New insights in cough

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Chronic cough is common, blights patients’ lives and is hard to treat. Chronic cough patients demonstrate high objective cough rates and as a group have increased cough reflex sensitivity. However, conventional cough challenge techniques show substantial overlap with normal subjects. This suggests that other important mechanisms have yet to be determined. For the last two decades, chronic cough has been considered to be caused by gastro-oesophageal reflux, post-nasal drip or Asthma. However, many patients with these conditions do not have cough, and in those with cough, the response to specific treatments is unpredictable at best. In addition, many chronic cough patients do not have an identifiable cause. This raises questions about the concept of a triad of treatable causes for chronic cough. Our current understanding of the neurophysiology of the cough reflex is largely derived from animal work with limited data in humans. By analogy with chronic pain syndromes, both peripheral and central sensitization may be important mechanisms in chronic cough, and are under active investigation. We need to understand the mechanisms underlying sensitization, how they interact with cough triggers and their relationship with the sensations that drive the urge to cough, and the subsequent motor cough response in chronic cough. Only then will we develop effective interventions.

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Chronic cough—a typical patient

Chronic cough is very common, with a prevalence of up to 12% in community surveys. A typical patient with chronic cough is most commonly a post-menopausal female, who has a cough for >5 years. She has a sensation of an irritation located at the back of the throat associated with an urge to cough. The cough may be an exaggerated response to irritants, changes in temperature and chemical sprays. It can also occur doing normal activities such as eating, even stretching her neck.
into a particular position. She has cough-induced stress incontinence, and will be taking an anti-depressant. She is socially isolated and sleeps separately from her partner. She has consulted many physicians in different specialities, been extensively investigated and irradiated, and tried many treatments, all to no avail. She carries a bottle of water at all times, because swallowing water gives temporary relief.

It is interesting to speculate why this chronic cough syndrome has not received more attention. Does it suffer from lack of a specific disease name? Or is it because individual physicians and pharmaceutical company executives have dismissed this as comparable with their own transient coughs that come and go with a URTI? On the contrary, this is an area of a major unmet need.

The cause of cough—the conventional view

Published guidelines on the management of chronic cough\(^1\text{–}^3\) recommend the investigation and systematic treatment of a triad of underlying triggers—asthma, gastro-oesophageal reflux disease (GORD) and post-nasal drip syndrome (PNDS). There are case series in the last 20 years attributing virtually all cough to these conditions, and describing a \(> 98\%\) response to specific treatments of these causes.\(^4\) However, more recent case series have described increasing numbers of patients with unexplained cough which is resistant to treatment.\(^5\text{–}^7\) In our specialist cough clinic, by very detailed investigation we have been able to identify specific triggers (often more than one) in most patients, but in two-thirds of patients the cough is completely or partially resistant to specific treatment of diagnosed triggers. Conversely, the large majority of patients with GORD, asthma and PNDS do not complain of cough at all.

Why do our chronic cough patients cough in response to often minor triggers? And why do not they improve when we treat them? The simplistic view that there are three treatable causes of chronic cough has held sway on both sides of the Atlantic for two decades and needs revisiting.

The neurophysiology of cough—parallels with pain

First a word of caution; most of what we know about the structure and function of the cough reflex comes from experiments in healthy animals, and the data needs careful interpretation in the context of patients with chronic cough. This article draws parallels with neuropathic pain, and especially examine(s) whether the concepts of peripheral and central sensitization could explain the persistence of cough in patients with chronic cough.
Airway nerves and cough

Based on animal work, there are at least five vagal afferent nerve sub-types that can be characterized by their electrophysiological, morphological and immuno-histochemical properties.\(^8\)–\(^10\) Airway nerves differ in their patterns of response to different stimuli, consequent on differences in ion channels. These are broadly described below:

- A putative ‘\textit{cough receptor}’ has been identified in the central airways of guinea pigs which is responsive to punctuate mechanical stimuli and rapidly changing pH (the latter probably via activation of ASIC3 ion channels).\(^11\) This cough receptor likely mediates the immediate protective cough reflex to aspiration of foreign material and especially gastric contents into the airways.

