Pulmonary Pharmacology & Therapeutics 35 (2015) 117–121

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Cough reflex sensitization from esophagus and nose

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ARTICLE INFO

Article history:
Received 8 October 2015
Received in revised form 14 October 2015
Accepted 18 October 2015
Available online 21 October 2015

Keywords:
Cough
Vagus nerve
Capsaicin
Nociceptor
Postnasal drip
Rhinosinusitis

ABSTRACT

The diseases of the esophagus and nose are among the major factors contributing to chronic cough although their role in different patient populations is debated. Studies in animal models and in humans show that afferent C-fiber activators applied on esophageal or nasal mucosa do not initiate cough, but enhance cough induced by inhaled irritants. These results are consistent with the hypothesis that activation of esophageal and nasal C-fibers contribute to cough reflex hypersensitivity observed in chronic cough patients with gastroesophageal reflux disease (GERD) and chronic rhinitis, respectively. The afferent nerves mediating cough sensitization from the esophagus are probably the neural crest-derived vagal jugular C-fibers. In addition to their responsiveness to high concentration of acid typical for gastroesophageal reflux (pH < 5), esophageal C-fibers also express receptors for activation by weakly acidic reflux such as receptors highly sensitive to acid and receptors for bile acids. The nature of sensory pathways from the nose and their activators relevant for cough sensitization are less understood. Increased cough reflex sensitivity was also reported in many patients with GERD or rhinitis who do not complain of cough indicating that additional endogenous or exogenous factors may be required to develop chronic coughing in these diseases.

1. Introduction

The diseases of the nose and esophagus are considered to be among the major factors contributing to chronic cough [1], although their contribution vary in different patient populations and may not be as prominent as concluded by the pioneering studies in the chronic cough research field [2,3]. Several mechanisms by which the diseases of the nose and esophagus may contribute to chronic cough have been proposed. Direct or circumstantial supporting evidence has been provided in clinical studies for some of these mechanisms. However, mechanistic studies occasionally arrived at conflicting conclusions (e.g. Refs. [2,4]). This is probably because different mechanisms may operate in different patients, and/or because a combination of two or more mechanisms may operate in an individual patient. Here we focus on the mechanism that is the most often observed in patients with chronic cough – the sensitization of cough reflex also termed cough hypersensitivity. Specifically, we will discuss neurally-mediated sensitization of cough reflex from nose and esophagus.

Sensitization of the cough reflex refers to a condition in which the cough reflex is more readily induced. Cough reflex sensitization can be demonstrated as decreased intensity of a stimulus required to trigger cough or increased coughing in response to a stimulus with constant intensity. Experimentally, the changes in cough reflex sensitivity are evaluated by measuring the cough threshold to inhaled irritant or by counting the number of coughs evoked by an inhaled irritant with defined intensity. The cough threshold is most often measured by a controlled inhalation of increasing concentrations of an aerosolized tussigen, commonly capsaicin or acidic solutions [5–7]. The cough threshold is defined as the lowest concentration of an irritant required to evoke a predetermined number of coughs (2 and 5 coughs are commonly used, denoted as C_2 and C_5, respectively).

The cough reflex hypersensitivity is often reported in patients with chronic cough attributed to disparate causes including the diseases of nose and esophagus [8–10]. It seems to be a straightforward conclusion that the sensitization of the cough reflex contributes to coughing. In patients with sensitized cough reflex, the endogenous and environmental stimuli are expected to be more effective to initiate coughing and thus these patients cough in the situations when their healthy counterparts do not. By analogy, the state of increased cough reflex sensitivity is often compared to the state of hypersensitivity to stimuli that cause pain in somatosensory system (hyperalgesia) and referred to as hypertussive state. Clinical observations that the cough hypersensitivity normalizes in

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http://dx.doi.org/10.1016/j.pupt.2015.10.007
1094-5539/

patients in with successful treatment of cough are also consistent with this notion.

Recent reviews indicate consensus that cough hypersensitivity is an important mechanistic concept in chronic cough [10,11]. Indeed, the cough hypersensitivity syndrome is defined as a disorder characterized by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure. Common feature of the diseases of the nose (exemplified by chronic rhinitis) and esophagus (exemplified by GERD) that are thought to contribute to chronic cough is that they often cause increase in the cough reflex sensitivity. We will therefore discuss them together in this review.

Experimental studies in humans and animal models provided evidence that the cough reflex is sensitized in certain diseases of the nose and esophagus that are implicated in chronic cough. Cough reflex sensitivity to inhaled capsaicin was increased in adult patients with allergic rhinitis who did not complain of cough and had a normal lung function [12]. Moreover, cough sensitivity to capsaicin was further increased during the pollen season in pollen-sensitive patients [13]. Cough reflex sensitivity in patients with allergic rhinitis was also increased in response to humidified hot air [14]. Patients with chronic rhinitis/sinusitis of etiology other than allergic had also increased cough reflex sensitivity to capsaicin [15]. Similarly, increased cough reflex sensitivity has been described in GERD [16,17]. Furthermore, cough reflex sensitivity in GERD decreased with effective treatment of gastroesophageal reflux [8,17–19].

