Therapeutic Approaches to Mucus Hypersecretion

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Mucolytic and related agents have been in use since prehistoric times. Although widely prescribed and used extensively in over-the-counter preparations, their efficacy and mechanisms of action remain in doubt. These agents belong to several distinct chemical classes. Mucolytic agents such as N-acetyl-cysteine are thiols with a free-sulfhydryl group. They are assumed to break disulfide bonds between gel-forming mucins and thus reduce mucus viscosity. Mucokinetic agents are thiols with a blocked sulfhydryl group. Expectorants such as guaifenesin increase mucus secretion. They may act as irritants to gastric vagal receptors, and recruit efferent parasympathetic reflexes that cause glandular exocytosis of a less viscous mucus mixture. Cough may be provoked. This combination may flush tenacious, congealed mucopurulent material from obstructed small airways and lead to a temporary improvement in dyspnea or the work of breathing. The roles of anticholinergic agents, DNase, and other drugs are also discussed with regard to their roles in reducing mucus production in rhinitis and other airway diseases.

Introduction

Airway mucus is the intraluminal product of glandular and goblet cell exocytosis, vascular permeability, cellular infiltration, and desquamation. Factors promoting each of these processes may contribute to a state of mucus hypersecretion (Fig. 1). The challenges of quantifying these processes in vivo have made it difficult to determine the relative importance of serous, mucus, and goblet cell exocytosis, leak, neural reflexes, and inflammatory cell infiltration in diverse nasal, sinus, middle ear, and bronchial diseases, and the effects of individual drugs on these processes in each organ (Fig. 2).

Submucosal glands of the upper and lower airways contain two populations of cells based on their Alcian Blue–periodic acid–Schiff (PAS) base staining characteristics [1]. Essentially all submucosal gland cells in the bronchial and nasal mucosa are PAS-positive, indicating the high concentration of branched carbohydrate side chains of mucins. Alcian Blue reacts with sialic acid and sulfate ($R\text{-}HSO_4^{2-}$) of the acidic mucins that are contained within mucus cells. The counter ions for these highly charged molecules are not yet defined. Mucin 5A/C (Muc5A/C) and Muc5B predominate. These mucins have cysteine-rich N- and C-terminal regions that form cross-linked gels [2]. In contrast, seromucous, or serous cells, are PAS-positive, but Alcian Blue stain–negative. They contain monomeric, neutral, soluble (non–gel-forming) mucins such as Muc8. Serous cells are factories for a wide variety of antimicrobial proteins. These include lysozyme, lactoferrin, secretory leukocyte protease inhibitor (SLPI), secretory component, and lipocalins. Secretory component is the transport protein for locally synthesized dimeric immunoglobulin A (IgA) (joining-chain-$[IgA]_2$) that is secreted as secretory (sIgA; SC-J-$[IgA]_2$) from serous cells [3]. Regulation of intracellular glycosyl transferases that construct the carbohydrate side chains of mucins and the molecular mechanisms of glandular exocytosis are beyond the scope of current therapeutics, but are targets for future drug development.

The complexity of mucus, multiplicity of mechanisms affecting mucus production, and diversity of diseases associated with mucus hypersecretion, combined with the lack of effective therapies and understanding of mechanisms of drug action, has severely hindered the rational scientific development of effective therapies for mucus hypersecretion [4•]. These difficulties can be appreciated from the human efforts to develop therapeutic modalities to treat mucus hypersecretion. This review owes much to the publications by Braga and Allegra [4•], Ziment [5], and Rogers and Lethem [6].

History of Mucus Hypersecretion and Its Therapy

Mucus hypersecretion is a component of many disease processes that have afflicted *Homo sapiens* for millennia [4•,5]. The search for effective therapies surely extends to Paleolithic times that predate written records. Shen Nung summarized the Chinese experience up to 3500 BC when codifying the contemporary Chinese Pharmacopeia in the initial Chinese *Book of Herbs* (Pen Ts'ao, *Legendary Red Emperor*) [7]. Ma Huang, the source of ephedrine, a sympathomimetic catecholamine, and numerous other herbal preparations were described.