- \textit{C-fibres} are subdivided into two types. Bronchial and pulmonary \textit{C-fibres} arise from jugular and nodose ganglia, respectively.\(^10\) Bronchial \textit{C-fibres} when activated strongly evoke coughing in conscious humans and animals, but not in anaesthetized animals, suggesting they may mediate a conscious perception of airway irritation that is suppressed during anaesthesia.\(^10,12\) They are activated by a family of ligand-gated ion channels of which the best characterized is the transient receptor potential vanilloid 1 (TRPV1) receptor which responds to noxious heat (42–53°C), low pH and capsaicin.\(^13\) At low tissue pH, TRPV1 is activated at physiological body temperatures. One study suggested increased expression of TRPV1 receptors in bronchial biopsies of patients with chronic cough.\(^14\) However, TRPV1 receptor immuno-staining may be non-specific and not limited to nerves and this finding has not been replicated. The TRPA1 receptor is co-expressed with TRPV1 on \textit{C-fibre terminals}, and may be sensitized by increased TRPV1 activity.\(^15\) TRPA1 responds to cold air and is activated by aldehydes in cigarette smoke, and 4-hydroxy-2-nonenal produced in response to oxidative stress at sites of tissue inflammation.\(^15\) Cinnamaldehyde activates TRPA1 receptors and induces cough when inhaled by humans.\(^16\)

- \textit{Rapidly adapting receptors (RARs)} and \textit{slowly adapting receptors (SARs)} are intra-pulmonary mechanically sensitive afferent nerves; SARs are activated during inspiration; RARs activate with bronchial constriction.\(^10\) They may facilitate cough but are considered less important in cough in human disease.

The vagus nerve

The vagus nerve transmits sensory information from the lungs to the brainstem, where vagal afferent nerves synapse on second-order relay neurones in the nucleus tractus solitarius (nTS). Vagotomy or vagal block with local anaesthesia abolishes cough in human subjects.\(^17\)
while the cough reflex is preserved in patients with cervical spinal cord injury.\textsuperscript{18}

**Central pathways**

Activation of the ‘cough receptors’ releases glutamate centrally since injection of an N-methyl-D-aspartic acid (NMDA) receptor antagonist into a discrete region of the nTS where cough receptors terminate blocks coughing evoked by citric acid in anaesthetized guinea pigs.\textsuperscript{19}

C-Fibres release neuropeptides, such as substance P, calcitonin gene-related peptide and neurokinin A, which bind to neurokinin receptors on the post-synaptic cell. C-fibres and RAR fibres are thought to converge onto the same second-order neurone in the nTS as co-activation of RAR fibres and C-fibres has a synergistic effect on cough responses in animal models.\textsuperscript{20} Neurokinins temporarily sensitize the post-synaptic cell by increasing depolarization and allowing NMDA receptors to open.\textsuperscript{21} This central up-regulation could become more permanent following prolonged sensory stimulation (central sensitization). Centrally acting neurokinin antagonists can produce antitussive activity in patients particularly if they are centrally sensitized.

