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Cough and viruses in airways disease: Mechanisms

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ABSTRACT

Acute cough is a major symptom of viral respiratory tract infection and causes excessive morbidity in human populations across the world. A wide variety of viruses play a role in the development of cough after acute infection and all of these manifest a similar clinical picture across different age groups. Despite the large disease burden surprisingly little is known about the mechanism of acute cough following viral infection. Both *in vitro* and *in vivo* experiments show that increased production of neuropeptides and leukotrienes mediate cough after viral infection, along with altered expression of neural receptors. Increased airway mucus production is also likely to play a significant role. This work is reviewed in this article.

Following the recent development of a mouse model for rhinovirus infection and the establishment of experimental models of rhinovirus challenge in human subjects with both asthma and COPD the field is expanding to translate *in vitro* research into clinical studies and hopefully eventually into clinical practice. Developing a clearer understanding of the mechanisms underlying virus induced cough may lead to more specific and effective therapies.

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1. Common respiratory viral infections

Upper respiratory tract infection (URTI) is the most common illness for which patients seek medical attention and cough is the most frequent symptom presenting to general practitioners [1]. Causing excessive morbidity in human populations across the world, URTI resulted in an estimated 84 million consultations in the United States during one year alone [2]. The financial costs top US\$40 billion, just over half in indirect costs, with 40–100 million school and work days lost to absenteeism each year [3]. There are no effective anti-viral therapies for most URTIs yet Americans spend US\$2.9 billion a year on over the counter cold remedies. Although generally self limiting, symptoms of cough often persist up to 3 weeks following viral infection [4]. Additionally a subgroup of patients can develop a chronic cough with symptoms being more prolonged and lasting months or years.

Acute coryza, the common cold, is primarily caused by viruses in the picornavirus and coronavirus families. Many other aetiological agents have been identified, however, including human metapneumovirus (HMPV), parainfluenza, influenza A&B and respiratory syncytial viruses (RSV). Clinically the identification of virus

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type is of minimal significance as all produce similar symptoms of nasopharyngitis and cough. The future development of specific anti-viral therapies however will necessitate accurate viral identification which at present is only performed in a research setting.

2. Epidemiology

2.1. Age

Cough in healthy subjects due to respiratory viral infection is a common symptom in childhood and falls in frequency during adult life. A prospective study following 197 children during their first year of life aimed to define the aetiology of respiratory tract infections [5]. Weekly symptom recording demonstrated that 62% of infants developed URTI and amongst these a virus was identified in 79% – predominantly rhinoviruses (23%) and coronaviruses (18%). All 112 infants who had an acute viral infection developed cough, demonstrating the significance of this symptom in childhood.

Acute cough in healthy adults is almost exclusively associated with respiratory tract infection. A gender related difference in both acute and chronic cough has been identified; amongst women the incidence of cough is higher with more presentations to medical care providers and a lower cough threshold to provocation tests [1,6]. This has been confirmed with objective cough monitoring [7] and is found in both acute and chronic cough.

2.2. Asthma exacerbations

Using sensitive molecular techniques it is possible to detect viruses in the majority of asthma exacerbations. In children 85% of exacerbations were associated with a virus [8] and 75% of exacerbations in adults [9]. Rhinoviruses are consistently the most frequent virus types detected, found in around two-thirds of cases where a virus is identified. The exact mechanism through which virus infection triggers exacerbations of airway disease is still unclear, but is likely to represent a constellation of host immune responses and specific viral actions. Infection of respiratory epithelium leads to a cascade of pro-inflammatory cytokines which recruit and activate immune cells in the airway. Mucus hypersecretion following virus infection is likely to be a key factor in airway obstruction and cough in the aetiology of airway disease exacerbations [10].

It has been postulated that asthmatic patients are more susceptible to virus infections, a longitudinal cohort study found that asthmatics were not at an increased risk of developing rhinovirus infection but did develop longer lasting and more severe lower respiratory tract symptoms when infected than healthy controls [9].

Reduced antiviral activity in asthmatic subjects may account for this; a recent study found peripheral blood monocytes from asthmatics exposed to rhinovirus were deficient in production of interferon-gamma (IFN- γ) and interleukin-12 (IL-12) compared to normal subjects [11]. Following experimental infection deficient induction of Th1 cytokines and IL-10 was demonstrated with augmented induction of Th2 cytokines in asthmatic subjects [12]; additionally the model demonstrated deficient levels of IFN- λ (lambda) in primary bronchial epithelial cells and alveolar macrophages which correlated with the severity of both exacerbation and virus load [13].

