Mechanisms of Dyspnea

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The mechanisms and pathways of the sensation of dyspnea are incompletely understood, but recent studies have provided some clarification. Studies of patients with cord transection or polio, induced spinal anesthesia, or induced respiratory muscle paralysis indicate that activation of the respiratory muscles is not essential for the perception of dyspnea. Similarly, reflex chemostimulation by CO₂ causes dyspnea, even in the presence of respiratory muscle paralysis or cord transection, indicating that reflex chemoreceptor stimulation per se is dyspnogetic. Sensory afferents in the vagus nerves have been considered to be closely associated with dyspnea, but the data were conflicting. However, recent studies have provided evidence of pulmonary vagal C-fiber involvement in the genesis of dyspnea, and recent animal data provide a basis to reconcile differences in responses to various C-fiber stimuli, based on the ganglionic origin of the C fibers. Brain imaging studies have provided information on central pathways subserving dyspnea: Dyspnea is associated with activation of the limbic system, especially the insular area. These findings permit a clearer understanding of the mechanisms of dyspnea: Afferent information from reflex stimulation of the peripheral sensors (chemoreceptors and/or vagal C fibers) is processed centrally in the limbic system and sensorimotor cortex and results in increased neural output to the respiratory muscles. A perturbation in the ventilatory response due to weakness, paralysis, or increased mechanical load generates afferent information from vagal receptors in the lungs (and possibly mechanoreceptors in the respiratory muscles) to the sensorimotor cortex and results in the sensation of dyspnea.

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Abbreviations: 5-HT3 = 5-hydroxytryptamine subtype 3; NTS = nucleus tractus solitarius; TRPV1 = transient receptor potential vanilloid type 1

Dyspnea, or shortness of breath, is perhaps the most common accompaniment of lung disease. The mechanism(s) and pathways of this sensation remain unclear, but recent animal and human studies have shed some light on this aspect of dyspnea.

Because of the nature of dyspnea, a sensation that can only be properly assessed in awake humans, studies of neural pathways, peripheral sensors, and

central mechanisms are difficult and progress has been slow. It is generally accepted that dyspnea involves central, peripheral (chest wall and lung receptors), and chemoreceptor mechanisms.^{1–3} Research in this field has consisted of studies of dyspnea or breathlessness in patients and normal subjects, as well as studies of related respiratory sensations, including the sensation of breath holding, the detection and perception of added respiratory loads, awareness of ventilation, and the ability to detect changes in PCO₂ and PO₂.

THE LANGUAGE OF DYSPNEA

Dyspnea has been distinguished from breathlessness in normal subjects, such as that induced by exercise,² but it is unclear whether dyspnea refers to several different sensations or one sensation expressed differently.⁴ It has been suggested that the sensation of “air hunger” is related to the stimulation of chemoreceptors, whereas the sensation of an “unpleasant urge to breathe” may reflect central respiratory motor command,^{5,6} although distinctions

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between the sensations based on verbal descriptors are by no means clear.⁷

PERIPHERAL RECEPTORS

Chest Wall Mechanoreceptors

Muscle spindles and tendon organs in the respiratory muscles act as mechanoreceptors. They sense muscle tension and contraction and are innervated via the anterior horn cells of the spinal motor neurons and project to the somatosensory cortex. The diaphragms are richly supplied with tendon organs but have few spindle cells; they are innervated by the phrenic nerves (Fig 1). The role of these chest wall and diaphragm mechanoreceptors in dyspnea has been examined in studies after transection or block of the spinal cord.

Spinal anesthesia to T1 revealed no effects on the sensation of CO₂ rebreathing, breath holding, or load-detection ability.⁸ In high-level (C1-C2) quadriplegics (ie, with denervation of both chest wall and diaphragm),⁹ the ability to detect lung volume change was still present, suggesting that pulmonary afferent information via the vagus nerves is perceived in the sensory cortex. Similarly, in a patient with spinal cord transection at C3, the ability to detect added resistive loads was the same as in a group of normal subjects.¹⁰ In summary, spinal cord block or transection does not prevent the ability to detect lung volume change or alter the sensations induced by an increase in PCO₂, breath holding, or added respiratory loads.

