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Respiratory Sensations Evoked by Activation of Bronchopulmonary C-fibers

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Abstract

C-fibers represent the majority of vagal afferents innervating the airways and lung, and can be activated by inhaled chemical irritants and certain endogenous substances. Stimulation of bronchopulmonary C-fibers with selective chemical activators by either inhalation or intravenous injection evokes irritation, burning and choking sensations in the throat, neck and upper chest (mid-sternum region) in healthy human subjects. These irritating sensations are often accompanied by bouts of coughs either during inhalation challenge or when a higher dose of the chemical activator is administered by intravenous injection. Dyspnea and breathless sensation are not always evoked when these afferents are activated by different types of chemical stimulants. This variability probably reflects the chemical nature of the stimulants, as well as the possibility that different subtypes of C-fibers encoded by different receptor proteins are activated. These respiratory sensations and reflex responses (e.g., cough) are believed to play an important role in protecting the lung against inhaled irritants and preventing overexertion under unusual physiological stresses (e.g., during strenuous exercise) in healthy individuals. More importantly, recent studies have revealed that the sensitivity of bronchopulmonary C-fibers can be markedly elevated in acute and chronic airway inflammatory diseases, probably caused by a sensitizing effect of certain endogenously released inflammatory mediators (e.g., prostaglandin E₂) that act directly or indirectly on specific ion channels expressed on the sensory terminals. Normal physiological actions such as an increase in tidal volume (e.g., during mild exercise) can then activate these C-fiber afferents, and consequently may contribute, in part, to the lingering respiratory discomforts and other debilitating symptoms in patients with lung diseases.

Index words

airway irritation; dyspnea; airway inflammation; lung diseases; cough; exercise

1. Introduction

The afferent activities arising from sensory terminals located in the lung and airways are conducted mainly by vagus nerves and their branches (Paintal 1973; Widdicombe 1981; Sant'Ambrogio 1982; Coleridge and Coleridge 1986), of which a vast majority (~75%) are non-myelinated (C-) fibers (Jammes et al. 1982). These vagal afferent C-fibers innervate the entire respiratory tract ranging from larynx, trachea to lung parenchyma, and project to the

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nucleus tractus solitarius in the medulla (Bonham and Chen 2005). The afferent activity arising from C-fiber endings in the lungs and airways plays an important role in regulating the cardiopulmonary functions under both normal and abnormal physiological conditions. Activation of these afferents either by chemical irritants or by physiological stresses elicits pronounced respiratory and cardiovascular reflex responses, such as airway constriction, mucous secretion, cough, tachypnea, hypotension, and chemotactic effects on inflammatory cells, etc. (Coleridge and Coleridge 1984; Lee and Pifarri 2001). These responses are mediated through both central reflex pathways and local axon-reflex mechanism (Coleridge and Coleridge 1984; Lee and Pifarri 2001; Lee and Undem 2005); the relative role of the latter varies considerably among different species. The afferent properties and functional significance of bronchopulmonary C-fiber sensory nerves have been discussed in depth in several recent reviews (Coleridge and Coleridge 1984; Coleridge and Coleridge 1986; Lee and Pifarri 2001; Lee and Undem 2005). This mini-review focuses primarily on the respiratory sensations that are evoked by the activation of these afferents in humans, and also discusses the limitations of linking the reflex responses generated in experimental animals to human sensations. Some recent advances in the study of possible mechanisms underlying the C-fiber activation are also briefly discussed in the context of the previous findings on respiratory sensations.

“Urge to cough” is one of the common respiratory discomforts and symptoms found in patients with various airway diseases, and its association with activation of bronchopulmonary C-fibers has been suggested (Canning et al. 2004; Mazzone et al. 2007). Because various physiological and pathophysiological mechanisms underlying acute and chronic coughs have been reviewed in details recently (Lee and Undem 2004; Page et al. 2004; Widdicombe and Undem 2006), they will not be included in the discussion here.

The first direct and convincing evidence of respiratory sensation mediated through vagal afferents in humans was reported more than half a century ago. Morton and coworkers showed that unilateral section of vagus nerve between recurrent laryngeal nerve and pulmonary plexus performed in patients with inoperable tumor in the bronchial region abolished the referred pain in the neck and chest region (Morton et al. 1951). It should be pointed out that afferent fibers innervating the lung structures are also carried by sympathetic nerves via the white rami communicants to the spinal cord, and their cell bodies reside in the thoracic (T₁-T₆) dorsal root ganglia (Kostreva et al. 1975). These “sympathetic afferents” are believed to be involved in generating the debilitating chest pain associated with lung abscess and tumor, pleurisy and severe pneumonitis (Robertson et al. 1993). The potential involvement of these sympathetic afferents in the respiratory sensations will not be discussed in this review because we do not yet have sufficient knowledge about the afferent properties and functional roles of these afferents.