**Central pathways and the ‘urge to cough’**

The difficulty with animal cough data is that it lacks an essential qualitative component of cough in human disease. Most patients with chronic cough have a sensation or irritation in the throat and/or upper chest that induces an urge to cough, which is to some degree under conscious control, (unless the sensation is overwhelming) and then results in the motor action of coughing.\textsuperscript{22} This urge to cough may be C-fibre mediated. Intravenous injection of lobeline evokes sensations of burning, tickling, irritation and suffocation in the throat, larynx and upper chest, followed by coughing bouts, in healthy subjects, asthmatics and patients with chronic bronchitis, probably via bronchial C-fibre stimulation.\textsuperscript{23} During a capsaicin cough challenge, an increasing urge to cough correlates with increased cough frequency and cough intensity.\textsuperscript{24} An urge to cough can normally be suppressed, which would be advantageous when coughing would cause social disruption, e.g. in an important meeting. We have shown that while normal subjects can suppress the cough threshold by three doubling doses, patients with chronic cough could only suppress the cough threshold by one doubling dose.\textsuperscript{25} This suggests that disordered conscious inhibition of coughing may contribute to chronic cough.
Recently there have been attempts to map central pathways in man with functional magnetic resonance imaging. Mazzone et al.\textsuperscript{26} performed a study in healthy subjects to measure cortical activation during a capsaicin cough challenge. Unfortunately, inhalation of capsaicin causes significant side effects with burning mouth and watering eyes. This may have been responsible for the widespread activation of the cortex (including the primary somato-sensory cortex, inferior parietal lobe, primary motor cortex, orbito-frontal cortex, inferior frontal gyrus, anterior cingulate cortex, anterior insula and cerebellar regions). More recent data with titration of citric acid at low doses suggest a much narrower field of activation, with more clearly defined sensory and motor centre involvement.\textsuperscript{27}

**Peripheral sensitization and cough**

Peripheral sensitization is the up-regulation of peripheral nerve sensitivity by local factors, for example the extreme sensitivity to touch with burn injuries. In chronic cough, conditions for peripheral sensitization are present, with elevated levels of inflammatory mediators (histamine, prostaglandin D2 and prostaglandin E2) in the airways of all patients with chronic cough compared to healthy controls.\textsuperscript{28,29} Inflammatory mediators sensitize peripheral vagal nerve terminals by binding to G-protein coupled receptors and activating a variety of intracellular mechanisms, including phosphorylation of ion channels, which subsequently lower the threshold for initiation of an action potential.\textsuperscript{30} This phenomenon has been confirmed in humans by a study in which prior inhalation of prostaglandin E2 increased the cough response to subsequently inhaled capsaicin.\textsuperscript{31}

**Central sensitization and cough**

Central sensitization is an enhanced central nervous system (CNS) response to peripheral nerve stimulation initially described in the study of pain. Chronic cough patients describe excessive coughing in response to minor exposures to inhaled irritants such as perfumes or cold air,\textsuperscript{32} which are the clinical features of a lowered threshold in response to cough-provoking stimuli; this could be due to central or peripheral sensitization. However, patients also describe coughing in response to normally innocuous stimuli such as talking on the telephone, laughing or singing.\textsuperscript{32} These stimuli are usually insufficient to evoke coughing and must indicate a change in the way the CNS responds to this sensory information. This is analogous to the pain perceived in response to an
innocuous stimulus surrounding an injury site (secondary allodynia) typical of central sensitization.\textsuperscript{33}

The visceral nervous system displays extensive central convergence of sensory nerves in the brain stem.\textsuperscript{34} Visceral hypersensitivity as a result of central sensitization could explain why coughing is provoked from extra-pulmonary sites such as the oesophagus (see below).

### The role of GORD as a trigger in chronic cough

**Gastro-oesophageal reflux disease**

What is the relationship between GORD and chronic cough? Between a third and a half of chronic cough patients are reported in large series as having GORD.\textsuperscript{4,35–37} But the definition of GORD in these series is unclear. Is GORD proximal or distal oesophageal reflux? Acid or non-acid? With or without oesophagitis? Occurring with or without reflux symptoms? Responding to reflux therapy? And what is the mechanism?

Most patients (~75\%) do not complain of classical reflux symptoms.\textsuperscript{38} With oesophageal impedance/pH studies, the majority of chronic cough patients have reflux events that fall within the normal range.\textsuperscript{39} This relationship is confounded by the fact that sometimes cough causes reflux and so reflux rates may be higher in patients with chronic cough (by reverse causation), even if reflux did not cause the cough.