Chest wall vibration has been studied to evaluate the role of mechanoreceptors. In-phase vibration of the chest wall (ie, vibration of inspiratory muscles during inspiration and expiratory muscles during expiration) results in a reduction in dyspnea induced by hypercapnia and resistive loading in normal subjects and patients with COPD, whereas out-of-phase vibration increases dyspnea.¹¹ These results indicate that chest wall mechanoreceptors innervated via the spinal neurons have an important modifying effect on dyspnea, but respiratory muscle activity does not appear to be essential to the perception of dyspnea (see "Chemoreceptors").

Chemoreceptors

In normal subjects, the induction of hypercapnia or severe hypoxemia causes breathlessness. However, patients with hypercapnia and/or hypoxemia are not invariably dyspneic. The preponderance of evidence indicates that hypercapnia can induce breathlessness in the presence of effective denervation at C1, and hypercapnia can be sensed in the presence of cord transection at C1.⁵

It is important to note that in these studies the afferent pathways from airway sensory nerves via the

vagus nerves were intact. In normal subjects and patients with lung disease voluntary hyperpnea to match reflex CO₂-induced hyperpnea causes little or no breathlessness¹²; thus breathlessness related to hypercapnia appears to be dependent on the level of effective reflex chemostimulation.

The first studies of the effects of induced neuromuscular paralysis on respiratory sensation by Campbell and colleagues¹³ reported an absence of the dyspneic sensation during breath holding and hypercapnia after curare-induced respiratory muscle paralysis. However, subsequent studies^{6,14} found that dyspnea induced by hypercapnia is preserved following total neuromuscular blockade. These studies do not explain whether the source of the CO₂-induced dyspnea lies in the peripheral or central chemoreceptors. Another possible source could be the bronchopulmonary vagal C fibers, which contain acid-sensing ion channels.¹⁵ In animals, CO₂ stimulates bronchopulmonary vagal C-fiber afferents in the presence of inflammation,¹⁵ and it is possible that stimulation of these receptors by increased CO₂ provides a signal for dyspnea.

The induction of acute hypoxia in normal subjects during exercise¹⁶ appears to increase the intensity of breathlessness in the absence of any specific effect on ventilation. During high-altitude hypoxia the intensity of exercise-induced breathlessness appears to be primarily related to the level of reflexly stimulated ventilation rather than to the level of hypoxia per se.¹⁷ In patients with dyspnea with chronic airways obstruction, however, it is unclear whether exercise-induced breathlessness is ameliorated with supplemental oxygen.¹⁸

Thus, the weight of current evidence suggests that hypercapnia is dyspnogenic in normal subjects and is dependent on the level of reflex stimulation of the respiratory centers; the source of the dyspnogenic signal, whether from the peripheral chemoreceptors, vagal C fibers, or central chemoreceptors, is unclear. Whether hypoxia is dyspnogenic per se remains uncertain.

Lung Receptors

Sensory information arising from the lungs is transmitted by the vagus nerves to the brainstem (Fig 2). These nerves consist of myelinated and unmyelinated fibers and the latter conduct >75% of the afferent neural traffic in the vagus nerves.¹⁹ Sensory receptors in the lungs consist of rapidly adapting receptors, slowly adapting receptors, and polymodal A δ -fibers in the large airways (the latter primarily in the larynx and trachea), all innervated by myelinated fibers of the vagus nerve,^{20,21} and unmyelinated vagal C fibers, present in the entire respiratory tract.

The rapidly adapting receptors and slowly adapting receptors are involved primarily in pulmonary stretch

FIGURE 1. Schematic representation of afferent pathways from respiratory muscle mechanoreceptors to the CNS. DRG = dorsal respiratory group; VRG = ventral respiratory group.

and cough reflexes, modulating airway caliber and ventilatory pattern²⁰; although they do not appear to play a major role in the genesis of dyspnea, the afferent information on lung volume changes they provide to the respiratory centers permits awareness of the level of ventilation and the “stretch” occurring in the lungs, which may be an essential part of the overall sensation of dyspnea.

Unmyelinated C fibers have been postulated as a possible source of dyspnea for many decades.²² Studies in humans^{23,24} have shown that the dyspneic sensation is decreased by vagal blockade or section, implicating the vagal nerves in this sensation. On the other hand, studies using chemical stimuli to the C fibers have given conflicting results. Capsaicin is known to stimulate transient receptor potential vanilloid type 1 (TRPV1) receptors expressed on C fibers.^{20,25} After intravenous capsaicin injection, Winning et al²⁶ noted a sensation of “raw, burning” feeling; no subject reported feeling breathless. These sensations were blocked by prior inhalation of anesthetic aerosol. Inhaled capsaicin induces cough²⁵ but has not been documented to have any dyspnogenic effect. Phenylidiguanide is a selective 5-hydroxytryptamine subtype 3 (5-HT₃) receptor agonist that can lead to stimulation of pulmonary C fibers.²¹ However, studies with phenylidiguanide²⁷ have not reported any breathlessness. Finally, lobeline has been believed to stimulate vagal C fibers²⁷; however, IV injection of lobeline in humans produces cough and sensations of respiratory discomfort referred to the throat and upper chest,²⁸ but sensations of breathlessness are not believed to be associated with lobeline stimulation of C fibers.²⁹

