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Tobacco Smoke Induced Cough: Mechanisms Driving Acute and Chronic Cough Pathology

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1. Introduction

Cough is an important protective mechanism that clears foreign material from the airway and aids in immune defence. However, chronic excessive cough of various aetiologies is a common presentation to specialist respiratory clinics, and is reported as a troublesome symptom by a significant proportion of the population (Ford et al., 2006). In extreme situations chronic cough can persist for several years, and is not only socially embarrassing, but can be painful and debilitating. Chronic cough is often associated with an underlying respiratory disease, several of which can be caused or exacerbated by exposure to tobacco smoke or environmental pollution, for example chronic obstructive pulmonary disease (COPD), emphysema, bronchitis, lung cancer and asthma. In addition, chronic cough can be of unknown cause (idiopathic) (Morice et al., 2007). Recently, the label chronic 'cough hypersensitivity syndrome' (CCHS) was proposed as a means of focussing the cough community and general practitioners on the symptomology of cough and understanding of the mechanisms behind cough sensation, with the ultimate goal of developing effective anti-tussive treatments (Millqvist et al., 1998; Chung, 2011).

At present, little is known about the mechanisms that drive the cough reflex, and even less about how these mechanisms are altered to lead to chronic cough. Numerous environmental irritants are known to induce coughing such as air pollution, tobacco smoke, smoke from burning vegetation, and vehicle exhaust. This chapter focuses on tobacco smoke (TS), which is one of the most common inhaled irritants (both as an active smoker, and as a secondary environmental pollutant), and is known to contain thousands of noxious chemicals (U.S. Department of Health and Human Services, 2010). Exposure to acute TS readily evokes coughing in both animals and human non-smokers (Andre et al., 2009; Lee et al., 1993; Lee et al., 2007), and prolonged exposure to TS can lead to an altered sensitivity to a range of tussive stimuli (Karlsson et al., 1991; Doherty et al., 2000; Bergren, 2001; Dicipinigaitis, 2003; Lewis et al., 2007). It is believed that if the mechanisms behind acute or chronic cough associated with TS exposure can be revealed it would lead to the development of truly effective cough therapies. The aim of this chapter is to discuss the current understanding of how exposure to TS can cause/alter the cough response and we will consider some of the most promising new therapeutic targets for the treatment of cough.

2. Cough: An overview

2.1 Background

Under normal conditions, cough is an important protective mechanism that clears foreign material from the airways and aids in immune defence (Fontana et al., 1999). Despite this, even an acute cough can be unpleasant and painful for the sufferer. It is therefore not surprising that cough is the most frequent reason for which patients consult with their family doctor or a general or respiratory physician (McCormick et al., 1995); and that antitussives are among the most widely used over-the-counter self medication therapies. In contrast to acute cough, chronic cough of various aetiologies often has no functional consequence, and can lead to a dramatic decrease in quality of life (Irwin et al., 1998; Morice et al., 2007). Chronic cough is defined as a cough which persists for longer than 8 weeks (Harding, 2006), and is often associated with underlying inflammatory airways diseases. Excessive coughing has also been observed as a side-effect of certain medical treatments, for example angiotensin-converting enzyme inhibitors which are used in the prevention of cardiovascular disorders (Fuller & Choudry, 1987; Irwin et al., 1998). However, there is not always an obvious associated underlying condition, and so chronic cough can also be thought of as idiopathic in nature (Morice et al., 2007). Currently, there are no safe and effective medications to suppress cough (Karlsson & Fuller, 1999; Schroeder & Fahey, 2002; Belvisi & Geppetti, 2004; Reynolds et al., 2004; Nasra & Belvisi, 2009).

2.2 The cough reflex

The physiology of the cough reflex has been well described. Briefly, rapid inspiration is followed by an expiratory effort against a closed glottis, and rapid generation of intrapulmonary pressure. Explosive expiration results from sudden opening of the glottis, causing a high linear velocity of gas flow which sweeps irritant material up towards the pharynx (Widdicombe, 2002). In order to initiate cough, the nervous system first needs to detect an irritant stimulus and relay this message to the brain. The “cough centre” of the central nervous system (CNS) is believed to be in close proximity to the nucleus tractus solitarius (NTS), where the afferent nerves which mediate cough are known to synapse with second-order neurons (Figure 1). It is also thought that this putative cough centre is likely to be linked to the respiratory centre of the brain, because a profound change in breathing pattern is an integral part of the cough reflex (Karlsson & Fuller, 1999). It is this afferent arm that initiates and controls the cough reflex which is likely to be altered in disease, and as such is the focus of research investigating cough hypersensitivity.

2.3 Sensory nerves and the cough reflex

Cough is initiated by a wide variety of chemicals, or mechanical stimuli, which act by stimulating specialised peripheral sensory neurons that terminate in the airways (Figure 1). Chemical irritants bind to receptors, which open ion channels on the terminals of the airway sensory nerves, leading to cation influx and membrane depolarisation. If membrane depolarisation is of sufficient magnitude, the peripheral nervous system will send signals to the CNS in the form of action potentials. Action potentials are carried by subsets of sensory nerve fibres via the vagus nerves and sensory ganglia (nodose and jugular), where the cell bodies are located, to the medulla where they terminate in the NTS. Second order neurons then relay the message to a respiratory pattern generator within the CNS, which interprets the afferent information, resulting in activation of motor neurons and ultimately initiation of coughing. Moreover, mediators can interact with the nerve terminals or ion channels in the

airways to inhibit or promote depolarisation, alter the response to activating stimuli, or lead to changes in gene expression modifying the function of the sensory fibre itself (Taylor-Clark & Undem, 2006).