The evidence does not support a major role for micro-aspiration. First, there is very little proximal reflux in chronic cough patients.\textsuperscript{40} Secondly, pepsin levels in broncho-alveolar lavage fluid (as a marker of gastric aspiration) were not elevated in chronic cough patients with or without GORD, compared to healthy controls.\textsuperscript{41}

A temporal relationship between individual cough and distal reflux episodes would provide some evidence for a causal relationship. Studies that count cough in conjunction with an oesophageal catheter are complicated by the fact that having the catheter in place reduces cough rates on average by about a third,\textsuperscript{42} presumably through a local effect. However, in spite of this proviso, it is clear that the majority of patients with chronic cough have significant temporal relationships between cough and distal oesophageal reflux (i.e. occurring within a specified time window).\textsuperscript{39,43,44} In our experience, just under half of chronic cough patients have significant association, where reflux precedes coughing, accounting for approximately 40\% of coughing bouts. Just over half of patients have the reverse association, i.e. cough preceding reflux, with a third of patients exhibiting both processes.\textsuperscript{39}
Since reflux rates are not generally increased, this close temporal relationship implies that even physiological levels of reflux can stimulate cough in patients. Vagal afferent nerves innervating both the respiratory tract and the oesophagus may converge on the same relay neurones in the brainstem, meaning that altered sensory input from the oesophagus could up-regulate the response of the CNS to airway irritants. This concept is supported by studies showing that distal oesophageal acid infusion increases cough reflex sensitivity in asthmatics and cough frequency/reflex sensitivity in patients with chronic cough. In this context, physiological levels of distal reflux could act as a trigger to coughing.

**Treatment of GORD and cough**

Occasional patients improve their cough on anti-reflux treatment. However, double-blind placebo-controlled trials of proton pump inhibitor’s are negative. There have not been any controlled trials of augmented anti-acid therapy, alginates or motility agents. Anecdotal data also suggest that occasional patients respond well with laparoscopic fundoplication, but many patients do not, and this is a potentially hazardous procedure, with long-term complications. The scientific data would suggest that we may have to abolish even physiological levels of reflux if we are to have a major impact on cough. At present, we have no predictors of clinical response to medical or surgical intervention; surgery should not be contemplated until we do.

**Post-nasal drip and asthma: association with chronic cough**

The relationship between nasal diseases and chronic cough has suffered from similar issues to those for GORD, with the addition of a controversy about the most appropriate terminology in spite of a poor understanding of the underlying mechanisms. Originally named the ‘post nasal drip syndrome’, it was thought that nasal secretions caused coughing by mechanical stimulation of cough receptors either in the larynx or in the trachea if aspirated, but little evidence is available to support such suggestions. Nasal secretions are normally carried backwards into the pharynx by ciliary action, and many patients with increased nasal secretions do not cough. However, the influence of nasal stimuli on the cough reflex has been confirmed in both animal and human studies. Intra-nasal administration of capsaicin does not cause coughing, but the cough responses to both mechanical (Aδ-fibre) and chemical (C-fibre) airway stimuli in guinea pigs are enhanced.
This sensitization can be reproduced in animal models of allergic rhinitis,\(^5\,5^3\) and by a nasal capsaicin challenge in human healthy volunteers\(^5^4\) and nasal histamine in subjects with allergic rhinitis.\(^5^5\) As distinct neural pathways mediate mechanical- and chemical-induced coughing, it has been suggested that nasal afferent stimulation can modulate the cough reflex via central mechanisms in a similar manner to that already described for oesophageal reflux events.\(^5^6\) Thus central sensitization in patients with chronic cough could link nasal stimuli and rhino-sinusitis to coughing.\(^5^7\) Recent data have supported this notion by demonstrating that intra-nasal capsaicin activates neurones not only in the trigeminal nucleus but also those in the nTS, providing evidence for brainstem convergence of trigeminal and vagal afferents.\(^5^8\)

