

The psychotropic effects of smoking cannabis are due to the pharmacological action of the active constituent (-)- Δ^9 -tetrahydrocannabinol (THC) within the CNS. In the airways, THC has been shown to cause both bronchodilation and bronchoconstriction in non-diseased subjects and asthmatic patients (Tashkin et al. 1977). However, an early report suggested that THC may have antitussive properties in an experimental model of cough induced by mechanical irritation of the tracheal mucosal surface in cats (Gordon et al. 1976). The discovery of cannabinoid (CB) receptors has renewed interest in the possible antitussive efficacy of CBs.

CB receptors are $G_{i/o}$ -coupled receptors that mediate presynaptic inhibition of neurotransmitter release (Freiman and Szabo 2005; Melis et al. 2004; Soya et al. 2005). CB_1 receptors are predominantly located within the CNS but are also expressed by non-neuronal cells (e.g. lymphocytes), whilst CB_2 receptors are primarily found on immune cells (Pacher et al. 2006). It was reported that within the airways, CB_1 receptors were found on sensory nerves and cough induced by capsaicin was augmented by the CB_1 receptor antagonist SR14167A, but not by the CB_2 selective antagonist SR144528 (Calignano et al. 2000). These findings could be explained by the well-known inverse agonist activity of SR14167A, although this agent did not cause cough per se when administered alone. It was concluded that the increased cough response following administration of SR14167A was most likely a consequence of the antagonism of the antitussive action of endogenously released endocannabinoids in the airways (Calignano et al. 2000). However, this conclusion is complicated by the fact that cough was elicited in guinea pigs following aerosol exposure to the endogenous endocannabinoid anandamide (Jia et al. 2002). Anandamide was initially described as an endogenous activator of CB receptors, but it can also activate TRPV1 receptors (Smart et al. 2000; Zygmunt et al. 1999). As a consequence, its effect on cough is variable and may be dependent on the balance between CB and TRPV1 activity (Calignano et al. 2000; Jia et al. 2002).

In stark contrast to these findings, an agonist selective for the CB_2 receptors was reported to suppress cough induced by citric acid in guinea pigs (Patel et al. 2003). A peripheral mechanism of action was implied since the CB_2 selective agonist JWH 133 inhibited the depolarization of isolated vagus nerve from both guinea pigs and humans, in response to capsaicin in vitro (Patel et al. 2003). Moreover, the antitussive action of CBs is not likely to be mediated by suppression of neuropeptide release from the peripheral terminals of C-fibres in the airways, since the non-selective CB agonist CP 55940 was without significant effect on the contraction of airway smooth muscle, owing to the release of sensory neuropeptides, following electrical stimulation of C-fibres (Tucker et al. 2001). However, it is not known whether the antitussive action of JWH-133 also occurred within the cough circuitry of the nTS as the nucleus is rich in CB receptors (Mailleux and Vanderhaeghen 1992).

4.5 Drugs Targeting Transient Receptor Potential Channels

Transient receptor potential (TRP) channels play an important role in a diversity of sensory function, including taste, smell, hearing and perception of pain. This family comprises proteins with six transmembrane-spanning domains that are assembled either as homotetramers or heterotetramers to form non-selective cation channels permeable to calcium and sodium ions. There are at least six subfamilies, including TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin), TRPML (mucolipin) and TRPP (polycystin) (Nilius et al. 2007).

One particular member of this superfamily (TRPV1) is predominantly localized to small-diameter peptidergic and nonpeptidergic neurones in dorsal and vagal sensory ganglia (Szallasi and Blumberg 1999) and activation of this channel by capsaicin gives rise to feelings of warmth and pain. The cloning and expression of TRPV1 has led to a greater appreciation of the role this channel plays in various pathophysiological pain states (Caterina et al. 1997). TRPV1 receptors are polymodal, activated by protons, heat (Caterina et al. 1997) and a range of lipid mediators such as 15-hydroperoxyeicosatetraenoic acid (15-HPETE) (Hwang et al. 2000), *N*-arachidonoyl dopamine (NADA) (Huang et al. 2002) and anandamide (Smart et al. 2000; Zygmunt et al. 1999) and indirectly by bradykinin (Chuang et al. 2001; Shin et al. 2002) and nerve growth factor (NGF) (Chuang et al. 2001). The release of these mediators during an inflammatory insult can result in the activation of TRPV1, thereby potentially leading to the cascade of events culminating in the sensitization of the cough reflex (Fig. 1).

