Neuro–pulmonary mechanistic interplay underlying chronic cough

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Both central and peripheral neuro–pulmonary mechanisms are important in chronic cough. Emerging treatments target these mechanisms, which aim to reduce cough for individual sufferers. https://bit.ly/4degiQu

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Abstract

Chronic cough is a highly prevalent debilitating condition. Chronic cough can be unexplained despite investigations (unexplained chronic cough) or persist despite guideline-based management of treatable traits (refractory chronic cough). Individuals with refractory and unexplained chronic cough (RUCC) often share similar clinical characteristics, including a dry cough, persistent urge-to-cough and throat irritation. Most individuals with RUCC display cough reflex hypersensitivity, coughing in response to chemical, thermal and mechanical triggers. Compared to controls, individuals with RUCC cough at lower concentrations of inhaled stimuli (hypersensitivity) and have increased cough responses across concentrations (hyperresponsiveness). Neuro–pulmonary mechanisms are also supported by treatment responses in RUCC to neuromodulatory medications and behavioural cough control therapy. Mechanisms leading to RUCC are complex but likely involve alterations in the neuro–pulmonary axis in the peripheral and central nervous system. Mechanisms are not fully understood, but RUCC may relate to alterations in airway receptors on vagus nerve terminals, (ATP) release and/or metabolism and plasticity of airway sensory nerves. A wide network of midbrain and higher cortical centres are involved in processing of airway sensations and top-down cough control. Top-down inhibitory control of cough may be altered in RUCC.

Educational aims

- Understand investigation of chronic cough and how to identify treatable traits.
- Understand the definition and characteristics of refractory and unexplained chronic cough (RUCC).
- Understand the possible neuro–pulmonary mechanisms leading to RUCC.
- Understand current and emerging treatment options in RUCC and how these relate to neuro–pulmonary mechanisms.

Introduction

Chronic cough, defined as a cough lasting more than 8 weeks, is a debilitating clinical problem affecting ~10% of adults globally [1]. Chronic cough can occur for a number of reasons, including smoking, medications, airway diseases, gastro-oesophageal reflux disease (GORD), and chronic rhinosinusitis [2]. In a proportion of sufferers, cough persists despite identification and treatment of these underlying traits, this is known as refractory chronic cough (RCC), or remains unexplained despite investigations, known as unexplained chronic cough (UCC) [2]. Refractory and unexplained chronic cough (RUCC) have indistinguishable presentations and are typically considered as a single condition. RUCC is more prevalent in middle-aged adults and females. It is a highly debilitating condition, associated with physical complications (*e.g.* incontinence, syncope, exhaustion), as well as psychosocial distress (*e.g.* anxiety, depression, social isolation), leading to significantly impaired quality of life.

A large proportion of individuals with RUCC display common characteristics. They typically report minimal sputum production, persistent throat irritation, an urge-to-cough, accompanied by increased cough frequency and/or intensity [3]. In clinical settings, many individuals with RUCC report multiple thermal, chemical and mechanical cough triggers. Cough can be triggered by usually innocuous stimuli such as talking, eating or exposure to perfumes (allotussia). Alongside this, patients have exaggerated responses to typical irritants such as smoke or viral infections (hypertussia).

Consistent with these clinical symptoms suggestive of neuronal dysfunction, individuals with RUCC display hypersensitivity (cough at lower levels of exposure) and hyperresponsiveness (increased number of coughs) to a range of inhaled stimuli when compared with healthy controls [4].The mechanisms leading to cough hypersensitivity in RUCC are complex and are thought to involve changes in airway receptors or their ligands, as well as peripheral and central neuronal pathways governing the cough reflex.

Approach to chronic cough and treatable traits

The British Thoracic Society clinical statement advocates a treatable traits approach to chronic cough, underpinned by a structured diagnostic evaluation to identify modifiable causes [2]. First a sinister cause for the cough needs to be excluded, followed by assessment of severity and symptom characteristics. There are multiple treatable traits in chronic cough, including but not limited to medication-related cough, airways disease, gastro-oesophageal reflux, chronic rhinosinusitis, inducible laryngeal obstruction, obesity, obstructive sleep apnoea and smoking. Cough reflex hypersensitivity is a specific trait that is frequently seen RUCC, but also in cough associated with other chronic lung conditions. As opposed to coughing that occurs in health, excessive cough seen in RUCC is due to specific disease mechanisms involving the airways, peripheral (PNS) and central nervous system (CNS).