Cough is an important symptom in asthma,\(^5^9\,6^0\) but the mechanisms behind cough in asthma are complex and relatively unexplored. For example, many asthma patients also have coexistent triggers such as nasal disease and/or oesophageal reflux. Airway inflammation could cause peripheral sensitization of airway nerves. Subjective symptom scores and cough reflex sensitivity are poor surrogates for objective cough frequency in asthma.\(^6^1\) While objective ambulatory cough counts do not correlate with bronchial hyper-responsiveness, pulmonary function or exhaled NO levels, they are related to asthma control. Sputum eosinophil counts and cough frequency independently predict asthma control, implying that coughing is not just a reflection of airway inflammation.\(^6^1\) Some patients presenting with chronic cough also have features of asthma including bronchial hyper-reactivity, and reversible airflow obstruction termed ‘cough-variant asthma’. In these patients, cough seems to be disproportionate to other measures of asthma control and apart from sputum eosinophilia, airway inflammation is similar to other patients with chronic cough.\(^2^8\) This suggests that in some patients a different process drives coughing and central sensitization could be important. We need to develop improved phenotyping of asthma patients if treatments for cough are to be targeted and successful.

**Two types of cough?**

In humans, it seems likely that there are two important mechanisms which can initiate a cough. Aspiration is detected by ‘cough receptors’ which initiate an airway protective motor reflex driving an immediate **protective cough**, which is not preceded by any period of an urge to cough.

Patients with chronic cough complain of a persistent sense of irritation, usually located in their throat, associated with an urge to cough, suggesting a sensory disturbance rather than an abnormal
reflex. The triggers of these sensations may be trivial (changes in temperature) or even physiological (eating). Coughing in response to such sensations is analogous to scratching an itch. It is largely a voluntary motor response to an unpleasant sensation. This *sensory-driven cough* is generally not an immediate motor response and is under a degree of voluntary control, depending upon the intensity of the sensations, but the urge to cough can become so intense that it is difficult to resist, just as it is difficult to resist pulling your hand away from a painful stimulus.

How sensory-driven coughing and the protective cough reflex are integrated in the CNS is not clear. It would seem likely that rather than discrete processes, these mechanisms form part of a spectrum from coughing which is entirely voluntary (under complete conscious control and independent of any sensory input) through to sensory-driven coughing (as the intensity of sensory experiences increases, the ability to consciously modulate cough responses will decrease) and finally to very intense sensations where the urge to cough may be impossible to consciously control (indistinguishable from a reflex cough). It is possible that such intense stimuli may exceed a threshold to activate a protective cough reflex. In pathological states the gain may be increased on such a system by sensitization of somatic and visceral afferent pathways. A defect of inhibitory control could also play an important role (see Fig. 1).

**Implications for the development of new treatments**

Unfortunately there are currently no effective cough suppressants. The efficacy of over-the-counter cough medications remains unproven.
Cough syrups for children containing dextromethorphan have been withdrawn in the United States by the FDA because of lack of data on efficacy and the presence of significant side effects. Low-dose morphine over 4 weeks did improve the quality of life for patients with treatment-resistant chronic cough compared with placebo, but the sample size was small, and there were no objective cough counts.64

Successful drug development depends on a greater understanding of the mechanisms responsible for chronic cough in order to identify promising therapeutic targets.

There is no evidence that suppression of the excessive urge to cough is harmful. Anti-tussive drugs could be targeted either against the sense of throat irritation, or the urge to cough, but designed to leave the ‘protective’ cough unmodified. Potential candidates might range from TRPV1 or TRPA1 antagonists to modify C-fibre function and reduce peripheral sensitization, to gamma-aminobutyric acid agonists or NMDA receptor antagonists which impact on central sensitization. The pharmaceutical industry has finally realized the unmet need and is putting major resources into novel therapeutics.

Conflicts of interest: Dr Smith and Prof Woodcock are co-inventors on a patent application from the University Hospital of South Manchester NHS Trust and Vitalograph for an ambulatory cough monitor. Neither have received any personal financial benefit from this. Dr Smith and Prof Woodcock have both acted as consultants to GSK, Almirall, Schering Plough and Merck on the development of novel tussive agents.

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