An upper respiratory tract infection can increase cough sensitivity to citric acid in humans (Empey et al. 1976). Similarly, cough induced by capsaicin is increased in subjects with respiratory inflammatory diseases such as asthma, COPD and idiopathic cough (Doherty et al. 2000; Hathaway et al. 1993; Hope-Gill et al. 2003; O'Connell et al. 1996), indicating that mediators released during an inflammatory response within the respiratory tract increase cough sensitivity. It is speculated that in chronic diseases this process may result in plasticity changes in sensory function and pattern of innervation within the respiratory tract. The density of TRPV1-immunoreactive nerves in the airways is elevated in bronchial biopsies from individuals with chronic cough (Groneberg et al. 2004) and it has been reported that the density of substance P (Lee et al. 2003) and CGRP (O'Connell et al. 1995) immunoreactive nerves is increased in cough-variant asthma and chronic cough of unknown cause, respectively.

These clinical observations suggest that neuronal innervation patterns and perhaps function might underlie the physiological manifestation of hypertussive cough responses in these pathological conditions. Interference with the function of these afferent nerves might offer a selective and novel therapeutic approach to the treatment of cough. A number of studies have shown that TRPV1 antagonists, including ruthenium red (Bolser 1991), capsazepine (Laloo et al. 1995), 5'-iodoresiniferatoxin (Trevisani et al. 2004) and *N*-(4-*tertiary*-butylphenyl)-4-(3-cholophyridin-2-yl)-tetrahydropyrazine-1(2*H*)-carboxamide (McLeod et al. 2006) reduced cough in response to a variety of tussive stimuli (e.g. capsaicin, citric acid and allergen).

Similarly, the chemical inactivation of sensory C-fibres suppressed the ability of guinea pigs to cough in response to capsaicin and citric acid (Forsberg et al. 1988), confirming the importance of C-fibres in this response. However, the role of C-fibres in causing cough per se has been questioned (see above) and in some experimental models stimulation of C-fibres does not evoke cough (Canning et al. 2004), and may even inhibit cough (Tatar et al. 1988, 1994), whilst subacute stimulation of C-fibres can lead to an increase in the cough response to tussive stimuli such as citric acid. This has led to the proposal that activation of C-fibres can alter the threshold for cough, an interaction that is likely to be modulated at the level of the nTS (Mazzone et al. 2005). Hence, drugs targeting TRPV1 may be of considerable utility as they might not inhibit defensive cough, but might serve to normalize the sensitized cough response.

Targeting the TRPV1 receptor may offer a new approach to the treatment of cough, since defensive cough might be unaffected. For example, chemical ablation of sensory C-fibres did not result in a loss of the tussive response following mechanical irritation of the airways (Forsberg et al. 1988), nor did capsazepine affect cough induced by hypertonic saline (Laloo et al. 1995). This would imply that TRPV1 antagonists would not affect the 'hard-wiring' pathways mediating defensive cough, but may be of potential use under conditions where there is sensitization of the cough reflex via activation of TRPV1-sensitive afferents. In contrast to these observations, one study has shown that whilst capsazepine did not inhibit cough in response to citric acid per se (Canning et al. 2006), it did inhibit the TRPV1-dependent sensitization of the cough reflex (Mazzone et al. 2005). Therefore, TRPV1 antagonists may actually reduce the sensitization of the cough reflex that occurs as a consequence of the activation of these receptors on afferent nerve terminals following release of endogenous activators (e.g. 15-HPETE, bradykinin, NADA, NGF, pH).

One study has suggested that TRPV1 antagonism may not be a useful approach in suppressing all forms of hypertussive cough. In a model of hypertussive cough following cigarette exposure, neither capsazepine nor 5'-iodoresiniferatoxin inhibited cough in response to citric acid or capsaicin, despite the fact that a dual NK_{1,2} receptor antagonist was effective in this model (Lewis et al. 2007). It was unclear from this study whether the two TRPV1 antagonists inhibited cough to these tussive stimuli in air-exposed animals, but if this is the case, then sensory activation occurred independently of TRPV1 during smoke exposure. The implication of these studies is that other ion channels (e.g. ASICs) play a complementary role in modulating cough under certain pathological conditions and, therefore, development of TRPV1 antagonists may not be applicable to all forms of hypertussive cough; and desensitization of sensory C-fibres with partial TRPV1 agonists may offer a better approach to suppress sensory input into the nTS than TRPV1 antagonists.