2.3. COPD exacerbations

The aetiological role of viruses in exacerbations of COPD is becoming increasingly clear. Infection can be identified in the majority of exacerbations; in one study 78% of exacerbations were associated with infection and these were more severe resulting in greater drops in lung function and prolonged hospitalisation compared to non-infective exacerbations [14]. Viruses are detected in 39–56% of exacerbations [15,16] but this is likely to represent an underestimate as 65% of subjects reported symptoms of a cold prior to exacerbation [16]. Detection rates vary depending on the methods of sample collection and analysis as well as exacerbation severity. Cough is the most common symptom in COPD and this is significantly increased during periods of exacerbation and infection.

2.4. Seasonal patterns

Incidence of viral respiratory tract infections varies throughout the year. Healthy individuals frequently develop URTI during early autumn associated with an increased incidence of cough and presentations to medical services. Epidemiological studies demonstrate the striking impact of seasonal factors on exacerbation frequencies in both asthma and COPD [17]. Asthma exacerbations in children peak around mid to late September strongly correlating with return to school [17]. A peak in COPD exacerbations follows in December which is associated with the Christmas holiday season and is seen in every northern hemisphere country studied [17]. These trends reflect a complex combination of many causative factors; but the primary cause of exacerbations is respiratory virus infection particularly with rhinovirus. Peak asthma exacerbations correlate with the highest incidence of rhinovirus infections in

the community but the reason for the delay in COPD exacerbations is not clear [8,15,17].

3. Mechanism of virus induced cough

Remarkably few studies have directly investigated the mechanism of virus induced cough. Those which have provided some insight have investigated airway hyper-responsiveness (AHR) rather than cough as an outcome measure. Conversely, studies that have specifically investigated cough have not studied experimental virus infections.

Coughing is a physiological response to airway irritation and an important defence mechanism for the respiratory tract. Inhibition of the normal host response to viral infection may not necessarily be desirable therefore. However the transmission of virus particles between individuals is enabled by coughing and it is likely that viruses have evolved mechanisms to produce and enhance cough production.

The causes of cough are complex and multi-factorial with many diverse aetiological agents other than infection identified. Several pathways, mediated via the vagus nerve, activate the central cough generator in the brainstem when stimulated by neurotransmitters in the respiratory tract [18]. Cough is generated by activation of laryngeal, oesophageal or tracheobronchial receptors in addition to voluntary control. Virus infection is just one example where cough may be stimulated via these pathways through both direct and indirect actions.

3.1. Specific mechanisms

Virus infection of the airway epithelium leads to inflammation and cytokine release as the host immune system is activated. Viruses, such as influenza, may be highly pathogenic and cause excessive epithelial cell necrosis and inflammation. However even rhinoviruses with milder pathogenicity, and less direct cellular necrosis, can lead to a marked symptomatic host response. A virus infected epithelial cell releases a wide range of inflammatory cytokines including IL-1, TNF- α , IL-6, IL-8, GRO- α , IL-11, RANTES, GM-CSF and eotaxin. In addition the expression of growth factors, adhesion molecules and immunity related molecules is up-regulated by virus infection [19]. A recent longitudinal study of exacerbations in severe asthmatics identified increases in IL-13 and IFN- γ producing T-cells during exacerbations; the deficiency of regulatory T cells found at baseline was also exaggerated during exacerbations [20]. This study offers new insight into the pathophysiology of asthma exacerbations, and although viruses were not investigated in this study future work should explore their role in these cellular changes.

3.2. Increased neurotransmitter levels

Virus infection in the lung leads to an increase in airway neurotransmitters particularly the tachykinin substance P, through a variety of different mechanisms. Tachykinins are neuro-excitatory molecules which act as potent vasodilators and cause contraction of airway smooth muscle and secretion of airway mucus. Substance P was found to be elevated in bronchoalveolar lavage (BAL) fluid from RSV infected mice [21] and this has been implicated in the lymphocytic response [22]. Further study in RSV infected mice again found elevated substance P levels, but also falls in the airway protective compound calcitonin gene-related peptide CGRP [23]. CGRP, a neuropeptide with vasodilating effects, is constitutively found in the airway and when deficient airways were found to be inflamed and hyper-responsive [24]. The central role of substance P in virus induced airway dysfunction was

confirmed when it was shown that selective blocking of the substance P receptor, neurokinin-1 (NK-1) receptor with Sendide abolished AHR [23].