There is a large volume of information in the literature describing the reflex responses elicited by stimulation of bronchopulmonary C-fibers in anesthetized animals (Coleridge and Coleridge 1984; Lee and Pifarri 2001). However, definitive evidence that links these reflex responses to respiratory sensation in humans is still lacking. Due to the experimental limitations, most of the evidence was indirect and largely based upon the correlation between the respiratory sensations expressed in human subjects and the electrophysiological activity of bronchopulmonary C-fibers recorded in anesthetized animals evoked by the same stimulus. In other studies, respiratory reflexes, such as apnea and bradycardia, known to be elicited by activation of C-fiber afferents in the lung of experimental animals are thought to occur in conjunction with certain sensations evoked in humans. However, most of these cardiorespiratory reflex responses are elicited by afferent signals converging on the brainstem and other subcortical neural structures, whereas the respiratory sensations are generated from further complex processing of these integrated signals at the higher centers in the brain

(Davenport 2008). Although the study based upon these correlation analysis can not offer conclusive evidence, they do provide useful insights into the link between the types of sensory receptors and the possible causes of respiratory discomforts.

2. Vagal Bronchopulmonary C-fibers

2-1. Transduction Properties

C-fiber sensory endings are found in the mucosa of all sizes of airways as well as in the lung parenchyma in various species including humans (Komatsu et al. 1991; Baluk et al. 1992; Adriaensen et al. 1998; Watanabe et al. 2006). Immunohistochemical studies clearly illustrate extensive axonal arborization of the terminal structure of these nerve terminals that either extend into the space between epithelial cells or form a network-like plexus immediately beneath the basement membrane of epithelium (Fig. 1; Baluk et al. 1992; Adriaensen et al. 1998; Watanabe et al. 2006). The superficial locations of these nerve endings in the airway lumen and in the alveoli suggest an important role of these afferents in regulating the airway responses to inhaled irritants. Indeed, the distinct sensitivity to various chemical irritants (e.g., capsaicin, acid, cigarette smoke, etc.) and air pollutants (ozone, acrolein, sulfur dioxide, etc.) is one of the most prominent features of bronchopulmonary C-fiber afferents (Coleridge and Coleridge 1984; Ho and Lee 1998; Lee and Pifarri 2001). In contrast, C-fibers have relatively weak and irregular response to lung inflation, as compared to their myelinated counterparts in the lung, namely slowly and rapidly adapting pulmonary stretch receptors (SARs and RARs, respectively) (Ho et al. 2001). Certain sensory neuropeptides such as tachykinins and calcitonin gene-related peptide are contained in the C-fiber terminals and can be released upon activation; these neuropeptides are known to induce potent effects on a number of effector cells in the respiratory tract (e.g., smooth muscles, immune cells, etc.) (Barnes and Lundberg 1991).

Recent studies have demonstrated the expression of a number of ligand- and voltage-gated ion channels and pharmacological receptors on the sensory terminals of C fibers in the airway structures, as well as on the isolated C neurons that innervate the airways and lung (Carr and Undem 2001; Kwong and Lee 2005; Lee and Undem 2005). The expression of the transient receptor potential vanilloid type 1 receptor (TRPV1), a member of the TRP channel superfamily (Caterina et al. 1997), on the sensory terminal is probably one of the most prominent features of pulmonary C-fiber afferents (Ho et al. 2001; Undem et al. 2004). Because capsaicin, the major pungent ingredient of hot peppers and a derivative of vanillyl amide, is a potent and selective activator of the TRPV1 receptor, capsaicin has been used as a common tool to search and identify the bronchopulmonary C-fiber afferents. Other ligand-gated ion channels expressed on the pulmonary C-fiber neurons include acid sensing ion channels (ASICs), 5-hydroxytryptamine subtype 3 receptor (5-HT₃), P2X₃ purinoceptor, nicotinic acetylcholine receptors, etc. (Undem et al. 2004; Kwong and Lee 2005; Lee and Undem 2005; Gu and Lee 2006; Gu et al. 2008). It should be pointed out that some of these channels are also present on the terminals of myelinated afferents (Canning et al. 2004; Xu et al. 2007).