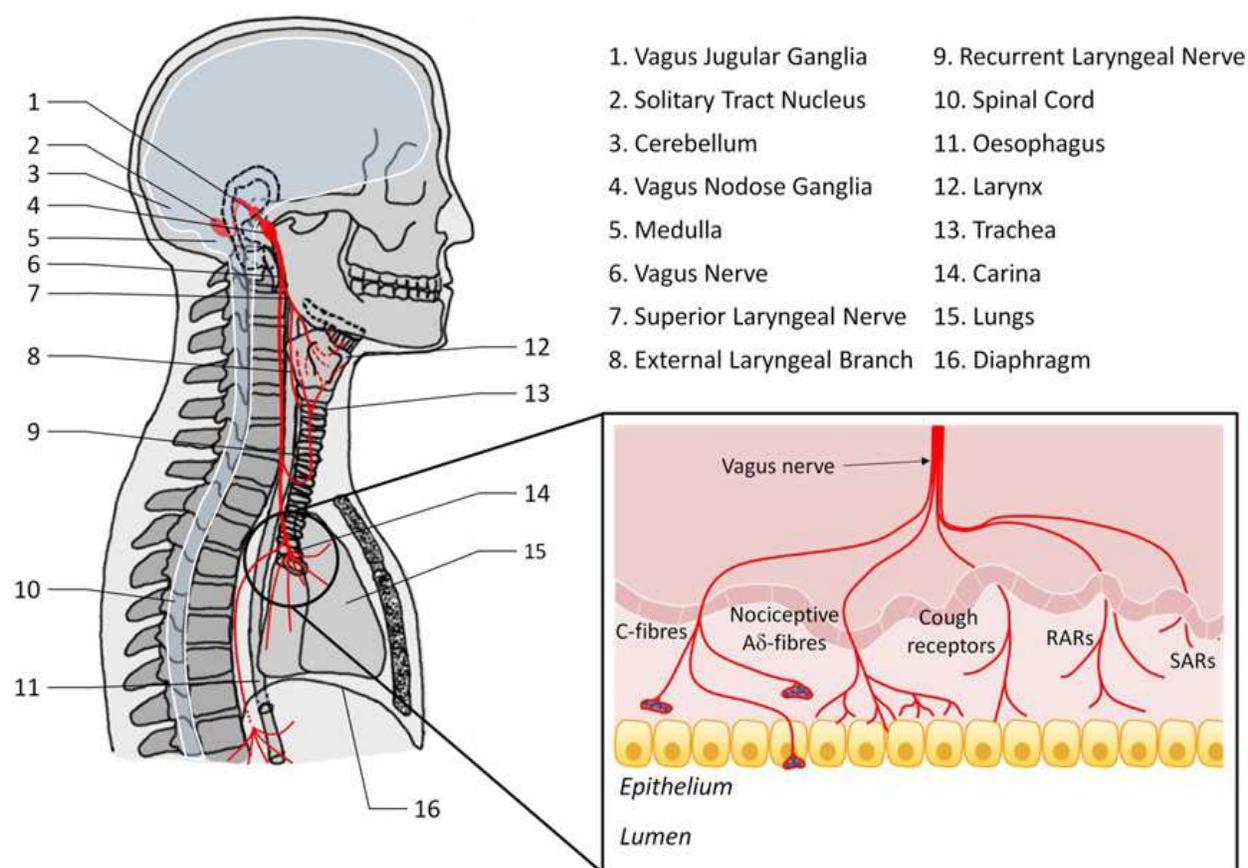


Fig. 1. Airway sensory nerves and cough.

Cell bodies for airway nerve fibres originate in two ganglia, the jugular and nodose, which are located under the ear bone within the head. Airway sensory nerves are mainly carried via the vagus nerve, where they terminate both in and under the airway epithelium (illustrated in the enlarged panel). These fibres consist of the C-fibres, A δ -nociceptors, polymodal A δ -fibres ('cough receptors'), rapidly adapting receptors (RARs), and slowly adapting receptors (SARs), which sense both chemical and mechanical stimuli. Of these fibres, the chemosensitive C-fibres and mechanosensitive polymodal A δ -fibres are thought to mediate cough. Once stimulated, information is carried along the vagus nerve via the nodose and jugular sensory ganglia to the solitary tract nucleus (NTS), located in the medulla. In the NTS the sensory fibres synapse to second-order neurons which relay the message to a respiratory pattern generator, activating efferent motor neurons, and leading to cough. The C-fibres also contain neuropeptides, which are released upon nerve activation in some species and lead to neurogenic inflammation (Nasra & Belvisi, 2009).

Airway afferent nerves express a large number of different receptors and ion channels that modulate nerve activity. Cell bodies for the vagus nerves originate in the nodose and jugular ganglia, which are located in the head (Figure 1). In addition to the airways, vagus

nerves innervate several organs in the body, including the oesophagus, heart and gastrointestinal tract (Berthoud & Neuhuber, 2000). Airway vagal sensory fibres branch in to the superior and recurrent laryngeal nerves, which carry the fibres to the bronchi and trachea (Belvisi, 2003). These fibres consist of the rapidly-adapting receptors, slowly-adapting receptors, C-fibres, A δ nociceptors, and 'cough receptors'. Characteristics of each of the different fibre types have been described elsewhere (Undem *et al.*, 2002; Reynolds *et al.*, 2004; Lee & Undem, 2008). In this section we will briefly cover the C-fibres and 'cough receptors' that are thought to be directly associated with cough. C-fibres are predominantly chemosensitive sensory nerves, with high-threshold mechanosensitivity. C-fibres that innervate the airways originate in both the nodose and jugular vagal ganglia, and are found predominantly within the airway epithelium. These nerves are activated by a wide range of stimuli, including food extracts (capsaicin, wasabi, ginger, allicin, mustard oil), environmental irritants (vehicle exhaust, air pollution, tobacco smoke, burning vegetation), endogenous inflammatory mediators (prostaglandin E₂, bradykinin), and acid (Mohammed *et al.*, 1993; Caterina *et al.*, 1997; Bautista *et al.*, 2006; Kaufman *et al.*, 1980). Exposure to aerosols of these compounds causes cough in conscious guinea-pigs, dogs and humans (Canning *et al.* 2006; Kaufman *et al.* 1980; Costello *et al.* 1985; Laude *et al.* 1993; Laloo *et al.*, 1995; Birrell *et al.*, 2009). C-fibres contain neuropeptides, and have been found to express Transient Receptor Potential (TRP) ion channels, which are thought to play a central role in the cough reflex. This makes them attractive pharmacological targets for antitussive treatment, and they have therefore been a main focus of research in the cough field. In contrast, the 'cough receptors' are extrapulmonary, low threshold mechanosensors that originate in the nodose ganglia. These nerves do not express neuropeptides, and are insensitive to classical C-fibre stimulants such as capsaicin and bradykinin (Canning *et al.*, 2004; Mazzone, 2004). However, they are extremely sensitive to low pH and dynamic punctate mechanical stimulation, and adapt only when the mechanical stimulus becomes static. It has been proposed that different types of cough and therefore multiple cough pathways may exist. These pathways theoretically contribute distinctly to defensive productive cough which aids in protecting the airways, and dry non-productive urge-to-cough sensations associated with disease states. It could therefore be possible to inhibit the non-productive cough pathway while preserving defensive cough (Canning, 2011).

2.4 Cough in inflammatory airways disease

The central and peripheral nervous systems are capable of adapting to their environment. External influences such as disease, injury and inflammation are able to induce changes in expression of various genes involved in the production of neuropeptides, neurotransmitters, and ion channels (Taylor-Clark & Undem, 2006). However, we do not yet understand this neuroplasticity with respect to mechanisms of cough linked with airway inflammation and other cough-associated pathologies (Lee & Undem 2008). It is possible that exposure to tussigenic agents could lead to long or short-term changes in the peripheral sensory nerves or CNS, or for example at the NTS where airway sensory nerves synapse (Bautista *et al.*, 2006). Studies in subgroups of patients have suggested that the cough reflex associated with viral infections, gastro-oesophageal reflux, COPD and 'cough-variant' asthma becomes hypersensitive to challenge with tussive agents when compared to normal controls (Doherty *et al.*, 2000; Pecova *et al.*, 2008). This suggests that there may be a common mechanism behind the augmented cough reflex in these diseases. Indeed, some of these airways

diseases (eg. asthma and COPD) are associated with enhanced release of inflammatory mediators (e.g. prostaglandin E₂ and bradykinin), and a lowering of physiological pH within the lungs. Interestingly, the threshold for sensory nerve stimulation and cough is reduced in the presence of inflammatory mediators, and inhalation of these mediators and low pH can induce coughing in both humans and animals. It could therefore be postulated that enhanced release of endogenous pro-tussive mediators could be at least partially involved in cough hypersensitivity seen in inflammatory diseases (Choudry et al 1989; Fox et al, 1996; Ho et al, 2000; Hunt *et al.*, 2000; Kostikas *et al.*, 2002).