Neuroanatomy of the cough reflex

The cough reflex is mainly initiated by activation of vagal afferent nerves that innervate the central airways in response to a variety of mechanical, thermal, and endogenous and exogenous chemical stimuli [5]. Two main nerve fibre types mediate cough: C-fibres and Aδ (A-delta)-fibres.

Bronchopulmonary C-fibres are chemosensitive unmyelinated fibres that form a web-like network within the airway epithelium and are activated by a range of chemical stimuli including capsaicin, bradykinin, prostaglandin E2, heat, anandamide, and environmental irritants such as ozone and nicotine [6].

Aδ-fibres are rapidly conducting myelinated fibres that predominantly innervate the sub-epithelium of the central airways. They are predominantly activated by mechanical and acid stimuli [5].

Ion channels

Expressed in the cell bodies and found on the cell membranes of vagal afferent nerves are a range of ion channels and G-protein coupled receptors including transient receptor potential (TRP) and purinergic (P2X) receptors. These are activated by a variety of endogenous and exogeneous stimuli (*e.g.* irritant environmental chemicals, temperature changes, inflammatory mediators and mechanical deformation) resulting in depolarisation of vagal afferent nerves. There are several ion channels thought to be important in evoking cough, many of which have been targeted by novel therapies (summarised in table 1).

Brainstem and cortical control of cough

Once depolarised, vagal afferent nerves synapse in cough brainstem centres, the nucleus tractus solitarius and paratrigeminal nucleus [5]. From here, second order neurones can activate motor neurones directly resulting in reflex cough. Simultaneously, neurones ascend to subcortical and cortical areas involved in sensory interpretation and behavioural control of cough. Midbrain structures, including the thalamus, integrate sensory input and subsequent motor commands, thereby gating cough responses between the PNS and CNS.

Higher cortical control of cough is complex. The somatosensory cortex is involved in the processing of airway sensations and perception of the urge-to-cough [5, 13]. The anterior midcingulate cortex and orbitofrontal lobe regions are involved in cognitive and emotional responses to airway sensations. The motor cortex and inferior frontal gyrus influence descending control of airway sensations, cough suppression and voluntary cough [5].

When an individual feels the urge to cough, it is possible to override this sensation by consciously suppressing cough. This urge to cough is often associated with unpleasant sensations within the larynx. Individuals can cough as a response to “clear” this sensation or attempt to suppress the cough.

TABLE 1 Receptors implicated in cough

Receptor	Anatomical location	Ligand	Drug development
TRPA1	Airway epithelium C-fibres	Acrolein (in cigarette smoke) Cinnamaldehyde Ozone	Inhaled antagonist effectively blocked citric acid evoked cough in preclinical studies Negative phase 2a study unpublished
TRPV1	C-fibres Subset of Aδ-fibres	Capsaicin Acid Temperature >43°C	TRPV1 antagonist reduced capsaicin evoked cough, but not spontaneous coughing in RUCC compared to controls [7] Concern of hyperthermia with dose escalation
TRPV4	Airway epithelium, fibroblasts, immune cells and smooth muscle cells.	Hypotonicity Shear stress	TRPV4 antagonist did not reduce cough frequency compared to placebo [8]
TRPM8	C-fibres Nasal trigeminal ganglia	Temperature 15–28°C Menthol (antitussive effect) Eucalyptus	TRPM8 agonist demonstrated significant reduction in cough frequency over 4 h compared to placebo in a phase 2a study [9]
P2X2/P2X3 and P2X3	Vagal afferent fibres	ATP	Phase 2 and 3 studies showing reduction in patient-reported cough outcomes and improved cough frequency [10, 11]
Voltage-gated sodium channels	All sensory neurones, generating and propagating action potentials	Changes in membrane potential	Reduction in cough frequency with lidocaine throat spray (sodium channel antagonist) [12] Phase 2a study of sodium channel blocker (NTX-1175) completed but unpublished
Mu opioid receptors	Mainly the thalamus, caudate putamen, nucleus accumbens, amygdala, cerebral cortex and periaqueductal gray; some evidence on airway neurones	Endogenous opioids (*e.g.* β-endorphin)	Reduction in cough quality of life with low dose slow-release MST in RCC Reduction in cough frequency and PROs with low dose slow-release MST in IPF
Kappa opioid receptors	Nucleus accumbens, amygdala, hypothalamus and periaqueductal gray; some evidence on airway neurones	Endogenous opioids (*e.g.* dynorphins)	Reduction in cough frequency and PROs with nalbuphine (kappa agonist and mu antagonist) in both IPF and RCC
NK-1 receptors	Widely distributed throughout the central and peripheral nervous systems; found in the nucleus tractus solitarius	Substance P	Reduction in cough frequency and PROs with aprepitant in cough in lung cancer Several negative trials in cough in RCC

TRP: transient receptor potential; P2X: P2X purinoceptor NK-1: neurokinin-1; RUCC: refractory and unexplained chronic cough; MST: morphine sulfate tablets; RCC: refractory chronic cough; PRO: patient-reported outcome; IPF: idiopathic pulmonary fibrosis.

