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Evidence for neuropathic processes in chronic cough

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ABSTRACT

Chronic cough is a very common symptom for which patients seek medical attention but can often be difficult to manage, because associated causes may remain elusive and treatment of any associated causes does not always provide adequate relief. Current antitussives have limited efficacy and undesirable side-effects. Patients with chronic cough typically describe sensory symptoms suggestive of upper airway and laryngeal neural dysfunction. They often report cough triggered by low-level physical and chemical stimuli supporting the recently emerging concept of 'cough hypersensitivity syndrome'. Chronic cough is a neuropathic condition that could be secondary to sensory nerve damage caused by inflammatory, infective and allergic factors. Mechanisms underlying peripheral and central augmentation of the afferent cough pathways have been identified. Successful treatment of chronic cough with agents used for treating neuropathic pain, such as gabapentin and amitriptyline, would also support this concept. Further research of neuropathic cough may lead to the discovery of more effective antitussives in the future.

1. Cough as a sensory neuropathic disorder

The concept of cough resulting from a sensory neuropathic disorder has been around for the last decade or so when cases of chronic cough have been labelled as laryngeal sensory neuropathy or post viral vagal neuropathy, cases seen by otorhinolaryngologists [1–3]. This condition was recognised often as following a post-viral upper airway infection that led to the daily dry reproductive cough precipitated by a throat tickle, dry sensation, laughter or speaking. In addition to the cough, these patients may also have dysphonia, vocal fatigue, effortful phonation, odynophonia, globus and/or dysphagia [3]. It was hypothesised that this was the result of a post viral vagal neuropathy, with similarities with other postviral neuropathic disorders such as glossopharyngeal neuralgia and Bell's palsy [4,5].

The combination of irritation in the throat or upper chest representative of laryngeal or pharyngeal or upper airway paresthesiae, of cough triggered by non-tussive stimuli such as talking and/or laughing termed allotussia, and of increased cough sensitivity to inhaled stimuli and number of triggers termed hypertussia suggest a disorder of airway sensory neural function. In 2011, two articles appeared that coined a new term of cough hypersensitivity syndrome that was used to describe chronic cough as a condition characterised by an afferent neuronal hypersensitivity [6]. That same year, an expert Committee within the auspices of the European Respiratory Society was convened and defined the cough hypersensitivity syndrome as being a disorder characterised by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure, in the management of patients with chronic cough [7]. This Committee found that the cough hypersensitivity syndrome was endorsed by respiratory opinion leaders as a valid and useful concept. Later, the potential pathophysiological mechanisms underlying peripheral and central augmentation of the afferent cough pathways were discussed, and compelling evidence was put forward for a neuropathy of vagal sensory nerves after upper-respiratory viral infections or exposure to allergic and non-allergic irritants to underlie the cough hypersensitivity syndrome [8]. Thus, chronic cough could result from a neuropathic disorder that arises from neural damage caused by a range of inflammatory, infective, and allergic factors.

This concept of chronic refractory cough as a sensory neuropathy is supported by such patients experiencing an abnormal

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sensation in the laryngeal area, and non-tussive stimuli such as phonation being most common cough triggers [9]. In another analysis, it was shown that patients with chronic cough had a high prevalence of abnormal upper airway, breathing and voice symptom scores, demonstrating overlap in sensory dysfunction in chronic refractory cough [10]. The Laryngeal Hypersensitivity Questionnaire has been developed as a simple, non-invasive tool to measure laryngeal paraesthesia in patients with laryngeal conditions such as chronic cough, paradoxical vocal fold movement (vocal cord dysfunction), muscle tension dysphonia, and globus pharyngeus [11], conditions which can be considered to be part of the cough hypersensitivity syndrome.

In a recent study of subacute/chronic cough reported from the field of respiratory medicine, the most common cough triggers were itchy throat, cold air, common cold, dry air, smoke/fragrance, talking, changing position, fatigue/stress, post-nasal drip etc., in this order [12]. Items suggestive of other than laryngeal paresthesia were rather prevalent in these patients many of which were managed by the conventional anatomic diagnostic protocol. It is now becoming evident that other areas apart from the larynx from where cough may be triggered may be sites of hypersensitivity changes, eg nasal mucosa, gastrooesophageal area, and lower airways.