3.3. Reduced neutral endopeptidases

Virus infection of the respiratory tract not only causes tachykinin release from A δ nerve fibres in guinea pigs [25] but also decreases the activity of neutral endopeptidases (NEs), important enzymes involved in degradation of airway tachykinins [26]. A rat study using RSV demonstrated significantly higher levels of substance P in lung tissue following infection; additionally stimulation with capsaicin further increased substance P release in infected lungs compared to controls [27]. Work in guinea pigs confirmed the high potency of substance P in cough generation and the effect of NE to limit this [28]. By inactivating cough generating tachykinins, NEs limit cough activity. Exogenous inhibitors of NE were able to increase the sensitivity to substance P with an increase in cough frequency and a lower dose response curve to capsaicin induced cough in guinea pigs [28].

3.4. Increased neural receptor levels

In addition to a total increase in tachykinin levels in the lung, expression of NK-1 receptor is increased, further amplifying virus induced neuro-stimulatory signals [29]. This effect was shown in young rats to be dependent on nerve growth factors (NGF) as neutralising antibody to NGF abolished the effect and exogenous addition of NGF up-regulated NK-1 receptor levels. Additionally levels of NGF fell with increasing age which may indicate a mechanism for exaggerated virus induced airway disease in the infant.

3.5. Modulation of neural activities

In addition to increases in neurotransmitters and receptors following virus infection, it has been shown that qualitative changes in afferent nerves occur. Experimental infection of guinea pigs with Sendai virus have shown that labelled afferent neurones from the trachea increased in size following virus infection and that this resolves in convalescence [25]. Tachykinins are synthesised in the neuronal cell body; the diameter of which was increased during acute infection, suggesting that virus infection can lead to changes in the vagal afferent innervations of guinea pig airways such that both small diameter nociceptive-like neurones and large diameter nonnociceptive neurones express tachykinins.

3.6. Cholinergic motor pathways

Despite the significant impact that virus infection appears to have on cholinergic pathways no research specifically on cough has been undertaken in this area. Surrogate markers such as bronchoconstriction and AHR have been used instead. Virus infection appears to activate bronchoconstriction through the vagus nerve. Acetylcholine levels are increased when the inhibitory effects of the muscarinic receptor (M2) are lost and virus infection has been shown to potentiate this [30]. Cells from animals infected with parainfluenza virus released more acetylcholine than non-infected cells and M2 receptor activity was disrupted by IFN-gamma (γ) exposure suggesting a potential mechanism for virus induced cough and possible increased sensitivity of afferent nerves [31].

Muscarinic receptors have also been shown to play a central role in airway vascular leakage and bronchoconstriction and mucus secretion; in a model of gastro-oesophageal reflux where cough may be a prominent feature, stimulation with acid activated muscarinic receptors (M1 and M3) and the effect was blocked with

specific antagonists [32]. Again no studies have specifically investigated cough and mechanisms of cholinergic activation.

3.7. Leukotrienes

Leukotrienes (LT) are potent mediators of bronchoconstriction, vascular dilatation, mucus production and AHR which again are used as surrogate markers for cough. They are produced from arachidonic acid by 5-lipoxygenase activating protein (FLAP) and 5-lipoxygenase (5-LO) leading to production of the cysteinyl-LTs (specifically LTC₄, D₄ and E₄) particularly in eosinophils and basophils. These are potent mediators in bronchial asthma and in aspirin induced asthma, inhibition of COX-1 following administration of non-steroidal anti-inflammatory drugs produces an excess of LTs with consequent worsening AHR and bronchoconstriction. Attempts to specifically inhibit the activity of these compounds have led to new therapeutic agents, such as Montelukast and Zafirlukast [33–35].

In a study of non-atopic normal subjects using experimental rhinovirus infection; bronchoscopy was performed 2 weeks prior to infection and repeated 4 days after virus inoculation. This identified increased airway inflammation with increases in macrophages and mast cells in bronchial biopsies during acute infection. In biopsy samples there were 9 and 3.6 fold increases in cells counts staining positively for 5-LO and FLAP respectively. In addition staining for the inducible enzyme COX-2, which is responsible for prostaglandin (PG) synthesis, was significantly increased. This study demonstrated an increased capacity for the production of LT and PG [36]. Cold symptoms were assessed during the study using the Jackson cold scoring system; which includes cough as a symptom indicator and scores correlated with stained cell counts of FLAP, supporting a link between symptoms and virus induced LT. LT levels have also been shown to increase after RSV infection and have a possible aetiological role in bronchiolitis, as a randomised control trial of the LT antagonist Montelukast found an improvement in lung symptom scores during RSV bronchiolitis [35]. Studies specifically investigating these pathways in cough would be of interest.