It is extensively documented that the sensitivity of vagal bronchopulmonary C-fibers can be enhanced by injury or inflammation of airway mucosa during both acute and chronic airway diseases (Undem and Weinreich 1993; Ho and Lee 1998; Lee et al. 2002; Zhang et al. 2008). Hypersensitivity of these afferents may, therefore, play an important part in generating the respiratory sensations and other symptoms manifested in certain airway diseases in humans (Spina 1996; Lee and Pifarri 2001; Barnes and Lundberg (1991)). Convincing evidence has been established in several experimental animal models. For example, the responses of pulmonary C fibers to lung inflation and chemical stimulation (capsaicin, lactic acid) were markedly enhanced for a sustained period of time (45-80 min) after airway inflammation was induced by acute exposure to ozone in rats (Ho and Lee 1998). Chronic airway inflammation

can be also induced by active sensitization of the airways with allergen (e.g., ovalbumin), which significantly elevated the baseline activity of pulmonary C-fibers and their sensitivities to chemical stimulants, particularly capsaicin, and lung inflation (Bergren 2001; Zhang and Lee 2007; Zhang et al. 2008). Airway infection caused by viruses (parainfluenza virus or respiratory syncytial virus) in guinea pigs has been shown to induce a significant increase in tachykinins released from activated bronchopulmonary C-fiber endings, accompanied by an increase in tachykinin synthesis in small-diameter myelinated afferents (Saban et al. 1987; Carr et al. 2002). Another example demonstrating an enhanced sensitivity of these afferents during airway inflammation was recently reported. Bronchopulmonary C-fibers generally do not respond to elevated inspired CO₂ concentration (alveolar CO₂ concentration > 10%) under normal physiological conditions. However, a stimulatory effect of high concentration of alveolar CO₂ on the same afferent endings became evident and consistent when an airway inflammatory reaction was induced (Lin et al. 2005); the stimulatory effect of CO₂ was probably mediated through the action of H⁺ ions on both TRPV1 and ASICs expressed on the terminal membrane of C-fiber afferents (Kollarik and Undem 2002; Gu and Lee 2006). Although the mechanisms underlying the inflammation-induced hypersensitivity of airway afferents are not fully understood and likely vary between different experimental conditions, the sensitizing effects of certain inflammatory mediators released in the airways are believed to play a major role. The signal transduction pathways vary among different mediators. Some autacoids (e.g., serotonin) act directly on specific ligand-gated ion channels expressed on the neuronal membrane, whereas others (e.g., prostaglandins) can alter channel functions via intracellular second-messenger signaling pathways (Gu et al. 2003; Chuaychoo et al. 2005; Lee and Undem 2005).

2-2. Difference in Afferent Properties between Bronchial and Pulmonary C-fibers

Coleridge and coworkers provided extensive evidence to establish that these C-fiber afferents can be generally divided into two major groups based upon the circulatory accessibility and anatomical locations of their sensory terminals: pulmonary C-fibers are those arising from the endings located in the lungs and airways receiving blood supply from the pulmonary circulation, whereas bronchial C fibers are those with endings located in the extrapulmonary airways receiving blood supply primarily from bronchial circulation (Coleridge and Coleridge 1984). Juxta-capillary receptors (type J receptors) described by Paintal also fall into the category of pulmonary C-fibers (Paintal 1973). Interestingly, pulmonary and bronchial C-fiber afferents exhibit different sensitivities to chemical and pharmacological agents; for example, phenyldiguanide stimulates pulmonary C-fibers, but not bronchial C-fibers in dogs (Coleridge and Coleridge 1984). Their finding gained further support from the recent studies by Undem and coworkers (Ricco et al. 1996; Undem et al. 2004) indicating that bronchial and pulmonary C-fiber afferents arise from different ganglionic origins and display different phenotypes. Cell bodies of C-fibers innervating the trachea and bronchi (bronchial C-fibers) are located primarily in jugular ganglia, and those of pulmonary C-fibers are mainly located in nodose ganglia. The neurons in these two ganglia have different embryonic origins; neurons in the jugular ganglia arise from the neural crest, whereas the neurons in the nodose ganglia arise from the epibranchial placodes. Whether different types of respiratory sensations are generated by activation of these two groups of C-fiber afferents is yet not known.

Because of the transit time of blood in the pulmonary circulation, respiratory reflexes and sensations evoked by activation of bronchial C-fiber endings are expected to occur 4-8 seconds later than those of pulmonary C-fibers when chemical stimulants are injected intravenously. On the other hand, when aerosols or particulate matters are inhaled, the site of their deposition along the respiratory tract is influenced by the size of the particles: larger particles will deposit in more proximal airways, and smaller particles can penetrate deeper into the lung periphery and alveoli (Hansson et al. 1992). Thus, in analyzing the respiratory sensations evoked by

inhalation challenges, it is important to recognize the influence of particle size on the respiratory sensations related to stimulation of bronchial and/or pulmonary C-fibers.