2.5 Section summary

Cough is an interesting and quickly-developing field of research. This section provided a brief introduction to cough, and of the afferent nerves that control the cough reflex. Great advances have been made in our understanding of the cough reflex in the last decade, however, there are still many questions left to answer. We still know little about what receptors on the airway sensory nerve endings are involved in provoking cough, and how these mechanisms are altered to cause hypersensitivity and chronic cough. The rest of this chapter will deal with tobacco smoke as a stimulus for coughing, the current theories on the mechanisms of action behind smoke-induced cough, and research addressing how smoke exposure leads to excessive cough associated with disease states.

3. Acute effects of tobacco smoke on the cough reflex

Various environmental irritants are known to induce coughing such as air pollution, tobacco smoke (TS), smoke from burning vegetation, and vehicle exhaust. These irritants contain many of the same chemical constituents, which can be used to study the mechanisms driving acute cough. These studies are important, as we first need to understand how cough occurs in the healthy state before we can determine how these mechanisms change to cause chronic or excessive coughing associated with disease.

3.1 Models of acute TS-induced cough

TS is one of the most common inhaled irritants, and reliably evokes airway irritation and coughing in both animals and human non-smokers (Lee et al., 1993, 2007; Andre et al., 2009). However, it remains uncertain which constituents in tobacco and other types of smoke are primarily responsible for evoking these irritant effects. Using several different methods, activation of airway sensory nerves and, in some cases, the cough reflex has been investigated in dog, cat, guinea-pig and mouse animal models, amongst others, which have provided some valuable insights in to the mechanisms driving the acute cough response. However, species differences have been observed for a multitude of physiological processes. As such, the results observed in these animal models may not all be applicable to human cough. This highlights the importance of replicating these studies in both *in vitro* studies using human tissue (where possible) and clinical trials, as the mechanisms driving acute and/or chronic cough may be different.

3.2 Mechanisms of action of TS in acute cough

3.2.1 Nicotinic receptors

Nicotine is a major constituent of TS, and nicotinic receptors are known to be present on a variety of cells in the airways, including neurons (Gu et al., 2008). As such, the nicotinic

acetylcholine (nACh) receptors were hypothesised to be responsible for acute cough induced by smoke inhalation. Lee and colleagues originally studied this hypothesis in both awake and anaesthetised dogs. Using single fibre analysis, the authors observed that a single puff of TS generated from high nicotine, but not low nicotine cigarettes triggered action potential generation in bronchopulmonary C-fibres and RARs. Moreover, the competitive selective nACh receptor antagonist hexamethonium inhibited sensory nerve stimulation in response to TS, but had no effect on other tussive stimuli, indicating a role for nicotine in the smoke-induced irritant response in dogs (Lee et al., 1983, 1985, 1986, 1989; Kou & Lee, 1990, 1991). The ability of nicotine to stimulate airway sensory nerves was corroborated in rat isolated vagal ganglia neurons by assessing calcium influx. Calcium is an important signal transduction molecule in neurons, and plays a pivotal role in the regulation of membrane excitability. Airway neurons were selectively tagged with a specialised fluorescent tracer, allowing them to be differentiated from vagal neurons that innervate other organs. Calcium entry in to airway neuronal cells was successfully stimulated by nicotine, a response which was all-but abolished with hexamethonium pre-treatment (Xu et al., 2007). In the same study, the authors also confirmed a stimulatory effect of nicotine on C-fibres and RARs (Xu et al., 2007).

However, as discussed in section 3.1, there are species differences associated with many physiological functions, and as such effects observed in animal models do not always reflect the mechanisms involved in human responses. Thus, Lee and colleagues went on to investigate the role of nACh receptors in TS-induced airway irritation in humans in a set of three studies (Lee et al., 1993). The first trial assessed the irritant effects of inhaling a single bolus of smoke generated from high or low nicotine cigarettes, or 'gas phase' control in healthy young non-smokers. Participants were blinded as to what stimulus they were receiving, and when the smoke bolus was to be delivered. Airway irritation was subjectively measured, with participants asked to push a button in response to the level of airway irritation they perceived. Smoke from high nicotine cigarettes triggered intense airway irritation in the lower neck and upper chest. In contrast, low nicotine cigarettes caused little to no irritation in comparison to gas phase. High nicotine cigarettes also triggered reflex coughing in the majority of participants. Whereas, coughing was absent with inhalation of both low nicotine and gas phase irritants. This corroborated their findings in the dog model (Lee et al., 1983, 1985, 1986, 1989; Kou & Lee, 1990, 1991). The second study assessed the role of nicotine in TS-associated airway irritation and cough. Pre-medication with the general nACh receptor inhibitor hexamethonium was reported to significantly attenuate airway irritation compared to placebo control. The number of coughs was also reduced with hexamethonium pre-treatment in comparison to placebo. Finally, the third study investigated whether aerosolised nicotine alone could induce airway irritant responses. Indeed, nicotine evoked intense and sustained irritation and vigorous coughing in comparison to placebo, which induced no irritation and few coughs. Lee and colleagues have summarised their research in two reviews (Lee et al., 2007, 2010).

From these studies, it was concluded that TS causes airway irritation and cough via activation of sensory nerve endings in the airways, and that nicotine is likely to be the primary causative agent for this nociceptive response. In addition, the irritant responses to TS stimulation were proposed to be mediated by vagal bronchopulmonary C-fibres and RARs (Lee et al., 1993). However, inhibition of the nACh receptors did not completely abolish coughing induced by TS inhalation. Furthermore, TS contains a multitude of potentially tussive noxious constituents in addition to nicotine; and not all smoke contains

nicotine but can still induce coughing, for example wood smoke. Tussive stimuli also act via diverse mechanisms, as different irritants target various membrane receptors expressed on airway sensory nerve endings. It is therefore likely that other noxious substances and one or more other receptors are involved in the TS-induced acute cough response. Indeed, it has recently been discovered that nicotine also activates the Transient Receptor Potential (TRP) class of ion channels, and that TS-induced cough can be inhibited by TRP-selective antagonists (Talavera et al., 2009; Andre et al., 2009).

3.2.2 Transient Receptor Potential (TRP) receptors

The TRP ion channels have been linked to various roles in sensory perception, including detection of noxious stimuli (Caterina et al., 1997; Nilius, 2007). A number of TRP receptor subtypes have been found to be expressed on sensory neurons, specifically Vanilloid (TRPV)1, TRPV2, TRPV3, TRPV4, Melastatin (TRPM)8, and Ankyrin (TRPA)1 (Caspani & Heppenstall, 2009). The TRPV1 ion channel has a well-established role in cough, and two known TRPV1 ligands (capsaicin and citric acid) are routinely used to assess the cough reflex in animal and clinical studies. More recently, the TRPA1 ion channel was also identified as a pro-tussive receptor in both humans and an animal model; an effect which was blocked by TRPA1-selective antagonists (Birrell et al., 2009; Andre et al., 2009). This is a significant finding, as TRPA1 is activated by a multitude of both environmental irritants and endogenous mediators. In fact, many constituents contained in tobacco smoke, wood smoke and air pollution are now known to activate TRPA1 ion channels, and thus it has become a key candidate for mediating the tussive effects associated with these pollutants.

