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The problem of cough and development of novel antitussives

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Abstract

Cough is a very common clinical symptom and current therapies are largely ineffective, indicating a major unmet medial need. There is a pressing need to develop novel and safe antitussive therapies. This is likely to arise from better understanding of the sensory nerves involved in cough and the signalling pathways that are activated. A major therapeutic target should be sensitization of the cough reflex which is a feature of patients with both acute (virally induced) cough and chronic cough, including chronic idiopathic cough. Studies on human cough mechanisms are limited. There are several novel therapeutic approaches that are currently being explored. Perhaps the most promising drugs are transient receptor potential vanilloid-1 ($TRPV_1$) antagonists, selective cannabinoid agonists (CB2 agonists), maxi-K channel openers and P2X3 antagonists. New cough therapies may target airway nerve sensitization and may best be delivered as inhalers to minimize any systemic effects. Understanding the intercellular signalling pathways involved in nociception may lead to novel drugs, such as p38 mitogen-activated protein (MAP) kinase inhibitors, being used in the treatment of cough in the future. It is also likely that several novel treatments that are developed as analgesics will also prove to be beneficial in the treatment of cough.

Keywords: Antitussives; Cough sensitization; Sensory nerves; Membrane receptors

1. Introduction

Chronic cough is a major unmet clinical need and safe and effective therapies are urgently needed. Cough is the commonest symptom for which patients consult a doctor in the UK and current therapies are unsatisfactory. Chronic cough is a major symptom in 10–30% of specialist respiratory clinics [1]. A large amount of money is spent on over-the-counter remedies for acute cough and all appear to be ineffective compared with a placebo, including codeine [2]. The total world market for cough remedies is estimated to be over $4 billion per year. Potent opiates are effective but cause addiction and have considerable side effects as they act centrally and cause sedation. This indicates a need to understand better the underlying mechanisms of cough, particularly when there is no treatable underlying cause, in order to develop more effective and safer therapies.

2. Chronic idiopathic cough

Chronic cough may be caused by many different disease mechanisms and usually responds when these underlying causes are treated [3]. For example, the chronic cough associated with asthma responds well to inhaled corticosteroids, whereas the cough secondary to gastro-oesophageal reflux responds to treatments that inhibit gastric acid production, particularly proton pump inhibitors. COPD is also associated with chronic productive cough but is difficult to treat with existing therapies, which do not have anti-inflammatory effects [4]. Less common causes of cough, such as bronchiectasis and interstitial lung disease, are usually clinically obvious [5]. There remains a group of patients with chronic cough where there is no identifiable cause [6]. These patients with chronic idiopathic cough (CIC) are difficult to manage as no current therapies appear to be effective. This problem seriously reduces their health status, their social interactions and some patients even resort to suicide. Patients with CIC more commonly report that their cough starts following a severe upper respiratory tract infection. There is a marked increase in

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the sensitivity to capsaicin cough challenge, suggesting that airway sensory nerves are hyperaesthetic, equivalent to the hyperalgesia in peripheral pain syndromes. CIC is associated with a low-grade inflammation in the respiratory tract, with increased numbers of neutrophils and inflammatory cytokines such as tumour necrosis factor-α, interleukin (IL)-8 and leukotriene B_4 which attract neutrophils and prostaglandin (PG) E_2 which activates the cough reflex [7,8], together with structural changes, such as goblet cell hyperplasia [9] and abnormal innervation with increased numbers of calcitonin gene-related peptide (CGRP)-containing nerves (C-fibres) [10]. These inflammatory changes are not reduced by inhaled corticosteroids [8]. It is not clear whether these inflammatory and repair mechanisms are causal or secondary to the mechanical trauma due to coughing. Acute cough following upper respiratory tract viral infections is the commonest cause of cough and although usually limited to under 3 weeks can be very troublesome and disruptive to normal daily living. The mechanisms are unknown but may also involve sensitization of airway sensory nerve endings [11].