3. Respiratory Sensations Evoked by Chemical Stimulation of Vagal Bronchopulmonary C-fibers

Investigators have been searching for selective chemical stimulants of C-fiber afferents in human lungs for many years. Many of the studies were based upon the ability of the chemical agents to elicit pulmonary chemoreflexes, a triad of apnea (or respiratory inhibition), bradycardia and hypotension, which are known to be produced by stimulation of pulmonary C-fiber endings in various species (Coleridge and Coleridge 1984; Ravi and Singh 1996; Lee and Pissarri 2001). Capsaicin, a potent and consistent stimulant of bronchopulmonary C-fibers in most mammalian species (monkey, dog, cat, rabbit, rat, guinea pig, mice), did not generate the classic “pulmonary chemoreflexes” in man (Winning et al. 1986). Winning and coworkers reported that capsaicin injected as a bolus at the dose of $>0.5 \mu\text{g/kg}$ into the superior vena cava produced sensations of “raw, burning” first in the chest and face after a short latency of 3-4 seconds, and then in the rectum and extremities several seconds later in three healthy human subjects (1986). The intensity of the sensations was dose-dependent. Furthermore, when local anesthesia was induced by inhalation of aerosolized bupivacaine that reached alveolar region (systemic plasma concentration of bupivacaine = $\sim 1 \mu\text{g/ml}$), it completely prevented the burning sensation in the chest in response to the same capsaicin injection (Winning et al. 1986). The blocking effect of local airway anesthesia and the short latency of the sensations suggested the involvement of sensory receptors in the lung, presumably C-fibers (see Section 2-1). However, a “breathless” sensation was not reported by any of the subjects. At a higher dose ($4.0 \mu\text{g/kg}$), intravenous injection of capsaicin produced “paroxysmal coughing” in one subject after about the same delay, and still failed to elicit apnea or bradycardia (Winning et al. 1986). In contrast, capsaicin administered by aerosol inhalation, presumably activating mainly bronchial C-fibers, invariably triggered vigorous cough responses in human subjects (Hansson et al. 1992; Karlsson and Fuller 1999; Dicipinigitis 2007). The immediate burning sensation in the facial area after intravenous injection of capsaicin (Winning et al. 1986) is interesting. It has been reported that patients suffering from sustaining unilateral “facial pain” were later discovered to have ipsilateral lung cancer, which was believed to generate the referral pain via the vagus because of the convergence of these visceral and somatic afferents at the level of descending nucleus of the trigeminal system (Bindoff and Heseltine 1988).

Lobeline, a natural alkaloid found in “Indian Tobacco”, is known to stimulate pulmonary C-fibers in a number of animal species (Coleridge and Coleridge 1984; Raj et al. 1995; Deep et al. 2001). Intravenous injections of lobeline (threshold dose $5\text{--}14 \mu\text{g/kg}$) evoked sensations of “burning, tickling, irritation and suffocation” in the throat, larynx and upper chest (mid-sternal region) in a dose-dependent manner in healthy human volunteers (Raj et al. 1995; Gandevia et al. 1998) and in patients with asthma and chronic bronchitis (Jain et al. 1972). Interestingly, these sensations were accompanied by respiratory inhibition, bradycardia and hypotension (Eckenhoff and Comroe 1951; Bevan and Murray 1963; Raj et al. 1995; Gandevia et al. 1998), resembling the pulmonary chemoreflexes observed in experimental animals (e.g., Fig. 2). At higher dose ($24 \mu\text{g/kg}$), lobeline also induced bouts of coughs along with increasing intensity of these sensations. Although the latency reported from different studies varied widely between 2.1 to 12 seconds, it is believed that the latency was mainly caused by the circulation delay between the injection site and the lung, and that the variation between studies was probably due to different rates of injections (bolus vs. slow injection) or different doses of lobeline injected (the higher the dose, the shorter the latency). The pulmonary site of reflex origin was supported by the fact that the same dose of lobeline failed to cause cough if injected into left ventricle (Stern et al. 1966). There was no or negligible difference in latency between the sensations and reflex responses (Jain et al. 1972; Raj et al. 1995; Gandevia et al. 1998),

suggesting that they are probably elicited by activation of the same sensory receptors. The observation made by Raj and coworkers in their experiments on anesthetized cats seemed to suggest a primary role for J receptors (pulmonary C-fibers), although a possible involvement of increased sensitivity of RARs by lobeline could not be totally ruled out (Raj et al. 1995).

In comparison, these studies indicated that intravenous injections of capsaicin and lobeline evoked respiratory sensations that were qualitatively similar. However, only lobeline, and not capsaicin, elicited the classical pulmonary chemoreflexes in humans. Aside from a possible difference in the intensity of afferent stimulation between the two chemicals applied in these studies, there is a distinct possibility that the difference may be due to different subtypes of C-fiber afferents activated by these two chemicals in the human lung. Bradycardia and hypotension are also major responses of coronary chemoreflexes, or Bezold-Jarisch reflexes, that are elicited by stimulation of chemosensitive afferents innervating the ventricles and atria of the heart (Hainsworth 1991). However, the argument against the involvement of these cardiac afferents is that they are accessible mainly from the coronary circulation and therefore a longer latency is expected. In addition, left ventricular injection of lobeline failed to elicit the same reflex responses in humans (Stern et al. 1966).