2. Cough sensors and afferent pathways for cough

Two types of airway sensory nerve subtypes for initiating cough are described [13]: nociceptors, which detect a range of noxious chemical irritants but are relatively insensitive to mechanical stimuli, and mechanoreceptors which have some chemosensory properties but are very sensitive to touch-like mechanical stimuli. Mechanosensors sensitive to touch are found in the larynx, the trachea and large bronchi. They are sensitive to intraluminal irritants or particulate matter and are sensitive to chemical and mechanical irritants with signals conducted along fast-velocity vagal myelinated (Aδ) fibres. Nociceptors such as C-fibre sensors found in the larynx, tracheal, bronchial, and alveolar walls are unmyelinated slow conducting C-fibres that respond to the chemical capsaicin, the active ingredient in hot chili peppers. These nociceptors are also responsive to pro-inflammatory molecules, including bradykinin, prostaglandins, leukotrienes and cytokines, as well as noxious irritants such as capsaicin, acid, nicotine, and acrolein [14]. C-fibre sensors may also release tachykinins, such as substance P, through an axon reflex, which in turn causes neurogenic inflammation [8]. These sensors also contain membrane channels that can be activated by acid and belong to the acid-sensing ion channel (ASIC) family, and the NaV1.7 subtype of voltage gated sodium channels [15].

Several transient receptor potential (TRP) channels are found in C- and Aδ-nociceptors, namely the temperature-sensitive transient receptor potential vanniloid-1 (TRPV-1) and transient receptor potential cation channel, subfamily A, member 1 (TRPA1) receptors. TRPV-1 receptors are directly activated by capsaicin, and are sensitized or indirectly activated by heat, protons, bradykinin, arachidonic acid derivatives, adenosine triphosphate (ATP) and phosphokinase C [16]. TRPA1 is co-expressed with TRPV1 on many vagal C-fibres in the airways [17] and is activated by allyl isothiocyanate (mustard oil), cinnamaldehyde (from cinnamon) and acrolein (from cigarette smoke). TRPA1 may mediate many sensory nerve-dependent processes and may interact with TRPV1.

3. Central nervous system control

Reflex cough is integrated in the medulla oblongata where the afferent fibres for coughing first relay in the nucleus of the tractus solitarius; the motor outputs send motoneurons to the respiratory muscles, and to the larynx and bronchial tree. Afferent inputs to the brainstem are relayed to higher brain regions where inputs are integrated in pontine, subcortical and cortical nuclei [18]. Using functional magnetic resonance imaging of the human brain during induced cough, many such areas are being shown to be important during the urge-to-cough [19,20]. The anterior insula cortex may play a role in monitoring the sensory input arising from the airways and the primary sensory cortex is activated in a perception-dependent manner, and may be involved in integrating sensory inputs and coding for the urge-to-cough intensity. Cough can also be initiated voluntarily, a process that originates in motor and premotor cortical brain regions. Greater understand of the central control of coughing may also help in understanding the central action of most antitussive drugs.

4. What augments sensory or neural drives in afferent pathways?

Cough hypersensitivity may occur at both peripheral and central levels or both. Sensory afferent nerves can be sensitised by neuroactive molecules such as nerve growth factor which changes the activity of cough afferent nerves, and facilitates afferent signals when stimulated [21,22]. Sensitization may also occur by increased expression of ion channels such as TRPV1 which regulates afferent nerve excitability to chemical stimuli (Fig. 1) [23]. There was a modest but significant correlation between capsaicin tussive response and the number of TRPV-1−positive nerves within the chronic cough patients (Fig. 1) [23]. Cough hypersensitivity can also be induced centrally when normal afferent signals are augmented by central events by the interaction of different afferent neurons in the brainstem. Thus, neuropeptides in airway nociceptors and airway mechanosensors can reduce the cough reflex threshold by converging onto common second order neurons in the brainstem [19], leading to the amplification of incoming signals in the brainstem cough nuclei. Thus, cigarette smoke exposure in primates caused increased excitability of second order neurons in the brainstem receiving inputs from the airways, an effect prevented by blocking the neuropeptide, substance P [24]. Induction of neuropeptide expression by airway mechanosensors following antigen or viral exposure [22,25] may negate the need for these convergent inputs to cause central sensitization. Neurons in the medulla receiving inputs from airway afferents also project to many subcortical nuclei in the pons, thalamus, hypothalamus, midbrain and amygdala, as shown by functional brain imaging during voluntary cough and the urge-to-cough [19,26]. However, whether these neural pathways are in a further state of enhancement during cough hypersensitivity syndrome is not known.

5. Inflammatory factors and neurogenic mechanisms

These peripheral and central mechanisms for sensitisation impute an interaction between inflammatory factors and neurones. Chronic inflammation in the lower airways of patients with chronic idiopathic cough has been amply demonstrated. Thickened airway walls on CT images [27], and damaged bronchial epithelium with goblet cell hyperplasia, basement membrane thickening and a chronic inflammatory infiltrate with mast cells have been described in airway biopsies and bronchoalveolar lavage studies in patients with unexplained chronic cough [28−30]. Some of these findings have been associated with capsaicin cough hypersensitivity [27,28]. Increased mast cells and neutrophils in bronchoalveolar lavage fluid, with increased levels of inflammatory biomarkers including histamine, prostaglandin D2 and E2, TNFα and IL-8 in induced sputum samples have been reported [31−34]. TGFβ levels are

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