3. Sensory nerves involved in cough

Identification of the sensory nerve fibres involved in the different causes of cough has been an important approach but animal studies have proved difficult as few species have proved suitable for experimental cough studies and it is desirable to measure cough in conscious animals. Both nonmyelinated C-fibres and rapidly adapting receptors, which have myelinated Aδ-fibres, appear to be involved in cough. Recent studies suggest that vagal afferent fibres not classified as a C- or Aδ-fibre (“cough receptors”) may also be involved [12]. These putative cough receptors have myelinated afferents and are found mainly in the larynx and the extrapulmonary airways; the fibres have slower conduction rates than classical RARs. However, there is little information on which afferent fibres are involved in cough in humans, although the same stimuli appear to elicit cough in conscious guinea pigs as in humans so it is likely that the same types of afferent nerves are involved. However, C-fibres in guinea pigs contain abundant substance P, neurokinin A and CGRP, whereas these neuropeptides are scanty in the afferent nerves of human airways, indicating that there are likely to be species differences. The pharmacologies of these different afferent nerves involved in coughing differ and this suggests that different treatments might be useful depending on the cause of the cough. By measuring impulses from single fibres in isolated tracheal preparations of guinea pig, it has been possible to demonstrate that different stimuli activate C-fibres and Aδ-fibres [13]. Aδ-fibres are activated by hypotonic and hypertonic saline, low chloride solutions and mechanical stimulation, whereas C-fibres are activated by capsaicin, bradykinin and acid. An exception is ATP, which activates both types of afferent fibre [14]. Although single fibre recording has not been reported from human airways using the same approach, vagus nerve depolarization in response to various tussive stimuli has shown that the same tussive stimuli that activate C- and Aδ-fibres in the guinea pig also depolarize the vagus nerve from the guinea pig and humans [15]. All of these stimuli evoke coughing in humans, suggesting that both types of afferent fibre are involved in the cough reflex in man.

3.1. Sensitization of the cough reflex

Most research has focussed on agents that activate afferent nerves to initiate the cough reflex, whereas there is relatively little research on the stimuli that sensitize the cough reflex to other tussive stimuli. These mechanisms may be particularly important in understanding chronic cough, where there is an increased sensitivity to tussive agents such as capsaicin. In developing new therapies for cough, it would be more logical to target the neural sensitization mechanism to reduce the responsiveness of afferent nerves back to normal than to inhibit the activation of these nerves since the latter would suppress a key airway defence mechanism. Many inflammatory mediators are not only able to activate airway sensory nerves, but also to induce sensitization to other tussive stimuli (Fig. 1). Bradykinin and ATP both sensitize the cough reflex and enhance the activation of C fibres [16,17]. PGE_2 appears to sensitize the cough reflex in humans [18,19]. $PGF_{2\alpha}$ also sensitizes the cough reflex [20]. In addition to peripheral sensitization, there may be central sensitization in spinal dorsal horn neurones or in the nucleus of the solitary tract, which can be long-lasting. More research is needed into the molecular mechanisms of sensitization in cough, but important lessons may be learned from the extensive research on the mechanisms of hyperalgesia in pain [21,22]. For example, specific voltage-gated sodium channels appear to lay a major role in

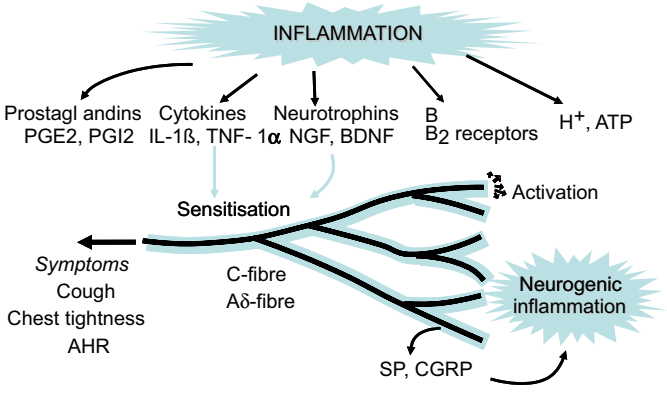

Fig. 1. Hyperaesthesia of airway sensory nerves may be induced by several inflammatory stimuli, acting on either Aδ-, C-fibres or both. Sensitized nerves are then more easily triggered by tussive stimuli and in patients with asthma this may contribute to airway hyper-responsiveness (AHR). Some C-fibres release neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP). PG, prostaglandin; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; IL, interleukin; TGF, tumour necrosis factor; B, bradykinin.