One of the most common inhaled chemical irritants in the human respiratory tract is cigarette smoke, and nicotine is primarily responsible for the airway irritation and coughing caused by inhalation of cigarette smoke (Lee et al. 1993). In healthy nonsmokers with local anesthesia of the upper airways, inhalation of a single puff of cigarette smoke or nicotine aerosol immediately triggered coughs, intense airway irritation in the lower neck and upper chest (substernal) region and a sensation of “tightness of chest” (Fig. 3A). The short latency of these responses (< 1 sec) indicated the location of the sensory receptors in the respiratory tract. This notion is supported by the findings that nicotine and cigarette smoke stimulated both C-fibers and RARs in the lung and airways of experimental animals (Lee et al. 1989; Kou and Lee 1991; Xu et al. 2007) (e.g., Fig. 3B). The relative roles of these two types of afferents in the airway irritation generated by inhaled cigarette smoke in human airways remain to be determined. The irritant effect of nicotine is probably mediated through an activation of neuronal nicotinic acetylcholine receptors (NnAChRs) expressed on the sensory terminals of these afferents because the cigarette smoke-evoked airway irritation in human subjects could be nearly completely prevented by a pretreatment with hexamethonium, an antagonist of nAChRs (Lee et al. 1993). This hypothesis was supported by the observation made in a psychometric study that nicotine administered by intravenous injection also caused coughing and airway irritation in human smokers (Henningfield et al. 1985). Recent studies using the whole-cell patch-clamp electrophysiological recording and RT-PCR analysis in isolated rat pulmonary sensory neurons identified by retrograde labeling have further demonstrated the expressions of $\alpha 4$ - $\alpha 7$ and $\beta 2$ - $\beta 4$ subunits of NnAChRs in these neurons (Gu et al. 2008) (Fig. 3C & 3D). However, the specific subtypes of the NnAChRs mediating the response of pulmonary sensory neurons to nicotine and their subunit compositions expressed in human airways are not yet known.

Adenosine is a commonly used drug by intravenous injection for treatment of patients with paroxysmal supraventricular tachycardia. However, patients receiving adenosine injection frequently experienced dyspnea and chest discomfort, and indirect evidence suggested a possible involvement of pulmonary afferents (Rankin et al. 1992). In a recent series of studies, Burki et al. demonstrated that the intravenous injection of adenosine evoked “chest tightness” and “shortness of breath”, assessed by hand-grip dynamometry, in healthy volunteers (Burki et al. 2005). Furthermore, these adenosine-induced respiratory sensations were not associated with an increase in airway resistance, and were markedly reduced, but not completely abolished, by inhalation of lidocaine aerosol (Burki et al. 2008), indicating a primary role of pulmonary afferents. Indeed, intravenous injection of adenosine at therapeutic doses stimulated

pulmonary C-fibers in anesthetized rats (Hong et al. 1998). However, adenosine is also known to stimulate other respiratory afferents, such as carotid body chemoreceptors (McQueen and Ribeiro 1983), which can lead to an increase in ventilation. RARs in the lung may also be activated indirectly by the adenosine-induced bradycardia and a subsequent increase in end-diastolic volume of the heart (Kou and Lee 1991; Hong et al. 1998). The fact that the stimulatory effect of intravenous injection of adenosine on pulmonary C-fibers exhibited an exceptionally long latency (3-18 seconds in rats) made it more difficult to differentiate the relative contribution of these afferents.

Phenyldiguanide, a structural analog of serotonin (Fastier et al. 1959) known to stimulate pulmonary C-fibers in several animal species (Coleridge and Coleridge 1984), does not seem to activate these afferents in humans. When phenyldiguanide was injected into the pulmonary artery at the dose that generated hyperventilation by stimulation of carotid body chemoreceptors, it did not cause airway irritation, respiratory discomfort or any sign of pulmonary chemoreflexes (Jain et al. 1972), confirming the species variation of its action on pulmonary C-fibers (Coleridge and Coleridge 1984).