Acrolein and crotonaldehyde are abundant in TS (Facchinetti et al., 2007; Andre et al., 2009), and have been shown to selectively activate TRPA1 (Bautista et al., 2006; Andre et al., 2008). In a set of studies demonstrating the role of TRPA1 in cough, Andre and colleagues established that both acrolein and crotonaldehyde induce robust coughing in guinea pigs, and that this effect could be inhibited by the selective TRPA1 antagonist HC-030031 (Andre et al., 2009). Because these irritants are common constituents in TS, the authors hypothesised that they might contribute to the cough associated with smoke inhalation. Indeed, TS exposure for 10 minutes caused vigorous bouts of coughing in conscious guinea pigs, which was inhibited approximately 50% by the cation blocker (ruthenium red) as well as a selective TRPA1 antagonist (HC-030031). Interestingly, the TRPV1-selective antagonist capsazepine was also reported to have a small inhibitory effect on TS-induced coughing, though not to the extent of TRPA1 inhibition (Andre et al., 2009).

A role for TRPA1 in TS-induced cough has been further substantiated by the finding that nicotine is also capable of activating this receptor (Talavera et al., 2009). Application of nicotine was observed to activate both mouse- and human-TRPA1 heterologously expressed in CHO cells via a direct gating mechanism. In addition, TRPA1-mediated nicotine responses were identified in mouse trigeminal neurons, a response that was blunted in genetically modified mice with the TRPA1 gene disrupted (*Trpa1*^{-/-}), and virtually abolished in *Trpa1*^{-/-} neurons in the presence of the nACh inhibitor hexamethonium. Moreover, using an *in vitro* isolated vagus nerve preparation, we investigated the ability of nicotine to induce membrane depolarisation, which is a measure of sensory nerve activation. The magnitude of depolarisation elicited by nicotine was observed to be significantly smaller in *Trpa1*^{-/-} mice in comparison to vagus nerves from wild-type mice ($p < 0.05$; data not shown), indicating a role for TRPA1 in nicotine stimulation of sensory nerves. Moreover, pre-treatment with either a nAChR or TRPA1 antagonist inhibited nicotine responses in wild-type mice; and

pre-treatment with a nAChR antagonist virtually abolished nicotine responses in *Trpa1*^{-/-} mouse vagus (Figure 2). Overall, these studies provide strong evidence for a role for both the TRPA1 and nACh ion channels in the response to nicotine. Thus, it is possible that part of the inhibition of acute TS-induced cough observed by Andre and colleagues (2009) could be caused by a reduction in the effects of nicotine with TRPA1 antagonism.

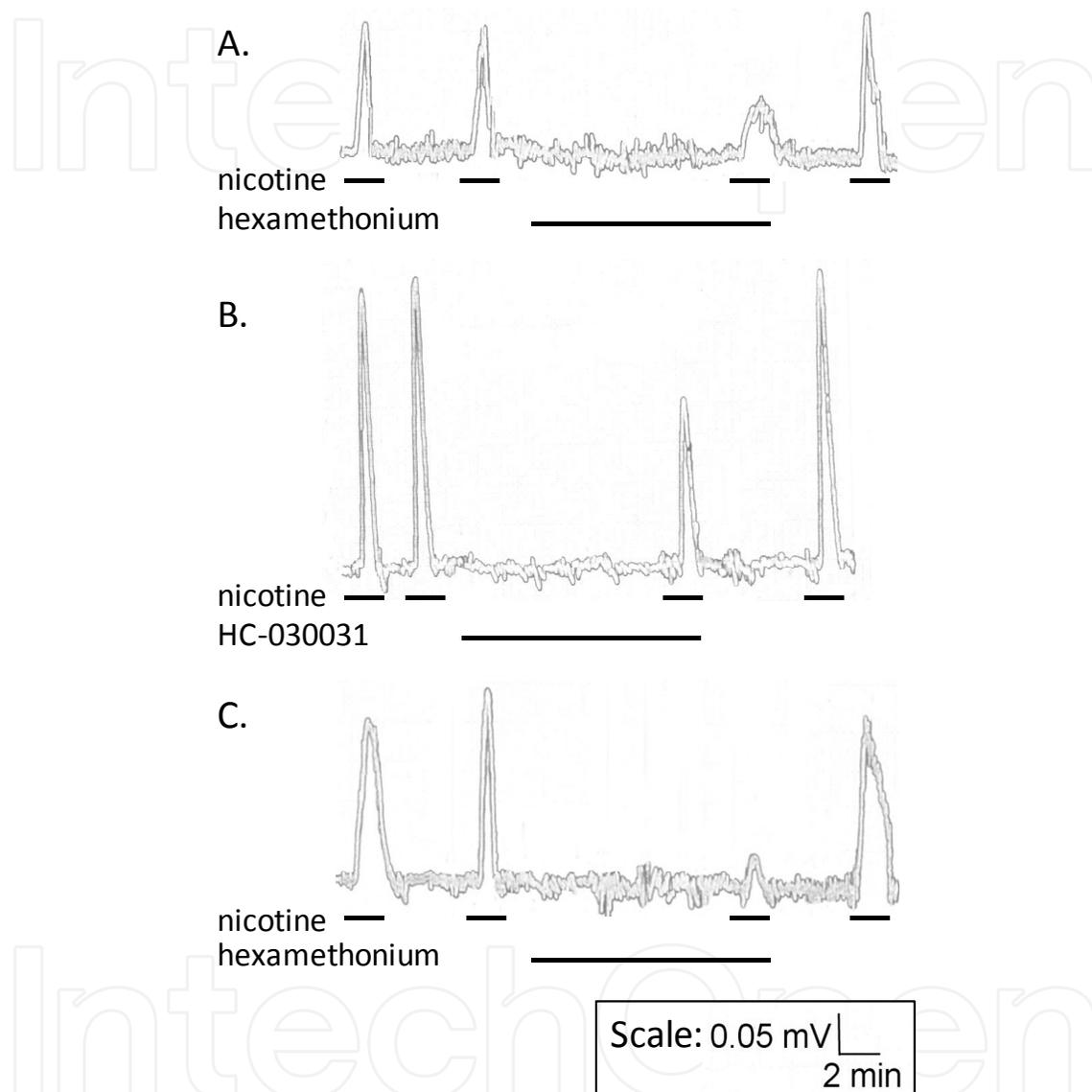


Fig. 2. Representative traces showing isolated vagus nerve responses to nicotine stimulation. Vagus nerve trunks from wild type (C57Bl/6j) or *Trpa1*^{-/-} mice were exposed to stimulations of nicotine with or without the presence of antagonist. Two 2-minute stimulations to nicotine alone were performed to establish reproducibility of the nicotine response. The nerve was then incubated for 10 minutes with an nAChR antagonist (hexamethonium) or TRPA1 antagonist (HC-030031) and a third stimulation with nicotine in the presence of antagonist. The nerve was washed, and a final stimulation with nicotine performed to ensure nerve viability. *A. and B.* Magnitude of nerve depolarisation (a measure of sensory nerve activation) in wild-type vagal tissue was inhibited by either nAChR or TRPA1 antagonism. *C.* Depolarisation was virtually abolished with nAChR antagonism in *Trpa1*^{-/-} vagal tissue.