Nonetheless, it should be emphasized that while many patients with rhinitis or GERD have increased cough reflex sensitivity, only a small fraction of these patients will develop chronic cough. This observation argues that the increased cough reflex sensitivity alone is unlikely solely responsible for chronic cough observed in patients with chronic cough attributed to chronic rhinitis or GERD. Other factors, either environmental or more probably endogenous, may be required in addition to increased cough reflex sensitivity to cause chronic cough in these patients. For example, an airway involvement that may be considered insignificant by itself (e.g. modest allergic airway inflammation in patients with allergic rhinitis [20]) combined with increased cough sensitivity may result in chronic coughing. This problem has been discussed in more details in our previous review [21].

2. Sensitization of cough reflex due to stimulation and/or inflammation of airway mucosa

In the diseases of the nose and esophagus it is possible that cough reflex sensitization is due to stimulation ("irritation") and/or inflammation in the areas from which the cough reflex can be normally evoked, i.e. the larynx and large airways. For example, gastroesophageal reflux can cause irritation and/or inflammation of the larynx in some patients whether due to acid or other components of the refluxed fluid or aerosol. The stimulation of cough-mediating nerves in the larynx and/or the inflammation in laryngeal mucosa can directly contribute to increased cough reflex sensitivity in these patients. We even speculate that repeated stimulation of laryngeal nerves (for example by low amounts of refluxed acid) that may not be sufficient to induce appreciable laryngeal inflammation, may cause central sensitization of laryngeal afferent pathways by a mechanisms analogous to central sensitization described in somatosensory system [22].

The causal link between gastroesophageal reflux, inflammatory changes in the larynx and chronic cough is difficult to establish because the detection of refluxed content in the larynx with currently available technology is challenging [23,24]. Nonetheless, the cough sensitization due to irritation/inflammation of the larynx and possibly other parts of airways is a plausible mechanism that should be rigorously addressed as technology improves. Similarly, in the diseases of nose the possibility exists that the inflammation is not limited to the nasal mucosa, but affects other parts of the airways. For example, patients with allergic rhinitis often have extensive inflammation in the lungs and airways although they do not suffer from asthma (e.g. Ref. [20]).

3. Sensitization of cough reflex by activation of sensory nerves in the nose and esophagus

In theory chronic coughing in patients with the diseases of nose or esophagus can be due to direct initiation of cough by the activation of sensory nerves in these organs. This possibility is not supported by clinical and experimental studies. Infusion of sensory stimulus acid (pH = 1.0) into the esophagus does not consistently initiate cough in patients with chronic cough and GERD. Cough is occasionally encountered during prolonged infusion of acid into the esophagus [4], but this is a rare finding [2,25]. Modest variable association between reflux and cough also does not provide support for the notion that cough is directly initiated from the esophagus in most patients [26–33]. Similarly to the observations in the esophagus, sensory activators applied to nasal mucosa also failed to initiate cough from the nose [34–38]. Thus, available data indicate that direct initiation of cough by stimulation of esophageal or nasal nerves is not a major mechanism of chough associated with the diseases of these organs.

Experimental and clinical evidence supports the notion that the activation of sensory nerves in the nose and esophagus leads to an increase in cough reflex sensitivity (Fig. 1). When applied to nasal mucosa in healthy humans the afferent C-fiber activators histamine and capsaicin that efficiently stimulate nasal sensory neurons [39] did not trigger cough, but sensitized the cough reflex [37,38]. Following the intranasal capsaicin or histamine, the number of coughs evoked by inhalation of a single dose of capsaicin was increased by 60–80%. Similarly, intranasal histamine caused the cough reflex sensitization in patients with allergic rhinitis [36]. Similar to human studies intranasal capsaicin sensitized the cough reflex in awake guinea pigs by approximately 70% [40]. Intranasal application of allergen ovalbumin in the ovalbumin-sensitized guinea pigs also induced sensitization of the cough reflex possibly by a mechanism involving leukotriene cys-LT_1 receptor [41]. These studies were previously reviewed in details [21].

It is important to note, that not every activator of nasal sensory nerves will enhance cough reflex. For example, nasal stimulation with water was reported to inhibit cough in anesthetized rabbits [42]. Similarly, intranasal application of the TRPM8 activator (–)-menthol inhibited cough in guinea pigs [43]. The data on the effect of intranasal TRPA1 agonists are thus far inconclusive. The observations that some intranasal stimuli sensitize and others inhibit coughing suggests that there are at least two separate afferent nerve

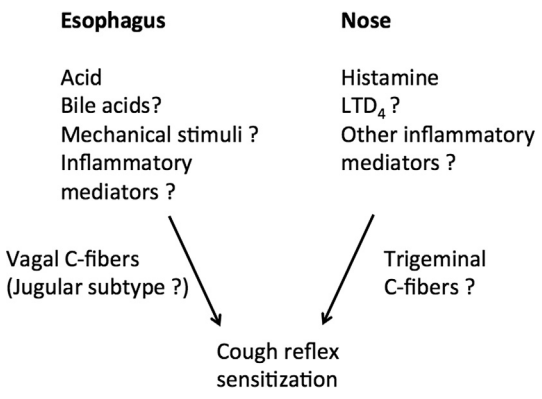

Fig. 1. Schematic drawing of cough sensitization from the nose and esophagus.