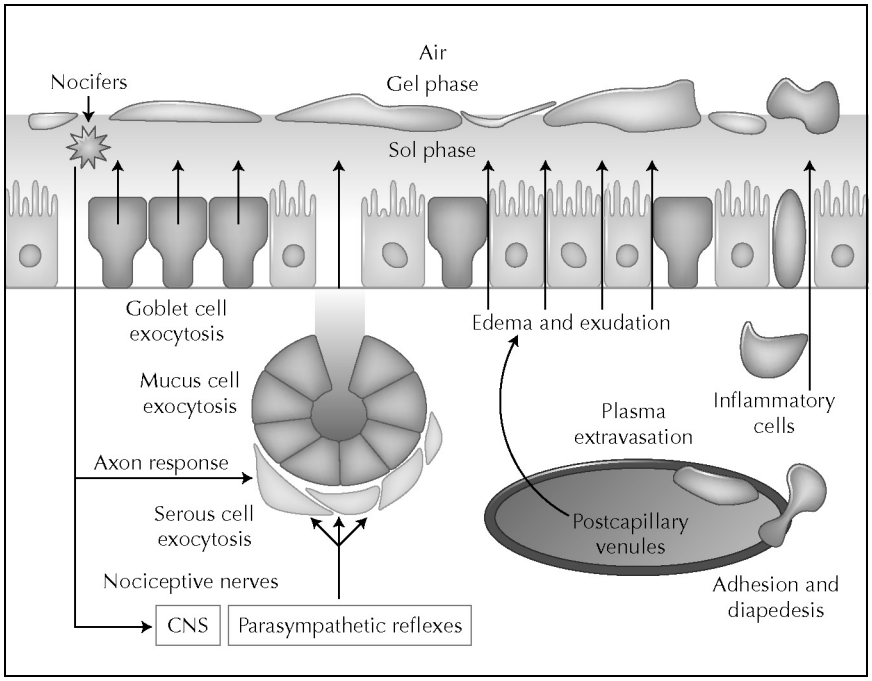

Figure 1. "Mucus" refers to the fluid lining the mucosal epithelium, and is composed of secreted macromolecules derived from glandular and epithelial goblet cell exocytosis and plasma components that exude across postcapillary venule and epithelial barriers. There is a constant influx of inflammatory cells, and these contribute significantly to the amount of mucus during inflammatory conditions. Regulation of these secretory processes by neural reflexes and inflammatory mediator release is complex.

Systemized drug therapy for cough and mucus hypersecretion was introduced by the Sumerians of Mesopotamia in approximately 3000 BC [8]. The objective of therapy was to drive evil from the body by inducing nausea, emesis, diarrhea, and coughing. This was associated with incantations and ceremonial procedures. The drugs included excreta, *Ammi visnaga* (may contain chromones), mandrake (anticholinergic properties), terpenes, aloes, belladonna, castor oil, and mint. Although most of these agents were not subjected to rigorous double-blind, placebo-controlled investigation, many of these components and their derivatives are still used as expectorant elixirs and prescribed along with the familiar incantations and machinations of the physician garbed in white cloak with ceremonial stethoscope necklace.

The most favored compounds of Mesopotamian culture had profound influence on the development of Egyptian and Greek medical therapy [5]. The School of Hippocrates (460–370 BC) applied scientific rationalization to their use, and appreciated their general lack of efficacy. Dioscorides (78 AD) recommended a number of expectorants, including cinnamon, radish, garlic, honey, flax, comfrey, mandrake, peppers, honey, and pine extract. Celsus (first century AD) and Galen (second century AD) recommended thymol, storax, turpentine, and other agents that persist as expectorants in current pharmacopeias.

Major advances for the treatment of mucus hypersecretion were made by Anglo Saxon herbalists in the first half of the 10th century with the introduction of leeches. Maimonides, in his famous 12th century *Treatise on Asthma*, recommended chicken soup flavored with ginger, cloves, coriander, and spikenard for coughing up phlegm.

Importation of Aztec and South American medical practices to Europe introduced the use of *Datura*, guaiac, tobacco, sarsaparilla, ipecacuanha, quinine, and chile peppers as mucokinetic agents. Guaiac wood imported from the north coast of South America was initially used for the treatment of syphilis, but late in the 19th century became one of the most popular oral agents for treatment of cough and cold in the United States.

The lengthy list of traditional herbal preparations from these diverse cultures has received relatively little intensive scientific scrutiny, despite forming the basis for many current mucotherapies. Stramonium was used in ancient Hindu medicine and became the first important European bronchodilator. Cigarettes made from the Malabar nut tree, Adhatoda vesica, led to the development of bromhexine and ambroxol. Cromolyn is derived from *Ammi*. Radish seedlings produce S-carboxymethylcysteine. Derivatives of the ginkgo biloba tree are potent inhibitors of platelet-activating factor [9].