Finally, it is important to note that, because TRPA1 and TRPV1 are co-expressed on sensory neurons, there is a possibility these TRP channels act in concert to elicit functional responses to noxious stimuli. Indeed, it has been suggested that TRPA1 channels could be activated by an overflow of calcium in the locale of other activated channels, without ever being modified by a reactive ligand. Furthermore, TRPA1 channels may act to amplify other calcium-mobilising pathways, including activation of TRPV1 (Zurborg et al., 2007; Cavanaugh et al., 2008). There is evidence for this type of coupling with bradykinin signalling in trigeminal neurons (Bautista et al., 2006). However, whether this sort of cooperation exists in generating cough has yet to be determined.

3.3 Section summary

The above studies suggest a significant role for both the TRPA1 and nACh receptors in acute tussive responses to TS inhalation. However, reduction in TS-induced cough with selective TRPA1 and nACh inhibitors is only partial, and there are thousands of constituents contained in TS, suggesting that there are likely to be multiple mechanisms and yet more receptors mediating the tussive effects of TS. For example, the TRPV1 ion channel has a well-established role in cough. It is highly possible that tobacco smoke also contains irritants, or induces the production of endogenous metabolites that directly or indirectly activate TRPV1. Furthermore, smoke inhalation reduces airways pH and increases temperature, both of which are known to activate the TRPV1 receptor. Indeed, there is some suggestion in the literature that TRPV1-selective antagonists may attenuate the acute tussive response to tobacco smoke, though the inhibitory effect was small (Andre et al., 2009).

4. Cough and disease

Chronic cough is reported as a troublesome symptom by 7% of the population (Ford et al., 2006). In extreme situations, cough can persist for several years, and is not only socially embarrassing, but can be painful and debilitating. Chronic cough is often associated with an underlying respiratory disease, several of which are associated with the inhalation of tobacco smoke and other air pollutants, for example asthma, COPD and lung cancer (WHO 2008a; WHO 2011). But the mechanisms by which smoking or air pollution causes exaggerated cough remains unknown (Morice et al., 2004; Smith & Woodcock, 2006).

4.1 Models of tobacco smoke and disease

A number of attempts have been made to simulate smoke-induced respiratory disease in animal models in order to study the mechanisms by which TS leads to cough hypersensitivity. The guinea-pig, as the only small animal that exhibits a functional cough reflex, is by far the cheapest and easiest animal in which to investigate cough in chronic models, and as such most disease research has been conducted using these animals. Both sub-chronic and chronic models of TS exposure using guinea-pigs have successfully induced an enhanced cough reflex when animals were subsequently exposed to tussive mediators (Karlsson et al., 1991; Bergren, 2001; Lewis et al., 2007).

4.1.1 Sub-chronic models of tobacco smoke exposure

Sub-chronic models of up to two weeks TS exposure have produced hypersensitivity to tussive stimuli in guinea-pigs. Compared to air-exposed controls, guinea-pigs exposed to

two weeks of TS for one hour per day exhibited a 3.7-fold and 2.5-fold increase in coughing in response to aerosolised citric acid and capsaicin stimulation, respectively (Karlsson et al., 1991). Enhanced responses to citric acid and capsaicin stimuli abated over the following three weeks, suggesting that cough hyperresponsiveness in this model is a very plastic phenomenon. Because prostaglandin E₂ has been previously shown to potentiate capsaicin-induced coughing in human volunteers (Choudry et al., 1989), the authors investigated whether prostaglandins could be involved in the augmented response to tussive stimuli seen after TS exposure. The general cyclo-oxygenase inhibitor indomethacin was injected 1 hour prior to stimulation with citric acid. Though a slight decrease in the number of coughs was observed with indomethacin pre-treatment compared to vehicle pre-treatment in TS-exposed animals, the effect was not significant, and was mirrored in air-exposed controls (Karlsson et al., 1991). It should, however, be noted that this was an acute exposure to indomethacin following 2 weeks of TS exposure, which would only prevent release of prostaglandins during the acute tussive stimulation. This experiment may engender more meaningful results if indomethacin was given throughout the two-week TS exposure, which would prevent chronic enhanced release of prostaglandins in the airways. Long-term effects of prostaglandins in the airways may be more likely to be involved in the hypertussive response than an acute release during irritant exposure.

A more recent study has corroborated the above findings, and established a brief time-course for the effects of TS on enhanced cough responses, which revealed remarkable differences in the enhancement observed with citric acid or capsaicin stimulation (Lewis et al., 2007). Specifically, enhanced cough to citric acid stimulation developed after exposure to TS for only 1 day; hypersensitivity peaked after 2 days of TS exposure and remained elevated for 10 days. In contrast, enhanced cough to capsaicin stimulation was not observed until guinea-pigs had been exposed to TS for 4 days, but thereafter cough sensitivity also remained elevated for 10 days.

Our group has also substantiated the findings of these previous studies, having developed a model whereby guinea-pigs are exposed to TS twice daily for 8 consecutive days. In this model we observed hypersensitivity to tussive stimuli in the smoke-treated animals in comparison to air-exposed controls. An increase in isolated sensory nerve responses to stimulation with capsaicin and citric acid was observed in the smoke-treated animals. This result was paralleled *in vivo* by an increase in cough sensitivity to capsaicin aerosol in smoked animals compared to air-exposed controls (Figure 3).

4.1.2 Chronic models of tobacco smoke exposure

Excessive cough is often one of the first presenting symptoms of COPD. Sub-chronic models of respiratory disease are therefore useful, as they can assess the mechanisms of enhanced cough at the beginning stages of disease. However, chronic models are also needed, because several physiological changes occur as the disease progresses. It is these structural changes which may lead to the chronic, irreversible hypertussive effects. For example, more advanced stages of COPD are associated not only with inflammation in the airway mucosa and parenchyma, but destruction of lung parenchyma and fibrosis. It is with these types of structural changes that we may begin to observe long-term enhancement of the cough reflex, rather than the reversible changes observed in, for example, Karlsson and colleagues (1991) sub-chronic model.