Less is known about the specific receptors and neurotransmitters involved in the pathways mediating cough in the CNS (see table 1). Opioids and their receptors have classically been considered anti-tussive and assumed to act in the brain; however, opioid receptors have also been identified in the lungs. Low dose morphine is thought to predominantly act on Mu receptors in the CNS and may have inhibitory effects through areas such as the periaqueductal gray (PAG). Recently, nalbuphine, considered to be a kappa agonist and mu antagonist (with some evidence of partial mu agonism), has been found to be effective in cough associated with both idiopathic pulmonary fibrosis and RCC, suggesting other opioid receptors may also play a role [14]. Neurokinin-1 (NK-1) receptors are known to be expressed widely in the brain but also specifically in the nucleus tractus solitarius. A trial of a licensed antiemetic drug, aprepitant, suggested significant effects in patients with cough associated with lung cancer but subsequent studies in RCC have not suggested benefit over placebo. Other potential CNS targets of interest to treat cough have included activation of GABAb receptors and antagonism of *N*-methyl-D-aspartate (NMDA) receptors (figure 1).

Mechanisms leading to RUCC

Peripheral nervous system

Chronic cough may evolve due to maladaptive changes in the sensory nervous system supplying the lungs. There is evidence that this may occur *via* more than one mechanism. First, plasticity of the pulmonary–neuro axis is known to occur. Neuronal plasticity represents functional and structural neuronal changes. In guinea pigs, for example, TRPV1 and TRPA receptor expression in neuronal cells increases following human rhinovirus infection increasing their sensitivity to environmental irritants [15].