4. Role of C-fibers in Respiratory Sensations Generated by Physiological and Pathophysiological Stresses

Dyspnea or breathlessness is one of the most common symptoms observed in patients with various pulmonary diseases, but it is “not a uniform sensation and has many different qualities” (Guz 1997). A number of sensors located in different parts of the respiratory system (e.g., mechanoreceptors in respiratory muscles, arterial chemoreceptors, etc) and other organs (e.g., heart), and multiple neural pathways and structures are involved in generating the sensation of dyspnea under various conditions (Guz 1977;Guz 1997). In a limited number of studies, blocking the conduction in vagus nerves has proven to be effective in attenuating the dyspneic sensation and other accompanying abnormalities in breathing in patients with certain pulmonary diseases (Guz 1977;Davies et al. 1987;Paintal 1995). However, although it is generally believed that pulmonary C-fiber is the vagal afferent type primarily responsible, the definitive evidence remains to be established. It should be pointed out that in the studies of responses to exogenously administered chemical stimulants described above, respiratory sensations evoked transiently by short burst and high intensity of pulmonary C-fiber activity may be quite different from those develop at a much slower pace with lower intensity and longer duration during physiological stresses (e.g., high altitude, exercise, etc.) or pathophysiological conditions (e.g., airway inflammatory diseases, pulmonary vascular obstruction, etc.). The central (cortical) activation pattern mediating these respiratory sensations is likely dependent upon the nature, duration, intensity and discharge pattern of the afferent signals, and how these signals are filtered, modified and processed at each of the neural structures and their synaptic transmissions along the neural pathway, including brainstem, midbrain, hypothalamus and various cortexes.

In a pioneering study, Guz and coworkers investigated whether blocking the cervical vagus nerves with local anesthetic could attenuate the debilitating dyspnea caused by a wide variety of cardiopulmonary diseases in a group of twelve patients (Guz et al. 1970). In patients suffering from pulmonary vascular obstruction, lung infiltration and asthma, bilateral vagal block not only effectively reduced the dyspneic sensation, but also improved the breath-holding time and attenuated the tachypnea that was unrelated to either hypoxia or hypercapnia in these patients. Based upon the evidence obtained in a companion experiment using the anodal block of myelinated vagal afferents in anesthetized rabbits, these investigators further suggested that pulmonary C-fibers were responsible for generating the dyspnea and tachypnea developed in these disease conditions (Guz et al. 1970).

Respiratory sensations mediated through pulmonary C-fiber activation can be also generated under certain normal physiological conditions. For example, Paintal and coworkers have suggested that an increase in interstitial fluid volume resulting from elevated pulmonary arterial and capillary pressures contribute to the breathless sensation after moderate and severe exercise (Paintal 1995). The fact that other sensory receptors in the respiratory system are also activated during and after exertional exercise makes it difficult to evaluate the specific role of pulmonary afferents in healthy individuals. However, Paintal's hypothesis is convincingly supported by the observation that in a patient with unilateral pulmonary venous obstruction, section of the ipsilateral cervical vagus drastically attenuated the dyspneic sensations (Davies et al. 1987) (Fig. 4). Indeed, it has been shown that pulmonary C-fiber activity was significantly elevated by increasing left atrial pressure during pulmonary congestion in anesthetized dogs (Coleridge and Coleridge 1977). Increases in pulmonary arterial and capillary pressures can also occur as a result of pulmonary vasoconstriction in healthy individuals exposed to the hypoxic environment at high altitude. Thus, it seems reasonable to suggest that the dry cough and dyspneic, choking sensations felt in the throat and upper chest of subjects with high altitude pulmonary edema are caused by activation of pulmonary C-fibers (Paintal 1995). Paintal further suggested that similar respiratory sensations that occur after moderate or severe exercise at sea level are also generated by stimulation of these afferent endings (Paintal 1995). However, it should be pointed out that an increase in pulmonary interstitial volume is also a potent and consistent stimulus of RARs in the lung, as extensively documented by Kappagoda and coworkers (Kappagoda et al. 1987). Therefore, a possible involvement of activation of RARs and their contribution to the respiratory sensations cannot be overlooked (Ravi and Kappagoda 2008).

Acute exposure to ozone is known to induce airway mucosa injury and inflammation (Holtzman et al. 1983). After exposure to ozone (0.6 ppm, 2 hours), healthy human volunteers developed airway hyperresponsiveness, resulting primarily from reflex bronchoconstriction mediated through the cholinergic pathway (Holtzman et al. 1979; Holtzman et al. 1983). In 11 of the 16 subjects, airway hyperresponsiveness was also accompanied by bronchial irritation and substernal discomfort, and these individuals also coughed upon taking a deep inspiration. A mechanistic role of C-fiber activation in generating these sensations is supported by the observation that ozone exposure increased pulmonary C-fiber sensitivity to chemical stimulations and lung inflation (Ho and Lee 1998).