The role of other TRP channels in regulating sensory nerve function has been investigated, although to what extent these channels contribute towards cough remains to be established. Of particular interest is the recognition that menthol, an ingredient of many over-the-counter cough remedies, is antitussive in humans (Morice et al. 1994) and guinea pigs (Laude et al. 1994), and, furthermore, is now appreciated to be an activator of TRPM8 (McKemy et al. 2002), a channel that plays a major

role in cold thermosensation (Bautista et al. 2007). Interestingly, menthol is also an antagonist of TRPA1 channels, which are activated by mustard oil and a range of lipid mediators derived from oxidative stress (Macpherson et al. 2007). Whether targeting these channels on sensory nerves will yield novel drugs with antitussive activity remains to be established.

4.6 Ion Channel Modulators

NS1619 is a selective opener of calcium-activated potassium channels resulting in hyperpolarization and reduced cell excitability. In the airways, topical application of NS1619 inhibited cough induced by citric acid and bradykinin, the mechanism of action of which has been suggested to be via the suppression of impulses in guinea pig tracheal A δ - and C-fibres (Fox et al. 1997); however, clinical studies have not yet been reported with such drugs.

Moguisteine is a peripherally acting antitussive that may act as an ATP-sensitive K⁺ channel opener and in clinical trials was shown to reduce the frequency of cough in patients with lung cancer to a level comparable to that resulting from administration of codeine (Barnabe et al. 1995).

Furosemide is a loop diuretic, and suppressed cough induced by low-chloride solutions but not by capsaicin (Foresi et al. 1996; Karlsson et al. 1992; Mochizuki et al. 1995; Stone et al. 1993a; Ventresca et al. 1990). This drug blocks the Na⁺/K⁺/2Cl⁻ cotransporter expressed in the peripheral terminals of the 'cough' receptor in guinea pigs (Mazzone and McGovern 2006) and laryngeal RARs in the dog (Sant' Ambrogio et al. 1993). The cotransporter facilitates the accumulation of chloride ions into the peripheral terminations of the cough receptor. It has been proposed that furosemide inhibits the effective accumulation of chloride ions into these terminations, thereby preventing nerve depolarization in response to opening of chloride ion channels in the membrane. Inhibitors of chloride channels, including 4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid (a non-selective anion-channel inhibitor) and niflumic acid (a selective inhibitor of calcium activated chloride channels), also inhibited cough in response to citric acid (Mazzone and McGovern 2006). These channels offer attractive targets for the development of novel antitussive agents, although to target receptors and ion channels present on the 'cough' receptor which triggers an essential part of the 'hard-wired' cough reflex would probably be unwise.

4.7 Leukotriene Receptor Antagonists

Zafirlukast, a cysteinyl leukotriene antagonist, has shown therapeutic efficacy in cough-variant asthma, even in patients unresponsive to inhaled bronchodilators and corticosteroids (Dicpinigaitis et al. 2002), whilst a similar drug, montelukast has also

been demonstrated to be of utility in various cough syndromes (Bisgaard 2003; Kopriva et al. 2004), although there are too few clinical trials to determine whether this drug should be routinely used in patients with cough (Chang et al. 2006). The mechanism of action of these drugs as antitussives could stem from their ability to reduce mucus secretion, oedema and bronchoconstriction, which are all stimulated by leukotrienes and thereby indirectly facilitate action potential generation in sensitized afferent nerves. Alternatively, there is evidence supporting the view that leukotrienes may directly increase the excitability of afferent nerves (McAlexander et al. 1998; Udem and Weinreich 1993).

4.8 Bradykinin Antagonists

Captopril and enalapril are angiotensin converting enzyme (ACE) inhibitors and are often used in the treatment of hypertension. Cough is a side effect of these drugs in patients with irritable airways and is a result of inhibition of ACE, leading to a decreased metabolism and subsequent accumulation of bradykinin in the airways (Dicpinigaitis 2006a). Bradykinin caused cough when administered topically to the airways of healthy subjects (Choudry et al. 1989). Similarly, cough sensitivity to capsaicin, but not other tussive agents such as citric acid or distilled water, was increased if endogenous levels of bradykinin were elevated following treatment with an ACE inhibitor (Morice et al. 1987). Furthermore, experimental models have also demonstrated that bradykinin increased cough sensitivity to tussive stimuli (Mazzone et al. 2005) and pharmacological treatment with HOE-140, a B₂ receptor antagonist, inhibited citric acid induced cough in the guinea pig (Featherstone et al. 1996). However, it remains to be seen whether B₂ receptor antagonists are antitussive in humans.

4.9 Opioids

Currently there are few effective cough suppressants and it has been concluded that patients requiring symptomatic relief in chronic cough derive a very low level of benefit from available drugs (Bolser 2006). Most effective are opioids such as codeine which produce a reduction in the frequency of cough of 19–60% (Bolser 2006; Morice et al. 2007). However, the usefulness of opioids is limited by their sedative properties and dependence liability (Bolser 2006).