Mucolytic Agents: Thiols with a Free-Sulfhydryl Group

After the role of disulfide bonds in formation of mucus gels and viscosity was discovered, the search was on for mucolytic drugs with free-sulfhydryl groups that could dissolve these bonds in vivo (Table 1).

Cysteine

L-Cysteine and its derivatives with free-sulfhydryl groups [4•] have mucolytic activity and reduce the viscosity of sputum in vitro. Cysteine is also a precursor for glutathione, so could promote antioxidant effects.

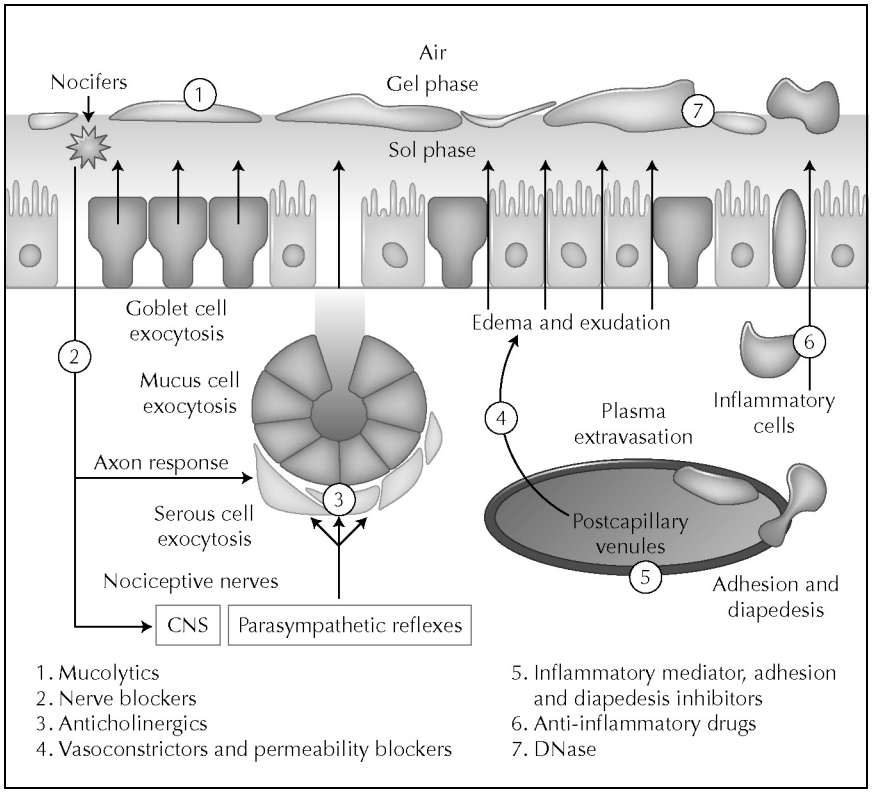

Figure 2. Therepeutic strategies are aimed at chemically reducing disulphide bonds in secreted mucoglycoconjugates, degrading mucus DNA, reducing cholinergically mediated glandular exocytosis, and interfering with postcapillary venule plasma extravasation and cellular infiltration. Antagonists of specific inflammatory mediators and glucocorticoids are effective in inflammatory conditions. Numbers refer to the point at which each listed therapy is directed.

Dithiothreitol

Dithiothreitol is the most potent mucolytic thiol but is too irritating for clinical use. It is commonly used to homogenize sputum specimens in laboratory investigations.

N-Acetyl-Cysteine

The mechanisms of action for N-acetyl-cysteine (NAC) may depend on its route of administration. Aerosolized, inhaled NAC may dissociate disulfide bonds of mucins and other disulfide-bond, cross-linked gel components to reduce viscosity. NAC reduces the specific viscosity of porcine gastric mucin extract with the maximal effect at 100 mM [4•,10]. In one clinical study of cystic fibrosis, nebulized NAC increased sputum volume and decreased sputum viscosity (10-minute inhalations of 20% solution) [11]. An early treatment effect was noted within 2 weeks with an increase in the volume of more dilute and less viscous sputum. A late effect developed over 6 months with progressive attenuation of bronchial hypersecretion and reduced incidence of acute exacerbations of bronchial infections. In chronic bronchitis, NAC does not alter forced expiratory volume in 1 second (FEV_1). Overall, aerosolized NAC was no different from placebo in chronic bronchitis or asthma. Oral NAC may reduce exacerbation rates in chronic bronchitis [12,13].