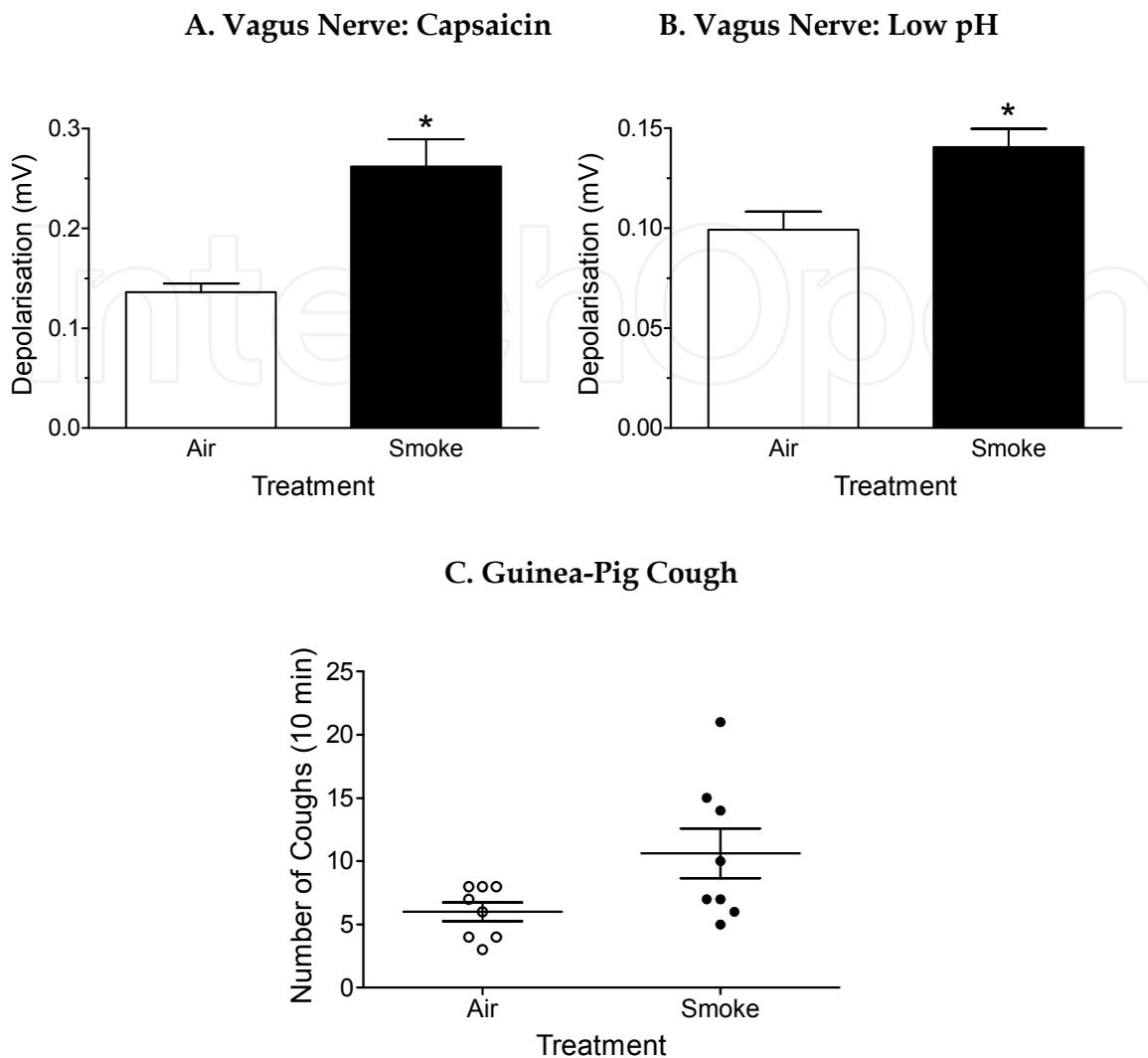


Fig. 3. Investigating *in vitro* sensory nerve and *in vivo* cough responses to tussive stimuli following sub-chronic tobacco smoke exposure.

Guinea-pigs were exposed twice daily for 8 days to either air (white bars and open circles) or tobacco smoke (black bars and filled circles). Twenty four hours after the final exposure either the animals were culled and vagus nerves removed; or conscious animals were exposed to tussive stimuli. Magnitude of vagus nerve depolarisation (a measure of sensory nerve activation) to (a) $1\mu\text{M}$ capsaicin, or (b) low pH 5 was compared between air and smoke-exposed animals ($n = 12$). (c) animals were exposed to $30\mu\text{M}$ aerosolised capsaicin for 5 minutes (coughs counted during this period and for a further 5 minutes; $n = 8$). * indicates statistical significance compared to air-exposed controls ($p < 0.05$, Mann-Whitney unpaired t-test).

There is a wealth of literature examining the effects of chronic TS on inflammation; however, to our knowledge only one study has directly assessed the effects of long-term smoke exposure on the cough reflex (Bergren, 2001). Guinea-pigs were exposed to either compressed air or TS for 30 minutes per day for a total of 90 days. In the TS group, spontaneous coughing was observed both during TS exposure and at other non-exposure times, with increasing

regularity as the study progressed. After 90 days, animals exposed to TS exhibited a significantly greater number of coughs to either capsaicin or bradykinin challenge than air-exposed controls. Moreover, hypersensitivity to capsaicin was further enhanced with ovalbumin sensitisation, which is an animal model of allergic asthma. This result holds implications for co-morbidity of patients suffering from more than one airway pathology.

4.2 Mechanisms of action

Thus far, the mechanisms driving chronic cough have been elusive. Models of excessive cough such as those reviewed above are useful for determining these mechanisms, and add to our understanding of the disease process. There is some evidence to suggest that an increase in receptor expression may be involved in the development of cough hypersensitivity, as evidenced by an increase in TRPV1 expression in the lungs of chronic coughers compared to healthy controls (Groneberg *et al.*, 2004). As-yet there are no documented studies investigating changes in the expression of TRPA1 or other receptors associated with cough. Alternately, it has been proposed that the lung environment during inflammatory airways disease may be sensitising the peripheral nerves, making them more likely to respond when exposed to a low level of irritant that would not normally reach cough threshold. For example, patients with inflammatory airways disease exhibit a decrease in lung pH, and high levels of endogenous inflammatory mediators within the airways (Profita *et al.*, 2003; Montuschi *et al.*, 2003; Hunt *et al.*, 2000; Kostikas *et al.*, 2002). Two inflammatory mediators, prostaglandin E₂ and bradykinin, have not only been shown to sensitise airway nerves to other tussive stimuli, but can in fact induce coughing themselves (Costello *et al.* 1985; Maher *et al.* 2009; Choudry *et al.* 1989; Katsumata *et al.* 1991; Fox *et al.*, 1996). Therefore, if the endogenous concentration of these irritants reaches high enough levels, coughing could be directly induced without any environmental challenge.

A qualitative change in the vagal afferent innervation of guinea-pig airways has also been documented in disease models. C-fibres are known to express neuropeptides on their nerve endings, which are released in response to nerve stimulation, where they can contribute to peripheral neurogenic inflammation. Activation of nociceptors can also cause central sensitisation via release of neuropeptides from their central terminals, where they enhance synaptic neurotransmission. Under normal circumstances, these neuropeptides are synthesised nearly exclusively in C-fibres, and are not expressed on other sub-sets of sensory afferents. However, in models of respiratory virus and allergic inflammation, Udem and colleagues have demonstrated that A δ -nociceptive neurons transiently produced neuropeptides, an effect that appeared to reverse with resolution of virus infection (Carr *et al.*, 2002; Myers *et al.*, 2002). This is a particularly important finding, as it suggests that sensory neuropeptide release from afferent nerve endings and central terminals may not require chemical stimulation, but could be provoked following activation of low-threshold mechanosensors.

4.3 Section summary

The studies discussed in this section have established the importance of the TRPV1 ion channel in development of excessive cough in disease states. What has not yet been investigated is the role that other ion channels may play. No-doubt future studies will assess hypersensitivity to TRPA1-selective irritants, now that TRPA1 has been identified as a promising target for cough. But it is also important to determine the function that other

tussive compounds play in this pathology. In particular, endogenous inflammatory mediators such as prostaglandin E₂ and bradykinin are known to be released in greater amounts in inflammatory airway disease. These mediators are not only able to sensitise airway afferents to stimulation by other tussive ligands, but can induce coughing themselves with acute exposure. In addition, the discovery by Lewis and colleagues (2007) that hypersensitivity to citric acid stimulation develops well before capsaicin could be important, and warrants further investigation. This could be to do with the fact that capsaicin acts solely on the TRPV1 ion channel, whereas the tussive response to citric acid is only partially mediated via TRPV1. Therefore the other ion channel(s) involved in the citric acid response (such as the acid sensing ion channels, or ASICs) could be upregulated or otherwise affected by TS more quickly than TRPV1.