Opioids such as codeine, morphine and dihydrocodone are all good antitussives primarily via their action at central μ -opioid-receptors (Kamei 1996). It is not known, however, whether this occurs within the cough circuitry of the nTS, even though it is recognized that this location is rich in this receptor (Monteillet-Agius et al. 1998). These receptors are G_{i/o}-coupled and mediate presynaptic inhibition of neurotransmitter release (Emmerson and Miller 1999). Recently, both

selective δ -opioid receptor antagonists (TRK-851) and agonists (SB-227122) have been found to be antitussive in animal models (Chung 2003). Additionally, κ -opioid receptor agonists have been reported to be anti-tussive (Kamei 1996). Therefore, modulation of previously untargeted central opioid receptors appears a promising avenue for the development of novel antitussive drugs.

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 codeine is not antitussive in humans challenged with capsaicin (Kamei 2002), and although the peripherally acting peptide BW443C is antitussive in animal studies (Adcock et al. 1988), there is only limited clinical evidence to support this antitussive effect in humans (Pavord et al. 1994).

4.10 Sigma Receptor Ligands

Dextromethorphan, the dextrorotatory optical isomer of the opioid levomethorphan, retains its antitussive action despite being inactive at opioid receptors. It has been reported that this drug is an agonist at the 'sigma-1' receptor (Guitart et al. 2004; Monnet 2005) and a non-competitive antagonist (channel blocker) of NMDA receptors (Franklin and Murray 1992; Netzer et al. 1993), actions that could have consequences for excitatory glutamatergic neurotransmission in the nTS.

It is thought that dextromethorphan and noscapine act on sigma receptors (centrally and peripherally) rather than at classic opioid receptors (Brown et al. 2004). However, the inhibitory effect of noscapine on the bradykinin B₂ receptor (Ebrahimi et al. 2003) and dextromethorphan's activity at NMDA receptors (Brown et al. 2004) may also contribute to the antitussive activity of these drugs. Some research has been undertaken with newer, more efficacious sigma agonists such as SKF-10,047 (Brown et al. 2004), although plenty of opportunities remain for further investigation in this area.

4.11 GABA Receptor Ligands

GABA is an inhibitory neurotransmitter present centrally and in the peripheral nervous system. The GABA_B receptor agonist 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 (Dicpinigaitis and Gayle 2003a). An analogue of baclofen that does not cross the blood-brain barrier has also been shown experimentally to be antitussive (Bolser et al. 1994), suggesting that peripherally acting GABA_B agonists may also be useful in the treatment of cough, particularly since the GABA_A agonist muscimol administered locally to the mucosal surface augmented cough induced by citric acid in guinea pigs (Mazzone and McGovern 2006).

5 Challenges to the Development of Novel Antitussive Drugs

The development of novel antitussives is a challenging area, not least because of the lack of good predictive models, both clinically and preclinically. For instance, it is highly debatable whether capsaicin challenge in healthy volunteers is a good cough model when many drugs which improve pathological cough fail to inhibit capsaicin-induced cough (Table 1). Similarly, the demonstration of antitussive activity of novel substances against stimuli used to induce tussive responses in humans rather than determining their effect on the natural history of cough is likely to lead to false-negatives. For example, opioids have been shown to reduce the frequency of cough in subjects with chronic cough, without altering cough sensitivity to citric acid (Morice et al. 2007). Therefore, non-invasive ambulatory monitoring of cough should be urgently validated as a method to assess the efficacy of novel antitussive agents.

Much of the preclinical work has also relied on using capsaicin-induced or citric acid induced cough in healthy guinea pigs and there are many examples of drugs that are antitussive in these preclinical models that do not show antitussive effects in humans. For example, NK₁ antagonists had promising preclinical antitussive data experimentally that were not confirmed in clinical studies in humans (Joos et al. 2003). Following a similar pattern, NK₁ antagonists attenuated nociceptive responses in animals but failed as analgesics in humans (Hill 2000). Furthermore, a dual dopamine D2 and β_2 -adrenoceptor agonist was recently found not to improve the symptom of cough in a large clinical trial of patients with COPD despite exhibiting antitussive activity in animals (Laursen et al. 2003). The value and limitations of animal models of cough has been discussed elsewhere (Karlsson and Fuller 1999) and 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 since 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 as importantly to consider the best way of evaluating novel antitussives in early clinical development for proof of concept before entering into larger clinical studies.