N-acetyl-cysteine may act as an antioxidant because it is required for glutathione synthesis that protects against free radical damage. NAC (200 mg three times a day orally for 8 weeks in healthy smokers) reduced superoxide radical generation by alveolar macrophages [4•].

Based on in vitro studies with cultured human nasal epithelial cells, NAC may inhibit absorption of epithelial lining fluid Na^+ [14]. This would reduce the flux of water into epithelial cells and maintain a marginally larger epithelial lining fluid volume. Mucociliary activity may be enhanced as long as ciliated cells have not been damaged or inactivated, and metaplastic changes have not altered the histology to goblet or squamous cell phenotypes. This effect of NAC has not been examined in vivo.

Side effects of aerosolized NAC include nausea and stomatitis. Hyperresponsive asthmatics can develop bronchospasm. Oral dosing is associated with dyspepsia, nausea, and diarrhea.

Thiopronine

In addition to mucolytic properties, thiopronine protects guinea pigs against histamine-induced bronchoconstriction [4•]. The effect was equivalent to theophylline.

MESNA

Sodium 2-mercaptoethane sulfonate (MESNA) has a free-thiol group, and has no irritating or bronchodilating activity. In placebo-controlled studies, MESNA nasal spray was similar to NAC, and more effective than bromhexine [15]. Sputum weights were significantly lower on MESNA in a crossover design, placebo-controlled study. Mild gastrointestinal discomfort was present in 4% of subjects.

Table 1. Mucoactive drugs

Mucolytic thiol drugs with a free sulfhydryl group
Cysteine and derivatives
Dithiothreitol
N-acetyl-cysteine
Thiopronine
Sodium 2-mercaptoethane sulfate (MESNA)
Mucokinetic drugs with a blocked thiol group
Carbocysteine
Letosteine
Stepronine
Expectorant drugs that may increase mucus secretion
Sobrerol
Bromhexine
Ambroxol
Inorganic and organic iodides
Domiodol
Guaiacol and derivatives
Guaifenesin
Ipecacuanha
Volatile inhalants and balsams
Proteolytic enzymes
Trypsin
Gelsolin
Others
Anticholinergic agents
Water
Hypertonic solutions
DNase
Glucocorticoids and nonglucocorticoid anti-inflammatory drugs
Macrolides
Purinergic receptor agonists
Antisense and interfering RNA (iRNA) inhibitors of mucin expression and glandular exocytosis
Mucus secretagogue antagonists

Mucokinetic Agents: Thiols with a Blocked Sulfhydryl Group

Some thiol drugs do not have a free-sulfhydryl group. They do not appear to break mucin disulfide bonds, but may act via alternative mechanisms.

Carbocysteine

Carbocysteine (S-carboxymethylcysteine) is a cysteine derivative with a blocked thiol group that does not reduce disulfide bonds [4•]. This and related drugs may require activation with S-oxidation mediated by phenylalanine hydroxylase (PAH, phenylalanine-4-monooxygenase) [16]. Carbocysteine protected against the macroscopic and microscopic alterations induced by SO_2 inhalation in rats [4•]. Carbocysteine (500 mg/kg/d orally) increased production of sialic acid–labeled mucin by 73% and reduced fucose-labeled mucins by 29% in 50 chronic bronchitis patients [17]. Goblet cell hyperplasia was reduced compared with placebo treatment. Sputum IgA content was increased, and albumin concentration (product of vascular permeability) reduced. This would suggest an increase in exocytosis of sIgA from serous cells rather than an increase in leak of plasma-derived monomeric IgA. Mucociliary clearance was reduced, but viscosity was unaffected [4•]. There were no consistent changes in FEV_1. Carbocysteine may be useful in the treatment of otitis media with effusion [16,18].

Letosteine

Letosteine, a cyclic derivative of cysteine, appears to have properties similar to carbocysteine, and may favor synthesis of sialomucins [4•].

Stepronine

Stepronine (2-thenoylthiopropionylglycine-lysine salt) is metabolized in the intestine to remove the thenoyl moiety and release thiopropionylglycine that has a free-sulfhydryl group [4•]. This metabolite can reduce mucin disulfide bonds, but may also activate sialyltransferase and increase acidic sialomucin production.

