CHEST

Secretory Hyperresponsiveness and Pulmonary Mucus Hypersecretion

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The term bronchial hyperresponsiveness is generally used to describe a heightened airway smooth muscle bronchoconstrictor response measured by bronchoprovocation testing. However, the airway also responds to inflammation or bronchoprovocation with increased mucus secretion. We use the term "secretory hyperresponsiveness" to mean increased mucus secretion either intrinsically or in response to bronchoprovocation. This is not the same as retained phlegm or sputum. Unlike smooth muscle contraction, which is rapidly reversible using a bronchodilator, mucus hypersecretion produces airflow limitation that reverses more slowly and depends upon secretion clearance from the airway. Certain groups of patients appear to have greater mucus secretory response, including those with middle lobe syndrome, cough-dominant ("cough-variant") asthma, and severe asthma. Secretory hyperresponsiveness also is a component of forms of lung cancer associated with bronchorrhea. An extreme form of secretory hyperresponsiveness may lead to plastic bronchitis, a disease characterized by rigid branching mucus casts that obstruct the airway. Secretory hyperresponsiveness and mucus hypersecretion appear to be related to activation of the extracellular-regulated kinase 1/2, signaling through the epidermal growth factor receptor, or secretory phospholipases A2. Recognizing secretory hyperresponsiveness as a distinct clinical entity may lead to more effective and targeted therapy for these diseases. CHEST 2014; 146(2):496-507

ABBREVIATIONS: BAC = bronchoalveolar carcinoma; BHR = bronchial hyperresponsiveness; CDA = cough-dominant asthma; CF = cystic fibrosis; EGFR = epidermal growth factor receptor; ERK = extracellular-regulated kinase; LPS = lipopolysaccharide; MEC = mucoepidermoid carcinoma; MLS = middle lobe syndrome; OPEP = oscillatory positive expiratory pressure; PB = plastic bronchitis; PBB = protracted bacterial bronchitis; ROS = reactive oxygen species; TKI = tyrosine kinase inhibitor; TNF = tumor necrosis factor; tPA = tissue plasminogen activator

In animal studies, exposure to secretory phospholipases A2 can make the airway hyperresponsive to secretagogues such as neutrophil elastase or bacterial endotoxin (lipopolysaccharide [LPS]).[1] In 2007, we named this "secretory hyperresponsiveness" to denote that the ferret airway produced dramatically increased mucus secretion in response to a known secretagogue. Unbeknownst to us at the time, Webber and colleagues[2] first used this term in 1997, to describe greatly increased mucus secretion with platelet-activating factor stimulation, remarkably also in the ferret trachea.

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Bronchial hyperresponsiveness (BHR) is a term generally used to describe increased airway smooth muscle contraction producing obstruction in people with asthma. In the pulmonary function laboratory, BHR is usually measured by bronchoprovocation tests using drugs like methacholine or osmotic agents, exercise, or cold air. The airway responds to these challenges not only with smooth muscle contraction but also with mucus secretion. Thus, although BHR involves each of these phenomena, because BHR is defined by the smooth muscle contraction, we use the term secretory hyperresponsiveness to refer to the increased mucus secretion. Unlike smooth muscle contraction, which is rapidly reversible using a bronchodilator, mucus hypersecretion produces airflow limitation that is more slowly reversible as secretions are cleared from the airway. While bronchospasm and its reversal with bronchodilators are straightforward measurements, secretory hyperresponsiveness is more difficult to quantify and is, thus, underrecognized.

Some people with asthma have a more predominant secretory response. This includes patients with middle lobe syndrome and airway obstruction because of mucus secretions, severe and fatal asthma, and possibly those with cough-dominant asthma (CDA). Secretory hyperresponsiveness also is a component of lung cancer associated with bronchorrhea. An extreme form of secretory hyperresponsiveness may lead to plastic bronchitis (PB), a condition characterized by rigid mucus bronchial casts that obstruct the airway.

Physiology of Mucus Hypersecretion

In health, mucus is secreted to coat the airway, prevent water loss, and trap inhaled material, which is removed by mucociliary clearance. Normal mucus is a mixture of mucin glycoproteins, electrolytes, water, and secreted lipids and peptides. Mucins are linearly linked core proteins encoded by mucin (MUC) genes. These core mucin proteins are heavily glycosylated. Of the identified human MUC genes, 11 are expressed in the airway at the messenger RNA or protein level. The principal airway gel-forming mucins are MUC5AC and MUC5B.[3]

Although acute mucus secretion is an effective airway defense, pathologic mucus hypersecretion and poor mucus clearance can lead to airway obstruction. Mucus secretion is increased in response to inhaled allergens, irritants including tobacco smoke, and infectious agents.[4] There can also be a chronic response with increased basal secretion rate and goblet cell hyperplasia.[5]

Mucins are stored in a highly compacted state in cytoplasmic granules of airway goblet cells and submucosal glands.[6] As the calcium in the granular contents dilutes, the compacted polyanionic mucin threads expand many hundredfold, filling the airway lumen. If the trigger remains or is repetitive, continued exocytosis is stimulated, resulting in hyperplasia, hypertrophy, and metaplasia of goblet cells or hyperplasia and metaplasia of submucosal glands.

Mucus accumulation in the airway can be the result of increased mucin production and secretion[7] or decreased mucociliary clearance.[8] Degradation can change mucin concentration after secretion. Airway mucins from patients with cystic fibrosis (CF) are rapidly degraded by bacterial serine proteases[9] causing a profound reduction in the mucin concentration.[10] During an exacerbation of asthma, there is inhibition of normal protease-driven mucus degradation leading to mucus accumulation; however, mucin degradation is restored during recovery.[11] In patients with COPD, we noted that protease-driven mucus degradation is inhibited at the beginning of an exacerbation and is restored during recovery (M. O. Henke, MD, unpublished data, 2009).

Mucin production and secretion can be initiated by signaling through the epidermal growth factor receptor (EGFR) activated by epidermal growth factor and also by transforming growth factor α, heparin-binding epidermal growth factor, amphiregulin, epiregulin, and β-cellulin. Each of these activators begins as proligands that are cleaved by proteases to release the active ligand to create the larger active complex with EGFR.[12] Many stimuli have been shown to increase the expression of these EGFR ligands but the mechanism of this expression has not been elucidated.[13] Mucin secretion can also be initiated by and signaled through the Toll-like receptors as part of the innate immune response. This has been established as important for host defense against gastrointestinal parasites[14] and in cancer.[15] This also appears to be a key mechanism for mucin production in airway bacterial infections.

Downstream of both EGFR and Toll-like receptor signaling, phosphorylation of the extracellular-regulated kinase (ERK) 1/2 with subsequent activation of transcription factors like nuclear factor κB is a common signaling pathway leading to mucin production and secretion. Mucoregulatory medications like the 14- and 15-member macrolide antibiotics that decrease excessive mucin production appear to do so by inhibition of ERK phosphorylation.[16]