3.8. Mucus production following viral infection

Mucus hyper secretion is well recognised in diseases of the airway, particularly COPD where mucus production forms part of the definition of chronic bronchitis. Production is also stimulated by virus infection and so mucus is likely to be a significant inducer of cough, at least in part by direct airway irritation [10]. *In vitro* investigations of MUC5AC, a prominent airway mucin, have identified key signalling pathways and molecules [37]. Specifically the signalling for MUC5AC gene promoter is activated by the transcription factor SP1 following stimulation with the model inflammatory stimulus PMA.

Subsequently *in vitro* rhinovirus infection of human tracheal cells and submucosal glands demonstrated an up-regulation of mRNA for mucin producing genes. Levels of MUC5AC mRNA, protein and total mucin concentration were also elevated [10]. This effect was attenuated following addition of an NF- κ B and mitogen activated protein (MAP)-kinase inhibitor, suggesting these signalling molecules are important for mucus hyper-secretion following virus infection and suggesting inhibitors of these as potential therapeutic targets. *In vivo* rhinovirus infection has been shown to induce MUC5AC levels in BAL and *in vitro* studies demonstrated that this occurs as a result of new mRNA synthesis. The signalling pathway has been characterised in detail and the transcription factors NF- κ B and SP-1 were shown to be involved. Following RV infection NF- κ B is activated and matrix metalloproteinase mediated release of transforming growth factor (TGF) occurs. This in

turn activates the epidermal growth factor receptor leading to activation of protein kinase signalling (MAPK, MEK and ERK). Finally through SP-1 signalling the MUC5AC gene transcription is increased and hence protein levels elevated [37] (C.A. Hewson et al., unpublished results).

4. Experimental infection *in vivo*

4.1. Mouse model of RV infection

Investigation of the mechanism of virus induced cough has suffered from the lack of a small animal model of virus induced cough, particularly for rhinovirus which is the most common virus infection in humans [38] and repeatedly identified as the most frequent virus in acute exacerbations of airway disease [8,14–16]. Major group rhinoviruses (90% of serotypes) bind to the human intercellular adhesion molecule-1 (ICAM-1) as their cellular receptor. However they are unable to bind to mouse ICAM-1. The recent generation of a mouse-human ICAM-1 chimera has enabled a mouse model of rhinovirus infection to be created [39]. In addition the model included sensitisation and subsequent re-challenge with ovalbumen to create features of atopy, which in combination with rhinovirus infection provides a model for asthma exacerbations. In the absence of coughing in mice AHR would have to be used as surrogate for cough, however guinea pigs, which are able to cough, may prove a more useful model in the future. Sendai and RSV infection are established in guinea pigs but RV infection has not presently been attempted. The availability of a small animal model will prove invaluable in the development of therapies for cough.

4.2. Human studies

Human challenge studies with rhinovirus have been performed in healthy subjects and in those with asthma and COPD [12,40–42]. Experimental infection in humans allows investigation of the complete physiological system and detailed characterisation of subjects at baseline, prior to infection and at regular intervals throughout infection until convalescence. This provides an opportunity for detailed investigation of cough symptoms throughout the full time-line of rhinovirus infection and the potential to further investigate *in vivo* mechanisms of virus induced cough in healthy subjects as well as those with airway disease.

4.3. COPD

Cough is the most frequent symptom in COPD yet it is used surprisingly infrequently in the monitoring of the disease or assessment of treatment response. In an experimental challenge study RV infection was performed in patients with mild to moderate COPD and age and smoking matched, non-obstructed controls. The model was shown to be a safe and valid model for the study of COPD exacerbations [42]. Subjects kept symptom diary cards throughout the study; these revealed a significant increase in cough scores for both groups during acute viral infection when compared to their baseline scores [42]. This new model provides an exciting opportunity to investigate mechanisms of cough in COPD and future studies with a non-smoking control arm are awaited with interest in order to permit separation of the effects of smoking from those of COPD.