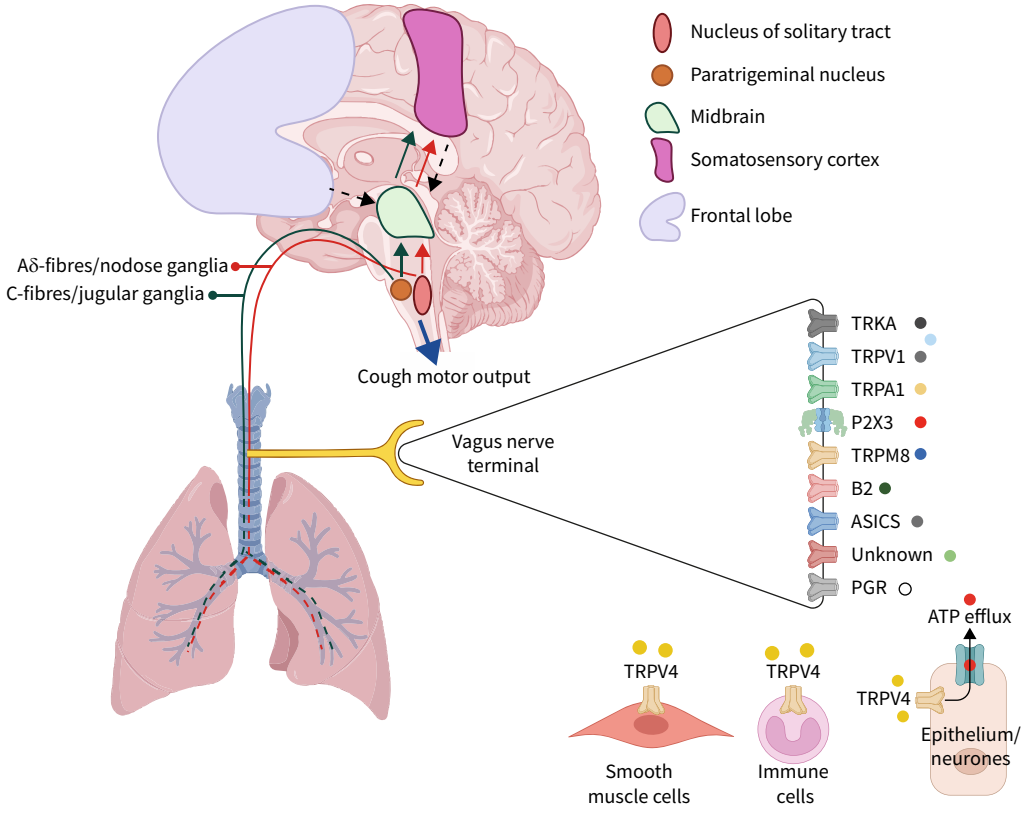

FIGURE 1 Neuroanatomy of cough reflex. Transient receptor potential vanilloid 4 (TRPV4) receptors found on smooth muscle, immune and epithelial cells activate to trigger bronchoconstriction, inflammatory mediator and ATP release. Receptors expressed by afferent Aδ- and C-fibres are activated in response to a wide range of stimuli, including ATP. These nerves terminate in the brainstem and activate the cough reflex arc. Simultaneously, second order neurones signal to the midbrain and higher cortical centres. Cortical control of cough also occurs *via* descending pathways from frontal lobe and midbrain regions. TRKA: tropomyosin receptor kinase A; TRPV1: transient receptor potential vanilloid 1; TRPA1: transient receptor potential ankyrin 1; P2X3: P2X purinoceptor 3; TRPM8: transient receptor potential melastatin 8; B2: beta-2 receptor; ASICS: acid sensing ion channels; PGR: progesterone receptor.

Phenotypic switching has also been observed in animal models; whereby allergic or viral inflammation causes Aδ-fibres (mechanosensors) to express receptors conferring new sensitivity to chemical and temperature stimuli [16].

Inflammation may also drive plasticity. In mice, eosinophil counts correlate with sensory nerve length and branching, with evidence that allergen exposure stimulates nerve growth factors [17]. Structural plasticity has also been demonstrated in humans; when compared to controls, individuals with chronic cough display increased bronchial epithelial sensory nerve density [18]. Endobronchial epithelial biopsies from a well characterised cohort of RUCC patients showed similar neurofilament expression (Aδ-fibres), but increased pan-neuronal protein expression, suggesting an expansion of C-fibres in this group [19].

Central nervous system

Central sensitisation occurs when there is increased responsiveness of nociceptive neurones in the CNS to their normal or subthreshold input. It is a well-known phenomenon in chronic pain, which shares many similarities with RUCC. Pain in response to non-noxious stimuli (allodynia) or excessive pain to known stimuli (hyperalgesia) are analogous to the allotussia and hypertussia, described earlier, in chronic cough. The mechanisms leading to central sensitisation are complex. In animal models, repeated C-fibre stimulation can result in long-term potentiation, a process involving CNS NMDA receptors, which results in strengthening of synapses and amplified signalling [20].

Our understanding of cortical processing and top-down control of cough has largely been gained from task-based functional magnetic resonance imaging (t-fMRI) studies in healthy volunteers inhaling irritant chemicals. These studies suggest that an extensive network of CNS activity in the brainstem, midbrain and higher cortical centres coordinates processing and control of airway sensations [13].

Specific areas of change in RUCC are less well understood. However, compared to controls, t-fMRI studies have shown that patients with RUCC display both central amplification of ascending signals from the airways and reduced capacity to suppress cough [21]. However, the potential impact of performing cough challenges within an magnetic resonance imaging (MRI) scanner on neuronal function unrelated to cough limits the interpretation of these studies, and further research is needed. An area of particular interest is the PAG in the midbrain. This area is involved in descending modulation of pain and can have both enhancing and inhibitory effects on nociceptive signals from the PNS [22].

Following capsaicin inhalation, PAG fMRI activity increases to a greater extent in RUCC compared to controls [21]. Use of a slightly different fMRI modality, resting-state fMRI (rs-fMRI), in well-characterised cohorts of patients with RUCC has identified differences in somatosensory resting-state networks compared to healthy controls [23].

As described earlier, impaired cough suppression in RUCC, compared to controls, has also been demonstrated using inhalation challenge. This impairment may reflect dysfunction of endogenous inhibitory pathways. Hilton *et al*. [24] studied one such mechanism, conditioned pain modulation (CPM). CPM refers to inhibition of spinal neuronal activity by a noxious stimulus applied to a remote body region. In this study, cough was evoked in healthy volunteers and patients with RUCC using inhaled capsaicin. Participants subsequently immersed a hand in noxious cold water to induce pain and activate CPM. During hand submersion, capsaicin-evoked cough was significantly reduced in healthy volunteers but remained unchanged in individuals with RUCC, suggesting impaired CPM and deficient descending inhibitory control of cough in RUCC.

Cough can be consciously suppressed, which involves input from higher cortical centres. However, individuals with chronic cough are less able to effectively control experimentally induced cough [25]. Bouts of coughing are observed in individuals with chronic cough, with longer cough bouts correlating to worse cough severity [26]. In the experience of the authors, patients with RUCC often describe bouts as extremely troublesome and difficult to control. Cough suppression therapy can be successful in controlling symptoms by exploiting conscious control. It employs several interventions including sipping water when an urge to cough appears which reduces cough and improves quality of life.