Expectorants: Drugs That May Increase Mucus Secretion

Expectorants increase the volume of sputum production [4•]. This often requires coughing or sneezing paroxysms to loosen and raise the mucoid material from the lungs or sinuses. Thus, expectorants may cause a transient, paradoxical increase in mucus secretion, or have a tussive effect. These seemingly harmful events may be interpreted as beneficial if mucus plugs that obstruct large, medium, or small airways can be dislodged. The result may be improved alveolar aeration and oxygenation, relief from neural irritation caused by the mechanical properties of the mucus plugs, or effects of their inflammatory components. These may reduce the mechanical work of breathing and sensation of dyspnea. The psychometric as well as the rheologic nature of these perceived benefits of increased expectoration require investigation, because they form the rationale for the use of expectorants. This is an important economic issue, because many over-the-counter and prescription cough, cold, and acute bronchitis preparations are expectorants. Metaanalysis of currently published testimonials, unblinded, and few placebo-controlled, double-blinded studies have been largely inadequate at showing benefits of these drugs [19••].

Sobrerol

Sobrerol is a cyclic terpene derivative [4•]. Sobrerol may increase mucus production and volume, and may also reduce overall sputum viscosity. Several open clinical studies suggest clinical benefits for increased expectoration. Sobrerol increased FEV_1 from 75% to 80% of predicted compared with no change in a placebo-controlled study group.

Bromhexine

Bromhexine (N-methyl-N-cyclohexane-3,5-dibromo-2-aminobenzylamine hydrochloride) is derived from vasicine, an alkaloid from *Adhatoda vasica nees* [4•]. Bromhexine has been

promoted for chronic bronchitis, bronchiectasis, mild asthma, sinusitis, and otitis media. Bromhexine may increase mucus secretion, reduce sputum viscosity, and facilitate expectoration, but has minimal effects on pulmonary function indices and rates of resolution of sinus disease. The molecular mechanism of action is unclear. In a single anecdotal case report, a mediastinal pancreatic pseudocyst due to intraluminal obstruction of the pancreatic duct was relieved by bromhexine [20].

Ambroxol

Ambroxol is related to bromhexine and appears to stimulate mucus secretion, yet promotes a normalization of mucus viscosity in viscid secretions. In studies of bronchitis, bronchiectasis, and chronic cough in smokers and emphysema subjects, ambroxol has shown a significant reduction in cough frequency and intensity. A morphologic study indicated that ambroxol normalized the epithelial histology compared with a placebo group. Significant improvements have also been claimed for FEV_1 and other pulmonary function measures, frequency of infective exacerbations, and days lost from work due to illness. Ambroxol may be marginally superior to NAC, bromhexine, thiopronine, and letosteine. Ambroxol decreased indomethacin-induced gastric lesions in a rat model [21]. The mechanism was not clear. The most common complications have been nausea, vomiting, diarrhea, rash, vertigo, and sleeplessness.

Inorganic and organic iodides

Although iodides have long been used as expectorants, clinical efficacy has not been demonstrated [4•,5]. Iodides should not be used clinically because of their indisputable toxicity for induction of thyroid disease.

Saturated solution of potassium iodide (SSKI) was formerly a commonly prescribed preparation [4•]. Benefits were reported to be improvements in cough, breathlessness, and sputum viscosity. However, dyspepsia occurred in 11% of subjects taking small doses and 40% on higher doses. Parotid gland swelling was due to excessive stimulation of salivary production. Hypersensitivity reactions include acne, other skin rashes, and adenopathy. Use by pregnant women led to neonatal thyroid suppression, cretinism, and goiter.

Iodinated glycerol was first introduced in 1915 for chronic asthma, cough, bronchospasm, and expectoration [4•,5]. Limited studies in chronic bronchitis suggested that the subgroup with the most copious sputum production had a significant decrease in mucus production. Iodinated glycerol reduces chest discomfort and coughing in some patients with chronic bronchitis without affecting dyspnea or lung function [22]. Nebulized iodine preparations cannot be advocated.

Domiodol

Domiodol (4-hydroxymethyl-2-iodomethyl-1,3,-dioxolane) is an iodinated organic compound [4•]. In a placebo-controlled, crossover study, domiodol significantly increased the volume of secretions in chronic bronchitis subjects [23]. Active control studies have compared domiodol to sobrerol and S-carboxymethylcysteine, but without placebos, it has been difficult to compare their efficacies.