4.4. Cough monitoring

Reporting of cough by patients is highly subjective; many factors such as mood, health belief and coexisting symptoms may bias reporting. Therefore more objective assessments of cough

monitoring have been developed. In these, sound from coughing is recorded digitally and numbers of individual coughs and time spent coughing are calculated by investigators. The system has been validated by correlation with video recordings and has been shown to be responsive to symptom changes following use in cystic fibrosis patients [43]. Objective monitoring of cough in stable COPD has been performed [44]; here it was shown that cough was more frequent during the day and did not correlate with lung function tests. Many different systems to measure cough have been developed for both research and commercial purposes. In addition to the system detailed above at least two other groups in the UK have developed cough monitoring systems [45,46]. Only moderate correlation with subjective scoring was observed. The opportunity to combine objective monitoring with experimental rhinovirus infection would provide a unique opportunity to study cough in controlled and well-defined populations; both those with and without airways disease. Both COPD and asthma exacerbations could be studied which would provide data of the duration and severity of cough following viral infection. Not only would this facilitate investigation of the mechanisms of cough but also provide the opportunity to test potential therapies.

4.5. Potential therapies

Few effective antitussive medications are available for virus mediated cough and these are not often used clinically. Strategies have traditionally concentrated on symptom reduction but advances in antiviral therapy are likely to result in direct attempts to modulate virus replication.

A recent placebo controlled study of non-smokers with an URTI found that tiotropium, a long acting anticholinergic, was effective at reducing the cough reflex sensitivity following stimulation with capsaicin. As there were no associated changes in lung function the authors suggest that the antitussive effects of tiotropium may be through a mechanism other than bronchodilation [47]. A double blind placebo controlled study of nasal ipratropium bromide reported decreased sneezing and rhinorrhea [48], however cough was not investigated specifically in this study.

A reduction in cough was also achieved after double blind administration of pseudoephedrine and brompheniramine, a first generation antihistamine [49], however this effect was not seen when newer non-sedating antihistamines were used [50], which may have less anti-cholinergic activity. Side effects are likely to limit the use of more sedating drugs in most routine practice, and particularly in children.

The NSAID naproxen decreased cough and associated symptoms in a double blind placebo controlled study using experimental RV challenge [51]. It was concluded that prostaglandins are among the inflammatory mediators that play a role in RV induced cold symptoms including cough.

Specific antiviral therapies have been studied but their use is likely to be limited by the wide variety of viruses responsible for URTI and the difficulty in prescribing appropriately in the absence of rapid accurate diagnostic testing. The antiviral rupintrivir was used in experimental RV colds and reduced the mean daily symptom score when given 24 hours after infection. Prophylactic use reduced the viral load but did not reduce the frequency of colds [52]. A review of RV chemotherapy concluded that effective drugs were available but studying these in trials and their use clinically are difficult as almost immediate diagnosis and treatment of virus infection is required [53]. Ribavirin is an effective antiviral for RSV, but larger clinical studies have lacked the power to demonstrate a benefit in bronchiolitis, although there is conflicting evidence in the literature [54–56] and it has not been specifically shown to reduce cough symptoms. Centrally acting cough suppressors are

not specific to virus induced cough and are generally avoided because of their side effect profile. A double blind placebo controlled study using both objective and subjective cough monitoring found very little support for conventional antitussives over placebo in an URTI associated cough [57]. Alternative therapies may be developed in the future, but these will need to have minimal side effects and a rapid onset of action if there are to be of use in URTI and control of cough.

5. Conclusion

Acute cough represents a highly significant burden to those with and without lung disease.

The majority of episodes of cough are due to acute respiratory virus infections and presently therapies directly targeting this are sub-optimal.

Our present understanding is that virus infection likely generates cough by selectively altering neural signalling. Neurokinin levels and their specific receptors may be increased in addition to a reduction in their degrading enzyme. Cholinergic pathways appear to show promise as targets for future therapies. Drugs acting here have a favourable side effect profile and both short and long acting compounds have shown beneficial effects.

Leukotrienes also may play a mechanistic role by promoting cough and excess production of mucus in both healthy and diseased lungs. They probably play a significant role in virus induced cough and this is an area which includes potentially promising therapeutic targets. Inhibition of prostaglandin synthesis has been shown to be beneficial in symptom reduction.

Our understanding of the mechanisms by which acute virus infection generates cough is poor. More research is required and the recent establishment of both human and animal experimental models will allow these to be adapted to specifically and objectively study cough, hopefully leading to a better understanding of the underlying mechanisms. In addition they would provide opportunities to test new therapeutic compounds when they become available.

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