Central sensitisation may also occur due the additive effects of afferent inputs. In autonomic nervous system signalling, motor output is governed by continuous graded neuronal signalling, resulting in a variable output, for example in heart rate control. The cough reflex, in contrast, is more binary (on or off) and relies on accumulation of incoming signals, also known as summation. Cough is elicited when a "threshold" of afferent input is reached. The effects of sub-threshold inputs accumulating have been demonstrated in guinea pigs. In these models, acidification of the lower oesophagus or evoked bronchoconstriction may not independently lead to cough. When both stimuli are applied synchronously, however, a threshold is reached and cough is stimulated [27].

Persistent cough triggers

Alongside PNS and CNS changes, cough may occur due to persistent triggers in a sensitised neuro–pulmonary axis. Cough is common in GORD, chronic rhinosinusitis and asthma, but in 59% of patients referred to specialist cough clinics, symptoms persist despite treatment of underlying conditions [28]. There is evidence that oesophageal dysmotility occurs in around two-thirds of individuals with refractory respiratory symptoms (including cough, wheeze and breathlessness) [29]. Despite this, in GORD associated cough there is little evidence that symptoms occur due to microaspiration of acid or non-acid reflux. Pepsin levels in induced sputum are no different in cough patients compared to controls [30].

There is some temporal association between reflux episodes (acid and non-acid) and cough events, suggesting neuronal crosstalk [31]. This suggests normal physiological reflux may activate the cough reflex when there is underlying neuronal sensitisation of vagus CNS circuits (figure 2).

Cough is a common asthma symptom that is often associated with poor disease control but correlates poorly with eosinophilic airway inflammation [32]. It is possible that debilitating cough in asthma, like chronic cough, has different treatable traits. Airway inflammation may be one such trait, but cough reflex

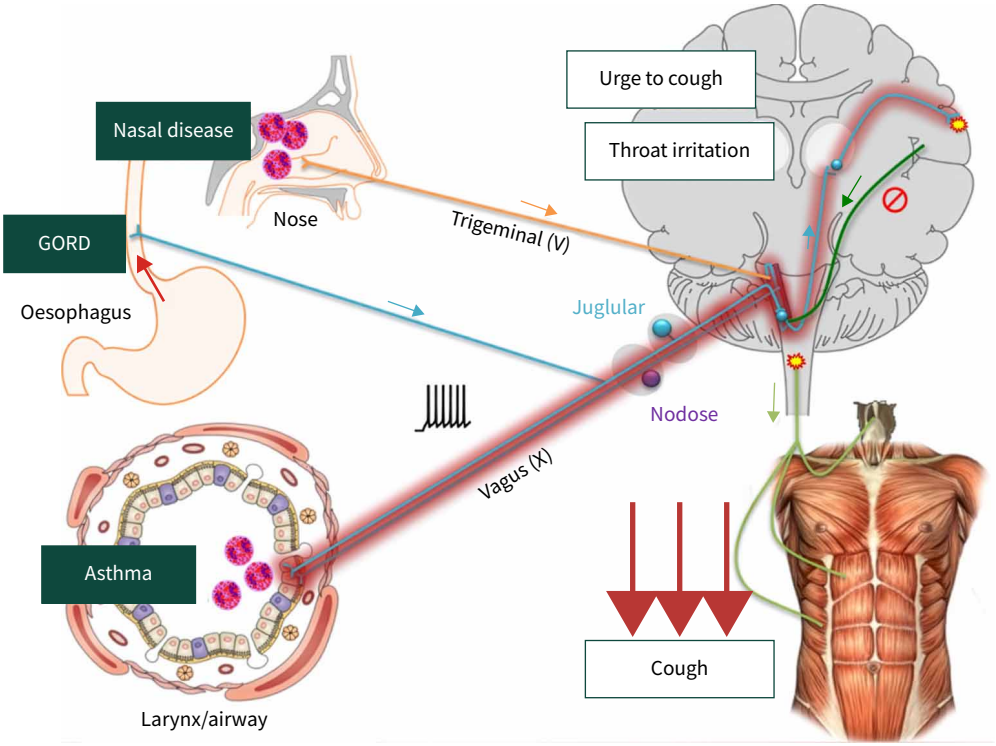

FIGURE 2 Cough reflex hypersensitivity and the impact of persistent cough triggers. Afferent and central signalling is increased in refractory and unexplained chronic cough. Physiological or low-level stimulation from nasal/oesophageal or airway afferents may induce cough in the context of a sensitised neuronal axis. GORD: Gastro-oesophegal refulx disease.

hypersensitivity is equally as important. Symptom perception and severity in asthma have been linked to markers of CNS central sensitisation [33].