FIGURE 2. Schematic representation of afferent pathways of dyspnea from vagal receptors and peripheral chemoreceptors to the CNS. The precise pathways from the nucleus tractus solitarius to the limbic system and cortex are not clearly delineated and, hence, are shown as broken lines. RAR = rapidly adapting receptor; SAR = slowly adapting receptor.

In contrast, in a series of human studies³⁰⁻³² we have shown that IV adenosine is dyspnogenic but does not cause coughing or bronchoconstriction. This dyspnogenic effect is increased in asthma³¹ and is attenuated by inhaled lidocaine³² or pretreatment with theophylline. These studies and previous animal data^{33,34} indicate that it is very likely that adenosine exerts its dyspnogenic effect by activating vagal C fibers by its action on adenosine A1 receptors and possibly A2 receptors.

The reason for these apparent differences in the effects of various substances known to act on airway C fibers, and the fact that only adenosine appears to be specifically dyspnogenic, may be explained by recent animal studies of vagal sensory fibers.^{20,21} The sensory terminals of the C fibers express a number of ligand- and voltage-gated ion channels and pharmacologic receptors; these include TRPV1, adenosine receptors, acid-sensing ion channels, 5-HT₃, P2X₃ purinoceptor, nicotinic acetylcholine receptors, and so forth.^{15,21,35} It has been shown in guinea pigs that C fibers arising from the jugular ganglion (neural crest) are primarily associated with the large airways (ie, extrapulmonary airways and large intrapulmonary bronchi), whereas C fibers deeper in the lungs (ie, the “pulmonary” C fibers or J receptors)²² have cell bodies more often situated in the nodose ganglia.^{20,21} The activation profile of jugular C fibers is distinct from the nodose (placodal) C fibers.

Nodose C fibers are stimulated by adenosine (via A1 receptors and, in some studies, also A2a receptors),

and purinergic agonists such as ATP (via P2X_{2,3} heteromeric receptors), as well as via 5-HT₃ receptors,^{21,27,35} whereas the jugular C fibers are unaffected by these stimuli.

We have shown that intravenous adenosine is dyspnoegenic in humans but does not cause any cough,³⁰⁻³² and that this effect can be attenuated by pretreatment with inhaled lidocaine (which blocks airway nerves by inhibition of the sodium channel and interruption of action potential conduction) and by blockade by systemic theophylline, a known, nonselective adenosine receptor antagonist.³⁶ Our data indicate a greater attenuation of the dyspnoegenic effects of adenosine with systemic theophylline than inhaled lidocaine, supporting the concept of an effect on the nodose C fibers.³⁶ These differences in activation profiles also probably explain differences between the effects of capsaicin and intravenous adenosine. First, inhaled capsaicin is probably preferentially deposited in the distribution of the jugular C fibers; in addition, since capsaicin acts on the TRPV-1 receptor²⁷ but not on the adenosine receptors, it is possible that the dyspneic sensation is specifically related to activation of a subgroup of C fibers that express adenosine receptors. Although lobeline and phenyldiguanide have not been studied in terms of their effects on these two different C-fiber phenotypes, it is probable that their primary effects are on the jugular C fibers.

CENTRAL MECHANISMS

How is information derived from the peripheral respiratory system translated into the sensation of dyspnea? Studies of related sensory modalities, such as the detection/perception of added respiratory loads, have provided some insights. The detection of an added respiratory load is likely when inspiratory muscle force exceeds 10% to 20% of the muscle force necessary for a normal unloaded inspiration.³⁷ In patients with chronic lung disease and equivalent degrees of mechanical abnormality, those with dyspnea had a significantly greater central inspiratory neuromuscular drive than the patients without dyspnea; furthermore, the ventilatory response for a given level of central drive was significantly less in the patients with dyspnea, indicating that it is the perturbation between central neuromuscular drive and respiratory response (ie, ventilation) that is related to dyspnea.¹

