Pulmonary Pharmacology & Therapeutics 26 (2013) 491–497

Contents lists available at SciVerse ScienceDirect

Pulmonary Pharmacology & Therapeutics

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

Acid-sensing by airway afferent nerves

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ARTICLE INFO

Article history:
Received 23 February 2013
Accepted 12 March 2013

Keywords:
Airway irritation
Cough
Proton
Acid-sensing ion channels (ASICs)
Transient receptor potential vanilloid type 1 receptor (TRPV1)
Inflammation

ABSTRACT

Inhalation of acid aerosol or aspiration of acid solution evokes a stimulatory effect on airway C-fiber and Aδ afferents, which in turn causes airway irritation and triggers an array of defense reflex responses (e.g., cough, reflex bronchoconstriction, etc.). Tissue acidosis can also occur locally in the respiratory tract as a result of ischemia or inflammation, such as in the airways of asthmatic patients during exacerbation. The action of proton on the airway sensory neurons is generated by activation of two different current species: a transient (rapidly activating and inactivating) current mediated through the acid-sensing ion channels, and a slowly activating and sustained current mediated through the transient receptor potential vanilloid type 1 (TRPV1) receptor. In view of the recent findings that the expression and/or sensitivity of TRPV1 are up-regulated in the airway sensory nerves during chronic inflammatory reaction, the proton-evoked irritant effects on these nerves may play an important part in the manifestation of various symptoms associated with airway inflammatory diseases.

1. Introduction

The concentration of hydrogen ion in body fluids can be elevated substantially during various physiological and pathophysiological conditions. For example, lactic acid is produced in large quantities by the skeletal muscles during anaerobic exercise in healthy individuals [1]. Because lungs are perfused by the total venous return, they are fully exposed to the lactic acid produced by the peripheral tissues. Furthermore, the production of lactic acid is known to be elevated locally in the inflamed and/or ischemic tissues [2,3]. Indeed, in patients during asthmatic attack, the pH of the airway vapor condensate of exhaled gas is reduced to 5.23, as compared to 7.65 in healthy individuals [4,5]. This abnormally low airway pH returns to normal after anti-inflammatory therapy, suggesting the tissue inflammation as the origin of airway acidosis [4]. In addition, acidosis resulting from retention of carbon dioxide in the body fluid is one of the most common and debilitating symptoms in patients with severe chronic pulmonary diseases. All these findings indicate that tissue acidosis occurs in the airways and lungs in health as well as in disease conditions. Although the airway responses evoked by an increase in acidity in the respiratory tract has been extensively documented, recent studies began to further identify the specific types of ion channels involved and uncover the underlying mechanisms of the airway irritation caused by tissue acidification.

2. Airway irritation evoked by acid

Inhalation or aspiration of acid solution causes airway irritation and triggers various airway defense reflex responses such as cough and bronchoconstriction. More than four decades ago, Simonsson et al. first reported that inhalation of citric acid aerosol (20% solution) evoked an abrupt increase in airway resistance in patients with asthma, and the response was completely abolished by a pretreatment with atropine [6] (Fig. 1A). Accompanying the immediate bronchoconstriction, citric acid aerosol inhalation challenge also evoked airway irritation and vigorous coughs in these patients, suggesting that cholinergic reflex elicited by acid stimulation of airway sensory nerves was responsible [6]. Similarly, the bronchoconstriction induced by right heart injection of acid solution was mostly abolished by atropine in anesthetized newborn dogs [7]. However, in anesthetized guinea pigs, the bronchoconstrictive response to inhaled citric acid aerosol was mediated in a large part through the action of sensory neuropeptides such as tachykinins and calcitonin gene-related peptide (CGRP) released from these sensory endings upon activation because the airway responses were blocked by pretreatment with specific antagonists of neurokinin receptors [8]. The evidence of a dominant role of tachykinins in regulating the airway responses to inhaled irritants such as acid is well documented in rodents [9], but their relative

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http://dx.doi.org/10.1016/j.pupt.2013.03.010

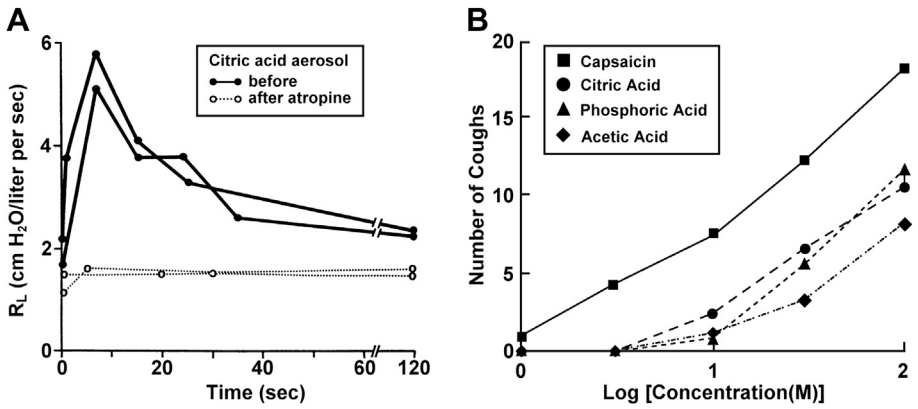

Fig. 1. Airway irritation generated by inhaled acid aerosol in humans. *Panel A*, changes in total lung resistance (RL) after inhalation of one breath of citric acid aerosol (20% solution) before (solid lines) and 10 min after injection of atropine sulfate (2 mg, intravenous; dotted lines) in a patient with asthma; the inhalation challenge was repeated in the same patient to test the reproducibility. *Panel B*, mean dose responses of cough to inhalation challenges of aerosolized capsaicin ($n = 18$), citric acid ($n = 48$), phosphoric acid ($n = 22$) and acetic acid ($n = 26$) in healthy subjects (age 18–60 years; each subject was tested in at least two study series). (adapted from Ref. [6,21]).

contribution (as compared to the cholinergic reflex) in the airway responses to these irritants remains to be clearly defined in humans.