The effect of sinus disease is also interesting. Trigeminal nerve afferents terminate in similar brain regions as vagus nerve afferents. Sensitisation of these pathways has also been shown in chronic cough. For example, Arnold's reflex, in which stimulation of the external auditory canal induces cough more readily in those with RUCC compared with controls [34]. These pathways are highlighted in figure 2.

ATP and the airways

ATP is a predominantly intracellular molecule with an important role in energy storage and supply. In a steady state, ATP is released into the extracellular space in small quantities; however, when cells undergo stress, either mechanical or chemical, it is released in larger quantities. In the airways, ATP acts on purinergic receptors on C-fibres and Aδ-fibres, causing bronchoconstriction and cough, as well as promoting cytokine activation [35].

The P2X3 channel, found on pulmonary vagal afferent nerves, is activated by ATP. Inhaled ATP induces cough at lower concentrations in RUCC than controls, as well as evoking cough and bronchoconstriction in airway diseases [36]. The role of ATP in RUCC has been further highlighted by phase 2–3 studies demonstrating reduced cough symptoms and a reduction in cough frequency *versus* placebo with the P2X3 antagonist gefapixant [10].

In RUCC, activation of TRPV4 with hypo-osmolar solution results in increased cough in RUCC compared to controls, possibly *via* Pannexin–ATP release mechanisms [37]. Ectonucleotidases (CD39), which break down ATP, are also upregulated in bronchoalveolar lavage fluid of patients with RUCC compared to controls, with a correlation between this and objective and subjective cough measures [38].

Genetic susceptibility

Coley *et al.* [39] have recently demonstrated a genetic basis for neuronal dysfunction underpinning chronic dry cough and angiotensin-converting enzyme inhibitor (ACEi)-induced cough in a genome-wide

association study. Their study identified multiple genetic loci linked to neuronal signalling in this group. Interestingly, there was a shared genetic correlation between ACEi cough and dry cough, suggesting overlapping mechanisms.

Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) is recognised as a genetic cause of chronic cough. Individuals can present with chronic cough several decades before any neurological manifestations become apparent. Individuals can suffer falls and balance issues, together with sensory loss and autonomic dysfunction. CANVAS is associated with polymorphisms of the RFC1 gene (which is involved in DNA repair and replication) [40].

The mechanism by which CANVAS leads to chronic cough is unclear, but interestingly, there is evidence of airway neuronal depletion, which is the opposite to what is observed in RUCC [41]. In individuals presenting with chronic cough and neurological symptoms, such as neuropathy, it is important to refer to a neurologist for further assessment (figure 3).

Current and emerging treatment approaches for RUCC

The management for RUCC has evolved substantially in recent years reflecting an individualised approach based on treatable traits [2]. While optimisation of these traits remains central, interventions targeting underlying neuronal sensitisation now form part of contemporary clinical practice (summarised in table 2).

Non-pharmacological treatment approaches

Behavioural cough control therapy, delivered by speech and language therapists, is thought to reduce cough reflex sensitivity and laryngeal irritation by interrupting coughing episodes. Based on peripheral and central sensitisation and cortical control, it combines cough control strategies, education, laryngeal care, psychoeducation and management of co-occurring laryngeal disorders, and is effective in improving cough frequency, severity and quality of life [42].

However, behavioural change requires capacity, opportunity and motivation, and access barriers persist. Virtual or group-based approaches may improve accessibility, although further research is needed.

Pharmacological treatment approaches

Pharmacological treatments include neuromodulators recommended in guidelines [2, 43]. These agents act on the CNS and PNS to modulate neural sensitisation by blocking nociceptive transmission. Low-dose