There is also the debate on whether hypersensitivity involves central or peripheral sensitisation of the cough reflex. That is, does hypersensitivity develop because there is an enhanced reactivity of the peripheral nerves to a stimulus; or is the stimulus amplified within the CNS, producing a response to otherwise non-noxious stimuli? Ultimately, it is the interplay between all of these factors that is likely to lead to excessive coughing associated with inflammatory airway diseases.

5. Therapeutic targets

Currently available anti-tussive therapies are largely offered over-the-counter (OTC) as self medication programmes, and are among the most widely used OTC drugs. However, OTC remedies show little efficacy in alleviating cough (Schroeder & Fahey, 2002); and opiates, the gold standard in cough treatment, are associated with moderate to severe side-effects (Karlsson & Fuller, 1999; Belvisi & Geppetti, 2004; Reynolds et al., 2004). In fact, it has been recognised that cough and cold remedies can cause adverse events in children under 11 years of age (American Academy of Paediatrics, 1997; Gunn et al., 2001; Centres for Disease Control, 2007; Vassilev et al., 2009). In early 2008, this led the U.S. Food and Drug administration to release an advisory notice recommending that OTC cough and cold medicines should not be used to treat children under 2 years of age, due to potentially life-threatening side-effects (U.S. FDA, 2008). The development of efficacious cough therapies with fewer, less severe side-effects is therefore urgently required.

The site of action of anti-tussive agents can be broadly classified as those that act peripherally, and those that act centrally. It is currently not known whether the enhanced cough seen in disease states is due to peripheral or central sensitisation, and as such targeted therapeutics specific to the enhanced response are difficult to identify. However, targeting either compartment would theoretically lead to attenuation in cough due to a general suppression of the reflex. This has led to concerns that targeting the tussive reflex in diseases could inhibit both excessive cough, and the functional cough associated with health benefits. Therefore, the ideal anti-tussive therapy would suppress only the enhanced cough associated with disease, while leaving the protective part of the reflex functional. Centrally-acting suppressants are generally associated with neurological side-effects such as sedation, nausea and physical dependence, which limits their effective use. In contrast, peripherally acting anti-tussives exert their effects by targeting peripheral sensory nerve afferents, and could potentially provide a better approach than centrally acting therapies. In this section we have discussed only a select few of the peripherally-acting anti-tussive therapies that are

either currently being pursued as potential therapies, or show promise in pre-clinical research and human trials. This is not an exhaustive list but covers some of the key targets currently being investigated.

5.1 TRPV1 inhibitors

Research over the last decade has revealed TRPV1 as a promising target in the field of cough. It has already been established that chronic coughers show higher expression of TRPV1 in the lung in comparison to 'healthy' individuals (Groneberg et al., 2004); and TRPV1 antagonists are efficacious in preventing cough in guinea pigs induced by capsaicin and citric acid aerosol (Laloo et al., 1995; Trevisani et al., 2004). However, TRPV1 is now known to be tonically active in thermoregulatory pathways, and as such one of the main issues with currently available TRPV1 antagonists is that they cause hyperthermia (Gavva et al., 2008; Lehto et al., 2008). This is a potential confounding factor in the clinical development of TRPV1 therapeutics. Research is currently under way to produce TRPV1 inhibitors that do not affect body temperature, with limited success thus far (Lehto et al., 2008). It is also of concern that TRPV1 appears to be widely expressed throughout the body, and thus may lead to other unexpected side effect issues. Despite these reservations, several TRPV1 inhibitors are currently under development both as antitussives and analgesics (Gunthorpe & Chizh, 2009).

5.2 TRPA1 inhibitors

The recent discovery of TRPA1 as a pro-tussive receptor and its role in TS-induced cough is a significant finding (Birrell et al., 2009; Andre et al., 2009). This opens up a whole new field of research for potential anti-tussive remedies that could help to alleviate cough, not only associated with the common cold and seasonal flu, but more importantly for those who suffer from excessive coughing associated with chronic inflammatory diseases. Specifically, activation of the TRPA1 receptor could be significant in several pathological situations given that it is known to be stimulated by a multitude of environmental irritants (including constituents of air pollution and burning vegetation), as well as endogenous products of oxidation which can be generated in the airways by inhalation of pollutants or during inflammation (Bessac et al., 2008; Andre et al., 2008; Taylor-Clark et al., 2008). This could be of particular importance in highly polluted areas such as large cities, or in occupations where workers are chronically exposed to environmental irritants.

TRPA1 is largely expressed by a subset of TRPV1-expressing neurons, and both are activated by tussive agents, so it could be possible that these two channels act in concert to elicit functional responses. The theory that TRPA1 and TRPV1 may co-operate comes from evidence that TRPA1 can be activated by an overflow of Ca^{2+} in the locale of other activated channels, such as TRPV1, without ever being modified by a reactive ligand. Moreover, TRPA1 could amplify other Ca^{2+} mobilising pathways (Zurborg et al., 2007; Cavanaugh et al., 2008). Both TRPA1 and TRPV1 inhibition can totally or partially block responses to a range of tussive agents (Maher et al., 2010). However, it has yet to be determined whether cooperation exists between these two channels in initiating the cough reflex. Information to date would suggest TRPA1 expression is more restricted which may make for a more optimal safety profile than TRPV1 inhibition, although this remains to be seen with the increased testing of TRPA1 antagonists in both pre clinical and clinical studies. Unfortunately, the tools available to probe this target are limited (Viana & Ferrer-Montiel,

2009), and it is therefore difficult to predict whether single TRPA1 or TRPV1 therapies or a combined drug would be more effective in treating heightened sensory nerve responsive disease states (Belvisi et al., 2011).

5.3 nACh receptor inhibitors

Neuronal nACh receptors are pentameric ligand-gated ion channels which are formed by assembly of five transmembrane segments. To date there are 17 known members of the nACh family expressed in humans, which assemble in numerous combinations to form functional ion channels with widely varying agonist and antagonist gating properties (Gu et al., 2008). In addition, nACh receptors are widely expressed throughout the body, including both the central and peripheral nervous systems. This limits development of nACh-based therapies without a more in-depth understanding of what receptor subtypes are involved in cough, and subsequent development of selective antagonists with which to inhibit these responses. Though selective ligands targeting specific subunits of nACh receptors are being developed as therapeutic agents for neurodegenerative diseases, the authors do not know of any current interest in developing such compounds as therapies for cough (Lee et al., 2007; Gu et al., 2008).

5.4 β_2 -adrenoceptor antagonists

Bronchodilators are a cornerstone of symptomatic treatment for COPD and asthma (Barnes, 2010a, 2010b). One of the most effective bronchodilators currently available are the β_2 -adrenoceptor agonists, which are widely used to alleviate the bronchoconstriction associated with respiratory diseases. In some clinical trials, treatment with β_2 -agonists has also been shown to possess anti-tussive properties in both healthy volunteers (Lowry et al., 1987) and chronic cough pathologies associated with allergic (Ellul-Micallef, 1983) or obstructive conditions (Campbell et al., 2005; Chong et al., 2005; Mulrennan et al., 2004; Pounsford et al., 1985). However, an anti-tussive effect of β_2 -agonists in clinical trials has not been universally observed (Chang et al., 1998; Smith et al., 1991). The lack of definitive data demonstrating an anti-tussive activity of β_2 -agonists in these studies may be due to the research protocols used, including the use of subjective symptom scoring; that few of these studies have been performed under double-blind, randomised and placebo-controlled conditions; and that cough is rarely a primary end-point of the research.