As described above, the sensitivity of pulmonary C-fibers is enhanced in various airway inflammatory diseases, and certain endogenously released inflammatory mediators are considered to play major roles in the development of the hypersensitivity. One of these candidates is prostaglandin E_2 , a potent autacoid derived from arachidonic acid metabolism during airway inflammation. Inhalation of PGE_2 aerosol did not change airway resistance or lung volume, but significantly increased the dyspneic sensation during exercise in healthy human subjects (Taguchi et al. 1992) (Fig. 5A). Inhalation of PGE_2 also enhanced the sensitivity of the cough reflex elicited by capsaicin in healthy volunteers (Choudry et al. 1989) (Fig. 5B), suggesting a PGE_2 -induced sensitization of pulmonary C-fiber afferents. Indeed, recent studies have shown that PGE_2 can markedly enhance the excitabilities of pulmonary C fibers to chemical stimulants and to lung inflation, but not the sensitivity of RARs or SARs, in anesthetized rats (Ho et al. 2000) (Fig. 6). Experiments in isolated pulmonary vagal sensory neurons further demonstrated that PGE_2 activates the G_s protein-coupled EP_2 and EP_4 prostanoid receptors and enhances the C-neuron excitability via the intracellular cyclic AMP-protein kinase A transduction cascade (Kwong and Lee 2002; Lee et al. 2002; Gu et al. 2003) (Fig. 6C).

It has been shown that several other autacoids (e.g., bradykinin, neurotrophic factors, certain lipooxygenase metabolites, etc) can also sensitize pulmonary C-fibers (Lee and Undem

2005). Since the synthesis and release of these mediators are known to increase during airway inflammation reactions, they may also contribute to the heightened respiratory discomfort found in patients with airway inflammatory diseases (Lee and Undem 2005).

5. Conclusion

Identifying the causes of different types of respiratory sensation is important for the diagnosis and understanding of the pathophysiology of various lung diseases. The respiratory discomfort can be evoked by activation of a number of sensors in the respiratory system, and is generated after complex processing of these afferent signals in the higher centers. Afferent activity arising from pulmonary C-fibers is one of these signals.

Studies in human subjects indicate that chemical stimulation of bronchopulmonary C-fibers evoke irritation, burning and choking sensations in the throat, neck and upper chest (mid-sternum) regions. Reflex responses that may be elicited in concert with these respiratory sensations include cough, bronchoconstriction, airway hypersecretion and hypotension. Together, these respiratory sensations and reflex responses play an important role in protecting the lung against inhaled irritants, and may also prevent overexertion under severe physiological stresses (e.g., during strenuous exercise, at high altitude, etc.) in healthy individuals (Coleridge and Coleridge 1984; Paintal 1995; Lee and Pisarri 2001). In acute and chronic airway diseases, certain endogenous inflammatory mediators may enhance the sensitivity of C-fibers in the lung and airways. Normal physiological perturbations such as an increase in tidal volume (e.g., a deep inspiration at rest, or hyperventilation during mild exercise) can then activate these C-fiber afferents and consequently lead to exaggerated sensory and reflex responses. Hence, under these pathophysiological conditions, hypersensitivity of pulmonary C-fibers may contribute, in part, to the lingering and debilitating respiratory sensations and symptoms that command medical attention and care.

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Fig. 1.

Confocal images showing the transient receptor potential vanilloid type 1 channel (TRPV1) (a, d) and calcitonin gene-related peptide (CGRP) (b, e) -immunoreactive axons in the guinea-pig trachea (a-c) and alveoli (d-f). Merged images illustrating co-localization of TRPV1 and CGRP are also shown (c, f). In the epithelium of the trachea (a-c), a fine network of co-existing TRPV1- and CGRP-immunoreactive axons is visible, derived from the subepithelial plexus. Arrows indicate double-labeled axons. In the lung, TRPV1-immunoreactive axons (arrows) are also visible within parenchymal lung tissue (d), and extensively co-localize with CGRP (e, f). Scale bars are 20 μm (a-c) and 100 μm (d-f). (Modified from: Watanabe et al. 2006)

Fig. 2.

Experimental records illustrating typical sensory and cardiorespiratory responses to an injection of lobeline via a vein at the right elbow of an awake human subject. Top trace shows the timing of the injection and the occurrence of cough. Second trace is from the potentiometer used to signal sensation (from left to right: first arrow, onset of burning in throat and upper chest; second arrow, onset of 'air hunger'; third arrow, end of 'throat' sensation; fourth arrow, onset of nausea; fifth arrow, 'back to normal'). Note that the onset of respiratory sensations induced by lobeline was accompanied by a brief hypopnea prior to coughing and that the later sensation of 'air hunger' was associated with hyperventilation (see signals of ribcage and abdominal movement in the fifth and sixth traces, respectively). The magnitude of the hyperventilation is evident in the reduction of end-tidal CO_2 beginning about 35 s after the injection. Abbreviations: BP, blood pressure; HR, heart rate (bpm, beats per minute); SaO_2 , arterial oxygen saturation. (Modified from: Gandevia et al., 1998)

Fig. 3.