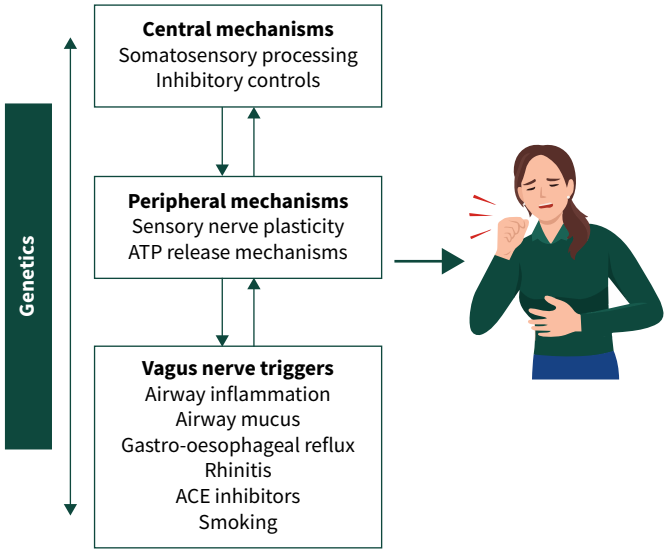

FIGURE 3 Mechanisms leading to refractory and unexplained chronic cough (RUCC). Neuro–pulmonary mechanisms are complex and may differ from patient to patient in RUCC. Persistent triggers or treatable traits, alongside peripheral and central nervous system mechanisms may result in excessive cough. There is probably an interplay between these mechanisms. ACE: angiotensin-converting enzyme.

TABLE 2 Summary of treatment options in refractory and unexplained chronic cough

Treatment approach	Proposed mechanisms	Strengths	Limitations
Behavioural cough control therapy	Improved higher cortical control of laryngeal function; voluntary cough suppression and laryngeal control	No physical side-effects; improves cough-related quality of life and severity	Requires capacity, opportunity and motivation; limited access to trained SLTs; variable availability
Gabapentinoids (gabapentin, pregabalin)	Central and peripheral modulation of neuronal calcium channels reducing neural hypersensitivity	Improves cough-specific quality of life and severity; greater benefit (pregabalin) when combined with behavioural approach	Poor tolerability; nausea; dizziness; fatigue
Low-dose morphine	Central suppression of the cough reflex *via* opioid receptor activation	Reduces objective cough frequency and improves Leicester Cough Questionnaire scores	Side-effects include constipation and drowsiness
P2X3 receptor antagonists	Blocking of ATP-mediated sensory nerve activation, reducing cough hypersensitivity	Significant reduction in 24-h cough frequency	Limited availability; taste disturbance; large placebo effects

SLTs: speech and language therapists; P2X3: P2X purinoceptor 3.

morphine has been shown to improve Leicester Cough Questionnaire scores compared to placebo and substantial reductions are reported in objective cough frequency, although common side-effects include constipation and drowsiness [44, 45].

Gabapentinoids and pregabalin studies have shown significant improvements in cough-specific quality of life and cough severity [46, 47]. However, gabapentanoids are poorly tolerated with frequent reports of nausea, stomach pain, dizziness and fatigue. All neuromodulators are unlicensed for chronic cough and are controlled drugs due to the risk of abuse.

Emerging pharmacological therapies

Novel pharmacotherapies target specific cough receptor sites to interrupt sensory pathways while preserving protective reflexes. P2X3 receptor antagonists, such as gefapixant, reduce ATP-nerve excitability and neuronal hypersensitivity, with randomised control trials demonstrating reductions in 24-h cough frequency [10]. Despite favourable outcomes, taste disturbances are common, placebo responses substantial, and availability remains limited. Other P2X3 antagonists, such as camlipixant, are in late-stage development, while agents targeting TRP, sodium channels, and NMDA and opioid receptors remain under investigation [48].

In summary, current and emerging treatments for RUCC reflect recognition of neuronal mechanisms as specific treatment targets. Evidence supports behavioural interventions and neuromodulatory treatments. Novel pharmacotherapies are approved in several countries, but are limited in terms of accessibility, and additional therapeutic agents are under development. Additional research is required to further understand treatment mechanisms, standardise treatment approaches, predict treatment response, and understand efficacy of multimodal approaches.

Conclusion

Chronic cough is a common debilitating problem and reason for presentation to healthcare professionals. RUCC is a specific clinical phenotype which commonly features unpleasant sensations within the larynx (hypersensitivity), with cough as a response. The predominant mechanism underlying RUCC is a heightened neuronal state that has developed due to sensitisation of either PNS or CNS circuits. Genetic predisposition, neuronal plasticity and persistence of vagal nerve stimuli may all contribute to the development of this condition, but the exact mechanisms are still not fully understood and further research is needed. In addition to peripheral mechanisms, the role of the CNS is becoming increasingly recognised as important, with dysfunctional descending inhibitory pathways playing a role in this condition. Advances in understanding of the mechanisms of RUCC have led to the development of new treatments targeting the PNS and CNS and further therapies are in development.