Recently, the ability of β_2 -agonists to inhibit the cough reflex was assessed in a pre-clinical model (Freund-Michel et al., 2010). The β_2 -agonist terbutaline was shown to attenuate guinea-pig cough responses to both capsaicin and citric acid *in vivo*. In addition, both terbutaline and fenoterol blocked sensory nerve activation in response to a number of tussive agonists in the guinea-pig isolated vagal nerve preparation; and fenoterol inhibited depolarisations of human isolated vagus nerve induced by capsaicin. The ability of these compounds to directly inhibit sensory nerve responses provides evidence against the existing dogma that the anti-tussive effects of β_2 -agonists are secondary to bronchodilation. Furthermore, the authors proposed a mechanism-of-action, whereby β_2 -agonists stimulate adenylyl cyclase, leading to cyclic AMP accumulation, activation of protein kinase G, and opening of large conductance calcium-activated potassium (BK_{Ca}) channels, thereby inhibiting sensory nerve depolarisation. Both short- and long-acting β_2 -agonists are already used in the clinic as bronchodilators for asthma and COPD; and have a proven acceptable safety profile in man. Furthermore, their mechanism of action appears to be via the opening

of BK_{Ca} channels, which provides non-selective inhibition of the cough reflex and thus would be effective against a range of tussive mediators. However, more studies need to be done to corroborate the findings of Freund-Michel and colleagues (2010), coupled with appropriate well-controlled and blinded clinical investigation with the use of objective cough monitoring.

5.5 Methylxanthines

Methylxanthines are another class of bronchodilator that are commonly used to alleviate the symptoms of COPD and asthma (Barnes, 2010a, 2010b). As with β_2 -agonists, methylxanthines have been proposed to inhibit the cough reflex. Clinical studies have suggested that theophylline acts as an anti-tussive in a range of conditions. In children and adults with poorly controlled asthma (Bose et al., 1987; Fairfax et al., 1990), theophylline significantly improved scores for cough and wheeze compared to placebo. Theophylline is also recommended for the treatment of cough in COPD (ACCP guidelines 2006) and has been shown to be effective for treating ACE-inhibitor related cough (Cazzola et al., 1993). Hypersensitivity of the cough reflex is a feature of all these conditions and whilst specific effects on the underlying disorders cannot be excluded, a general inhibitory effect on cough reflex sensitivity would seem more plausible. Indeed, in subjects with ACE-inhibitor cough, theophylline was shown to reduce cough reflex hypersensitivity in addition to ameliorating symptoms. Furthermore, theophylline has been shown in clinical trials to be an effective treatment for pain (mechanical nociception, renal colic, non-cardiac chest pain, post lumbar puncture headache) which may indicate an effect on nociceptive processes (Rao et al., 2007; Pechlivanova & Georgiev, 2005). Our preliminary data (described below) demonstrates that theophylline directly inhibits sensory nerve activation and the cough reflex (Dubuis et al., 2011). More recently, Usmani and colleagues (2005) investigated the anti-tussive effects of another methylxanthine theobromine in a comprehensive set of studies. Using an *in vivo* conscious model of cough in guinea-pigs, the authors established that theobromine dose-dependently inhibited citric acid-induced cough in a similar fashion to the established systemic opiate codeine. This result was replicated in normal volunteers in a study where theobromine significantly attenuated capsaicin-induced cough. In comparison, codeine did not significantly affect capsaicin-induced cough in human participants. Finally, it was demonstrated that the effects of theobromine were being mediated peripherally by direct inhibition of sensory nerves, using an *in vitro* isolated vagus preparation. However, it should be noted that the participants in this clinical trial were all healthy individuals with no indication of respiratory disease. Therefore, these studies need to be replicated using participants exhibiting excessive cough, to see if the beneficial effects of theobromine are maintained in disease states. Furthermore, the mechanism by which theobromine attenuates cough is unclear, thus further pre-clinical trials are also required. Finally, it is not clear whether theobromine will exhibit a preferable anti-tussive profile compared to theophylline which is already approved for use in respiratory disease.

5.6 Section summary

There is currently a number of promising peripherally-acting anti-tussive targets being investigated. Of those that target specific ion channels, TRPA1 and TRPV1 antagonists are two of the most exciting. These inhibitors provide the potential for selectively suppressing ion channels that are directly involved in the cough reflex. However, there have been some

issues in the development of these compounds, due to inherent side effects, e.g. hyperthermia associated with TRPV1 compounds; or the apparent difficulty in developing efficacious selective antagonists in the case of TRPA1. Alternatively, compounds such as β -agonists or methylxanthines are thought to suppress cough by generally inhibiting sensory nerve activation to tussive stimuli. The mechanisms by which these antitussives exert their effects are not fully understood, but they provide potential therapeutic remedies that could reach the market in a much quicker timescale, due to the fact that they are already widely prescribed bronchodilator agents.

6. Conclusions

Despite a decreasing trend for smoking in some developed countries over the last decade, smoking worldwide is still on the increase, particularly in developing nations (Office for National Statistics, 2010; WHO, 2010). Moreover, indoor and outdoor air pollution is a major environmental health problem in both developed and developing countries alike (WHO, 2008b). In contrast to most other diseases, the global burden of chronic respiratory diseases is also on the increase (WHO, 2005; WHO, 2008a; WHO 2011). In combination, these trends represent a major concern for respiratory health worldwide. Prolonged, excessive coughing is a symptom associated with a large number of respiratory diseases, and is thus likely to be an increasing issue over the next several years. The findings discussed in this chapter represent a breakthrough in the field of cough, and could hold major implications for understanding the pathogenesis of chronic cough. Though further investigations are required, we are now beginning to establish likely mechanisms that lead to acute cough to smoke exposure, and excessive cough associated with smoking- and pollution-related chronic diseases. It is probable that the ideal therapy for chronic cough will involve multiple targets, but the TRP family of ion channels in particular should be considered highly promising for the development of future novel anti-tussive treatments.

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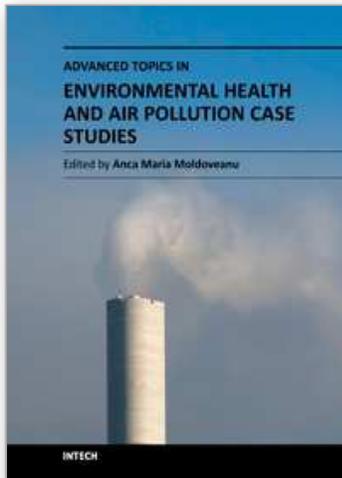
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The book describes the effects of air pollutants, from the indoor and outdoor spaces, on the human physiology. Air pollutants can influence inflammation biomarkers, can influence the pathogenesis of chronic cough, can influence reactive oxygen species (ROS) and can induce autonomic nervous system interactions that modulate cardiac oxidative stress and cardiac electrophysiological changes, can participate in the onset and exacerbation of upper respiratory and cardio-vascular diseases, can lead to the exacerbation of asthma and allergic diseases. The book also presents how the urban environment can influence and modify the impact of various pollutants on human health.

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