However, although respiratory muscle activity per se is not essential to the perception of dyspnea, chest wall mechanoreceptors, vagal C fibers, and chemoreceptors all play a fundamental role in dyspnea genesis. Because of the difficulties inherent in neuroanatomic studies in humans, little is known about central neural processing of afferent pulmonary information. Vagal

C fibers carrying afferent information from the peripheral sensors project to the nucleus tractus solitarius (NTS) in the medulla.³⁸ Similarly, the putative central chemoreceptive areas project second-order neurons to the NTS³; indeed, NTS neurons are putative central chemoreceptors themselves and the NTS is considered a key relay site for all respiratory afferent signals to the higher centers. Signal processing at synapses in the NTS, which incorporates activity in local circuits and upstream efferent signals, determines the output of sensory information from the lungs and airways to all downstream synapses in the reflex pathways, including higher brain regions.^{38,39}

Anatomic afferent input from the NTS to the thalamus has been documented in rats,⁴⁰ and in monkeys the thalamus is activated by vagus nerve afferents.⁴¹ In cats and rats, stimulation of the cervical vagus nerves results in activation of the somatosensory cortex⁴² and insular cortex.⁴³ Thus, afferent information transmitted via the vagus to the NTS is believed to ascend by a thalamocortical pathway to the viscerosensory insular cortex.⁴⁴ A direct connection between the NTS and the limbic system has also been suggested.⁴⁵

In humans, studies of respiratory-related evoked potentials indicate that the forebrain is activated with inspiratory occlusion.⁴⁶ However, many of the respiratory sensations studied may or may not be related to dyspnea. Indeed, divergent areas of the cortex are stimulated by different respiratory stimuli: Inspiratory loads affect the left inferior frontal gyrus,⁴⁷ whereas expiratory loads affect the right lateral frontal gyrus,⁴⁸ and hypercapnia activates the middle frontal gyrus.⁴⁹ Although these studies of different respiratory sensations have provided useful information, this may not be specific to dyspnea.

Banzett and colleagues,⁵⁰ using functional brain imaging with PET scans, showed that the anterior insula was activated when air hunger was induced by restricting tidal volume.⁵¹ Neural activation occurred in the right anterior insula, the cerebellar vermis, and the medial pons when respiratory discomfort was induced by external resistive loading.⁵²

Additional studies by von Leupoldt and colleagues^{53,54} and Schön and colleagues⁵⁵ using functional MRI confirm that induced dyspnea is associated with neuronal activations in the right anterior insula and in the right amygdala, and the perception of dyspnea and pain was blunted with neurologic lesions in this area.⁵⁵

Thus, currently available information permits a general understanding of the neural mechanisms of dyspnea (Fig 2). The sensation appears to have two primary peripheral sensors—chemoreceptors and vagal C fibers; the chemoreceptors probably include the aortic and carotid bodies and/or vagal C fibers. Additional afferent information is provided by chest wall mechanoreceptors and vagal stretch receptors.

Afferent neural information is conveyed to the NTS in the medulla and from there, probably via the thalamus, to the insular cortex and limbic system, especially the anterior insula, and the sensorimotor cortex. Thus, it can be speculated that dyspnea occurs when there is an increase above usual levels of reflex afferent information from the peripheral sensors, which is processed in the insula and cortical network and generates a neural output to the respiratory system; afferent feedback on the effects of this neural output (ie, pulmonary volume change, airflow, and ventilation), is provided by the pulmonary stretch and other receptors innervated by the vagal nerves and by chest wall mechanoreceptors. This information can be translated clinically: If central neural output does not produce the expected result (airflow or ventilation), either because of muscle paralysis or abnormal lung mechanics (eg, in COPD, asthma or restrictive lung disease), a sensation of dyspnea is generated. In asthma and COPD the relationship between inspiratory neural drive and ventilatory output, and therefore dyspnea, may worsen (increased functional residual capacity) on exercise and improves with bronchodilation. This assumes that the cortical centers have a pre-existing memory of “normal” afferent input and “normal” respiratory system response, in terms of effort required to achieve a given airflow or ventilation. The extent of the mismatch between the new afferent/efferent information and preexisting memory, (“a change in the relationship between central respiratory drive and output, ie, ventilation or effort”)² determines the intensity of dyspnea. Continuing research on the peripheral sensors and central neural pathways holds the promise of further clarifying mechanisms of this common sensation.

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