Summary and key points

Chronic cough, lasting more than 8 weeks, is a common and debilitating condition that significantly impacts quality of life. While treatable traits, such as asthma, GORD and chronic rhinosinusitis can be identified and

treated, a subset of patients have RUCC. Changes in airway receptors, neuroplasticity and altered sensory processing in the brain may all contribute to the pathophysiology of RUCC. Treatment of RUCC can include pharmacological approaches with low-dose morphine and gabapentinoids, or non-pharmacological therapies aimed at improving behavioural control of cough.

Key points

- Individuals with chronic cough should undergo systematic evaluation and treatment of underlying cough traits.
- RUCC is important to identify and represents a distinct clinical phenotype. It is usually characterised by a dry cough, urge to cough with sensations in throat/upper airways and a number of underlying cough triggers.
- Mechanisms leading to RUCC are complex, but likely involve alterations in sensory fibres innervating the airways, extracellular ATP and the CNS.
- RUCC can be successfully treated with neuromodulatory medications and behavioural cough control therapy. Emerging treatments, including P2X3 antagonists, may become more widely available in the future.

Case vignette and self-evaluation questions

A 54-year-old woman was seen in the respiratory outpatient clinic with a 10-year history of daily dry cough. The cough started following a viral upper respiratory tract infection. It was associated with an urge to cough and tickle in her throat. There were multiple cough triggers including: aerosols, perfume, exercise, stress and laughing. The cough could be partially alleviated by taking sips of water. She reported no breathlessness, dyspepsia or post-nasal drip symptoms. There was no significant past medical history. She had never smoked and worked in a nursery. Her cough had not improved following trials of inhaled/nasal corticosteroids and a proton-pump inhibitor. Cardiorespiratory examination and examination of the ears, nose and throat was unremarkable.

Spirometry was normal with a forced expiratory volume in 1 s of 94% predicted. Biomarkers for eosinophilic airway inflammation were normal including fractional exhalation of nitric oxide of 10 ppb and a normal blood eosinophil count. IgE and specific IgE tests to grass, pollen, house dust mite and *Aspergillus* were also normal. Previous computed tomography (CT) imaging of the thorax was normal.

1. What is the most likely diagnosis in this case?
    a) Undiagnosed eosinophilic asthma
    b) GORD
    c) RUCC
    d) Bronchiectasis
    e) Cerebellar ataxia with neuropathy and vestibular areflexia syndrome
2. Which of the following is/are treatable traits in chronic cough?
    a) Airways disease
    b) Inducible laryngeal obstruction
    c) Chronic rhinosinusitis
    d) Gastro-oesophageal reflux
    e) Smoking
    f) Angiotensin-converting enzyme inhibitor use
    g) Obstructive sleep apnoea
    h) Obesity
3. Which of the following is/are common clinical features of RUCC?
    a) Recurrent chest infections
    b) Cough triggered by perfumes and strong smells
    c) Cough preceded by a sensation of irritation in the throat
    d) A barking quality to the cough
    e) Cough duration <8 weeks
4. Which of the following neuro–pulmonary mechanisms may be important in RUCC?
    a) Heightened cough responses to a range of stimuli activating peripheral airway receptors
    b) Impaired control of cough
    c) Alterations in ATP signalling
    d) Plasticity of vagus sensory nerves innervating the airways
5. Which of the following treatment strategies is/are used in the management of RUCC?
    a) Opioids
    b) Inhaled bronchodilators
    c) Gabapentinoids
    d) Speech and language therapy
    e) Prophylactic antibiotics

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Suggested answers

1. c. The patient described in the vignette most likely has a diagnosis of RUCC. There are some typical clinical features including an urge to cough in the throat and multiple cough triggers. The normal investigations including spirometry, markers of eosinophilic airway inflammation and CT imaging are key and not suggestive of an alternative diagnosis.

2. All of the options (a–h) are treatable traits in chronic cough. As discussed in the "Approach to chronic cough and treatable traits" section of this review.
3. b and c are correct. Although individuals with RUCC can be misdiagnosed with recurrent infection initially, correctly diagnosed recurrent chest infections (*e.g.* with positive sputum microbiology) would be more typical of airway conditions such as bronchiectasis. Barking cough is most associated with tracheobronchomalacia/excessive dynamic airway collapse (EDAC).
4. All of the options (a–d) are neuro–pulmonary mechanisms that may be important in RUCC. As discussed in the "Mechanisms leading to RUCC" section of this review.
5. a, c and d are correct. Opioids, gabapentinoids, and speech and language therapy for cough suppression are commonly used for the management of RUCC. Inhaled bronchodilators are not typically used for chronic cough and may be used for small airways disease. Prophylactic antibiotics are often used in the management of COPD and bronchiectasis.