Acute effects of inhalation of a single breath of nicotine aerosol (2% in saline) on healthy human subjects with local anesthesia of the upper airways. **A**: airway irritation (measured by the number of push-button signals generated following aerosol inhalation) and number of coughs evoked by inhalation of aerosolized nicotine and vehicle. *, significant difference ($P < 0.001$; $n = 5$) between the responses to nicotine and vehicle. Lower panel shows the locations of the irritant sensation evoked by inhaling nicotine aerosol or cigarette smoke. **B**: Experimental records illustrating the stimulatory effects of nicotine on a pulmonary C-fiber (receptor location: right lower lobe) and a RAR (right middle lobe), recorded simultaneously from a thin vagal filament, in an anesthetized rat. Upper panel: receptor responses to lung inflation ($P_t = 15$ cmH₂O) and to lung deflation (removing the positive end-expiratory pressure for five consecutive breaths). Notice that only the RAR was activated, whereas the C-fiber was not, by this low level of lung inflation. Further, the RAR was also activated by lung deflation and C-fiber was not. Middle and lower panels: responses to right-atrial bolus injections of capsaicin (Cap; 0.5 μ g/kg) and nicotine (Nic; 75 μ g/kg), respectively. Notice that only the C-fiber was stimulated by capsaicin, whereas both were activated by nicotine (a shorter latency and more intense discharge for the C-fiber, but a longer duration of discharge for the RAR). The irregular P_t was caused by the spontaneous respiratory movements after nicotine injection. AP, action potential; P_t , tracheal pressure; ABP, arterial blood pressure. **C**: Whole-cell responses (upper panel: voltage-clamp recording; lower panel: current-clamp recording) to nicotine (Nic; 10, 30 and 100 μ M, 4 s) in a single pulmonary nodose neuron (capacitance: 27.2 pF); insets, action potentials shown on an expanded time scale. Lower panel: group data showing the concentration-dependent response to nicotine. **D**: RT-PCR analysis of nicotinic acetylcholine receptor mRNA in rat vagal pulmonary sensory neurons. M, 100 bp DNA marker. (Modified from: Lee et al., 1993; Xu et al., 2007; Gu et al. 2008)

Fig. 4.

Responses of a patient with obstructed venous outflow from right lung. Pulmonary artery and wedge pressures in left lung after supine cycling at 50 watts are shown schematically in **A**. Because venous outflow from right lung was obstructed, pulmonary capillary pressure in the right lung must have risen to ~60 mmHg. A work load of 50 watts produced a marked increase in respiratory rate (**B**) due to intense J receptor traffic in right vagus. This caused a marked increase in ventilation (**C**) and a consequent fall in end-tidal Pco₂ (**D**). Responses of the patient after vagotomy (closed circles) were similar to responses of 6 normal subjects (open triangles). All points represent mean values from several trials as given in Table 1 of Davies et al. (1987). Notice there are no points beyond 50-watt work load before vagotomy (open circles), apparently because patient was too dyspneic to exercise at further work load. PAP, pulmonary artery pressure; PCP, pulmonary capillary pressure; V_E, ventilation. (Modified from: Davies et al., 1987; Paintal, 1995)

Fig. 5.

A: Relationship between the dyspneic sensation (expressed in Borg scale) and oxygen consumption ($\dot{V}O_2$) during exercise after saline and PGE₂ inhalation in 8 healthy subjects. Data are means $\pm$ SEM. * ($p < 0.05$) and ** ($p < 0.01$) indicate significant difference in the dyspneic sensation between after saline and after PGE₂ at a given level of $\dot{V}O_2$. **B:** The median number of coughs after increasing doses of capsaicin before, and 5 min and 30 min after inhaling five breaths of prostaglandin E₂ (PGE₂; total dose 0.76 μ mol) in 6 subjects. S, saline aerosol as control. (From: Choudry et al., 1989; Taguchi et al., 1992)

Fig. 6.

A: experimental records illustrating responses to right-atrial injections of capsaicin (Cap) of a pulmonary C fiber arising from an ending in the right lower lobe of an anesthetized, open-chest rat. Conduction velocity of this fiber was 0.93 m/s. Left, control responses; right, responses during a constant infusion of PGE₂ (1.5 µg/kg/min, iv). AP, action potentials; P_t, tracheal pressure; BP, arterial blood pressure. **B:** experimental record in current-clamp mode shows that pretreatment with PGE₂ (1 µM, 5 min; middle panel) increased the number of action potentials elicited by capsaicin (Cap) in a cultured pulmonary nodose ganglion neuron (capacitance 18.0 pF; identified by retrograde labeling). **C:** schematic illustration of the hypothesized signaling pathways and intracellular processes involved in the sensitization of pulmonary C neurons induced by endogenous PGE₂. EP, prostanoid receptor subtype; AC, adenylyl cyclase; PKA, protein kinase A; TTX-R I_{Na}, TTX-resistant Na⁺ current; I_K, delayed outward K⁺ current; I_{sAHP}, Ca²⁺-dependent slow after-hyperpolarization current (Modified from: Ho et al., 2000; Kwong and Lee, 2002; Lee et al., 2002).