In patients with gastroesophageal and laryngopharyngeal reflux diseases, aspiration of gastric acid is known to trigger reflex bronchoconstriction and cough [10]. It has been clearly demonstrated in experimental animals that these reflex responses were elicited by acid stimulation of the sensory nerves innervating larynx and trachea [11–13]. In addition, gastric acid can also stimulate the vagal afferents innervating the distal segment of the esophagus, which may be involved in eliciting the reflex bronchoconstriction triggered by gastroesophageal reflux in asthmatics [10,14].

Association of inhaled acid and asthma symptoms is also frequently reported when asthmatics are exposed to acid fog or aerosol in the environmental air [15–17], and the airway irritation, bronchoconstriction and coughing are also attributed to acid stimulation of airway sensory nerves [18]. These symptoms can be further aggravated during exercise because air (and acid) intake is increased during hyperventilation and the filtering function of the nasal passage is bypassed when breathing via the mouth.

Inhaled citric acid aerosol was first used for experimental production of cough in man about six decades ago [19], and remains as one of the most frequently used agent for testing cough responsiveness in humans [20–23]. The cough response to inhaled citric acid increased in a dose-dependent pattern in healthy subjects (Fig. 1B). Other forms of acid solution (e.g., acetic acid, phosphoric acid, etc.) in the same range of pH (approximately 1.5–2.5) were similarly effective in generating cough, indicating a key role of hydrogen ion in the stimulatory effect on airway sensory nerves [20,21] (Fig. 1B). The cough sensitivity to citric acid was heightened in patients with airway inflammatory diseases such as COPD [24,25].

3. Airway sensory nerves stimulated by acid

It is well documented that increasing acidity in the extracellular fluid activated nociceptive nerve endings in various somatic and visceral tissues, and evoked pain sensation [26–29]. In the respiratory tract, indirect evidence of an activation of C-fiber sensory nerves by proton was first reported in an isolated perfused guinea-pig lung preparation. Constant perfusion of pulmonary arteries with the acid buffer at pH of 5.0 caused the release of tachykinins and CGRP from these sensory nerves, which could be blocked by capsazepine, a selective antagonist of the "capsaicin receptor", suggesting that "capsaicin receptors" were activated during acid stimulation [30,31]. Direct evidence of acid stimulation of C-fiber sensory nerves was established by Fox and coworkers in an isolated airway-nerve preparation [32]. They demonstrated that C-fiber afferents innervating the guinea pig trachea, but not Aδ fibers, were stimulated when the pH of the perfusing buffer was reduced to 5.0. Their study further showed that the stimulatory effect of proton is mediated through activation of the capsaicin receptor because it could be abolished by capsazepine [32].

In anesthetized rats, lactic acid injected as a bolus into the right atrium caused a transient decrease in pulmonary venous blood pH (dropped from 7.41 to 7.09–7.29), and a short but intense burst of afferent activities in pulmonary C-fibers [33] (e.g., Fig. 2). This stimulatory effect of lactic acid was dose dependent. Formic acid, with a pK_a value (the negative logarithm of the acid dissociation constant) similar to that of lactic acid (3.79) and thus at the same molar concentration decreasing blood pH to the same degree, evoked a similar response in pulmonary C-fibers, further suggesting that hydrogen ions were primarily responsible for the action [33]. The stimulatory effect of lactic acid was abrogated by capsazepine in 75% (8 out of 12) of the pulmonary C-fibers tested but was not altered in the remaining 25% (Fig. 2), despite that this dose of capsazepine was sufficient to block the stimulatory effect of a large dose of capsaicin (five folds of its threshold dose). This finding suggested that an activation mechanism not mediated through the capsaicin receptor was also involved in the action of hydrogen ion on some of pulmonary C-fiber endings. In addition, right atrial injection of lactic acid also stimulated a small sub-population of the rapidly adapting receptors (RARs) in the rat lung [34] (Fig. 3A), which was somewhat surprising because RARs are recognized as mechanosensitive airway afferents, and generally do not exhibit chemosensitivity [34].

It has been reported that acid solution can act on the airway tissue surrounding the sensory terminals or circulating blood, and trigger the release of certain chemical mediators such as thromboxanes and prostaglandins [31,35], which may in turn cause a secondary stimulatory and/or sensitizing effect on these nerve endings [31,32,36]. However, a possible involvement of cyclooxygenase metabolites in the stimulatory effect of lactic acid can be ruled out because the responses were not affected by pretreatment with indomethacin [37].

In a more recent study, Kollarik and Undem recorded separately from vagal nodose and jugular ganglia in an isolated airway-nerve preparation similar to that used by Fox et al. [32], and found that