Furthermore, given the place of the nTS in the afferent arm of the cough reflex, we hypothesize that drugs that inhibit excitatory synaptic transmission in this nucleus will possess antitussive activity. Additionally this region of the brain lacks a complete blood-brain barrier and is therefore accessible to blood-borne drugs (Gross et al. 1990). Agonists acting at a range of receptors have been shown to act presynaptically to inhibit excitatory neurotransmission in the nTS (Brooks et al. 1992; Chen et al. 2002; Glatzer and Smith 2005; Kato and Shigetomi 2001; Sekizawa et al. 2003), though not in the context of the cough response.

Table 1 Results of clinical trials investigating the efficacy of selected antitussive compounds

Class/drug	Capsaicin	Low Cl ⁻ concentration	Citric acid	Angiotensin converting enzyme inhibitor	Pathological cough ^a	Postinfectious cough	Clinical use in cough treatment
Opioids	±(Davenport et al. 2007; Fuller et al. 1988)		±(Empey et al. 1979; Morice et al. 2007)		✓(Bolsler 2006; Morice et al. 2007)	×(Eccles 1996; Herbert and Brewster 2000)	Gold standard
Dextromethorphan			✓(Grattan et al. 1995; Karttunen et al. 1987)		✓(Braman 2006)	×(Lee et al. 2000)	Yes
Baclofen	✓(Dicpinigaitis and Rauf 1998)			✓(Dicpinigaitis 1996)	✓(Dicpinigaitis and Rauf 1998)		Yes
Noscapine			×(Empey et al. 1979)	✓(Mooraki et al. 2005)			
H ₁ -antagonists	×(Dicpinigaitis and Gayle 2003b; Studham and Fuller 1992)		✓(Packman et al. 1991)		±(Danzon et al. 1988; Liliensfield et al. 1976)	±(Dicpinigaitis and Gayle 2003b)	Primarily used as an antiallergic drug

Table 1 Continued

Class/drug	Capsaicin	Low Cl ⁻ concentration	Citric acid	Angiotensin converting enzyme inhibitor	Pathological cough ^a	Postinfectious cough	Clinical use in cough treatment
Furosemide	×(Ventresca et al. 1990)	✓(Foresi et al. 1996; Stone et al. 1993b; Ventresca et al. 1990)					
Glaucone			×(Rees and Clark 1983)		✓(Ruhle et al. 1984)	✓(Gastpar et al. 1984)	
Local anaesthetics	✓(Choudry et al. 1990; Hansson et al. 1994)	✓(Sheppard et al. 1983)	✓(Midgren et al. 1992)		✓(Chong et al. 2005; Fuller and Jackson 1990; Trochtenberg 1994)		
β ₂ -agonists	×(Smith et al. 1991)	✓(Higenbottam 1987; Lowry et al. 1987)	✓(Pounsford et al. 1985)		±(Chong et al. 2005; Mulrennan et al. 2004; Nichol et al. 1990)	×(Pillay and Swingle 2003)	Primarily used as a bronchodilator
Sodium cromoglycate	×(Collier and Fuller 1984)	×(Fuller and Collier 1984; Sheppard et al. 1983)		±(Hargreaves and Benson 1995)	±(Chang et al. 2004)		Primarily used as an antiallergic drug

Expectorants and mucolytics			✓ (Ishiura et al. 2003)	✓ (Dicpinigaitis and Gayle 2003a)	Over-the-counter 'cough remedies'
Muscarinic receptor antagonists	× (Smith et al. 1991)	± (Fuller and Collier 1984; Lowry et al. 1987; Sheppard et al. 1983)	✓ (Pounsford et al. 1985)	✓ (Holmes et al. 1992)	Primarily used in the treatment of chronic obstructive respiratory disease
LT-receptor antagonists	× (Dicpinigaitis and Dobkin 1999)		± (Chang et al. 2006; Dicpinigaitis et al. 2002; Kopriva et al. 2004)	✓ (Bisgaard 2003)	Primarily used as an antiasthma drug
Moguisteine			± (Aversa et al. 1993; Barnabe et al. 1995)		

✓, significant antitussive effect; ×, no significant effect; ±, conflicting data
 a)Includes cancer, chronic obstructive respiratory disease, chronic non-productive cough, cough associated with other respiratory diseases

6 Conclusion

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 when compared with bronchospasm and airway inflammation. However, there remains a clear need to develop a non-opioid antitussive drug that ideally modulates abnormal heightened cough reflexes, whilst leaving the normal cough reflex unaltered (Table 1, Fig. 1). 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 there is more research into this important clinical problem.

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