The efficacy end points contribute to the confusion regarding mucoactive drugs. In these studies, increased mucus production was deemed beneficial because patients were able to cough up sputum more easily. It was not clear if there were changes in the physical properties of the mucus or concentrations of constituent macromolecules. The use of increased volume of mucus production as an end point may have great utility. However, this again underscores our ambiguous attitude toward transient versus chronic mucus hypersecretion. On the one hand, it is of interest to stop mucus production, but in some cases it has been the aim to generate a less viscous mucus that may be expectorated more easily. This ambivalence highlights our poor understanding of mucus hypersecretion and the actions of mucokinetic and other mucoactive drugs.

Guaiacol and derivatives

Handelich identified a resin from guaiac wood that yielded creosote, guaiacol, and other phenolic resins [5]. Guaiacol derivatives have been widely marketed, including "Thiokol," which helped launch the success of Hoffman-La Roche pharmaceutical company (Nutley, NJ) [4•].

Guaifenesin

Guaifenesin (glyceryl guaiacolate) has been successfully marketed in many products [4•,5]. Guaifenesin has no mucolytic action but may decrease the surface tension of bronchial sputum. There is no evidence to suggest antiseptic or antitussive properties. It may have a mild anesthetic effect, because one guaiacol derivative led to the synthesis of benzocaine. Guaifenesin's principal benefit appears to be as an expectorant (but not antitussive) for the symptomatic treatment of coughs that produce scanty amounts of thick, viscous secretions. Doses of 100 to 200 mg four times per day have been recommended, although up to 2400 mg per day may be required.

Ipecacuanha

Ipecacuanha was derived from the Brazilian *Cephaelic ipecacuanha* plant, and has long been advocated for asthma, bronchitis, and related diseases [4•,5]. Its more common use is as an emetic, an effect that may be mediated by direct stimulation of central nervous system receptors in the medulla, and gastric nociceptive vagal afferents that recruit efferent reflexes.

Ziment [4•,5] has proposed that the vagal efferent parasympathetic reflexes may stimulate gastric and bronchial glandular secretion to produce a "mucokinetic" pulmonary effect ("gastropulmonary vagal mucokinetic reflex"). Although ipecacuanha can augment the outflow of respiratory tract fluids, there have been no quantitative clinical eval-

uations of this mechanism in humans. However, Ziment [4•,5] has noted that the emetic effect of ipecacuanha and similar drugs can be reduced by milk, presumably by adsorption of the drug to bovine proteins. This would reduce ipecacuanha's ability to stimulate gastric irritant receptors and may reduce the beneficial pulmonary reflex effects. Milk has a reputation for impairment of mucokinesis, but does not in general increase mucus viscosity or production.

Eucalyptol, balsams, and other volatile inhalants

A large number of volatile oils have been used in cough, cold, and mucokinetic preparations [4•]. Despite widespread use, few of this class of compounds have been subjected to scientific investigation. Camphor, a component of Vicks products (Proctor & Gamble, Cincinnati, OH), has a traditional reputation as a mild expectorant.

Eucalyptol (1,8-cineol) was studied in a double-blind, placebo-controlled, oral-steroid, dose-sparing study in steroid-dependent asthmatics [24•]. Daily prednisone doses were decreased 36% by eucalyptol (range 2.5 to 10 mg; mean 3.75 mg) compared with a 7% decrease (2.5 to 5 mg; 0.91 mg) with placebo ($P = 0.006$).

Proposed mechanism of action of expectorants

Ziment [4•,5] proposes that many expectorants act as nonspecific irritants of vagal afferent nerves in the gastric mucosa that recruit central parasympathetic cholinergic reflexes to stimulate gastric and bronchial secretion ("gastropulmonary mucokinetic reflexes"). Hence, a common property of many of these "expectorants" may be their ability to activate irritant neurons and recruit parasympathetic glandular secretory reflexes. In the bronchi, these cholinergic reflexes may stimulate serous cell transport of secretory IgA and other serous cell products to produce a thin "serous" secretion with decreased viscosity. The general lack of clear efficacy of these irritant drugs suggests that this reflex mechanism is unlikely to affect bronchorrhea over the long term. The apparent steroid-sparing effect of eucalyptol in severe asthma suggests that these drugs should be further evaluated in other diseases to determine both efficacy and mechanisms of action.

Anticholinergic Agents

Cholinergic parasympathetic nerve activity is the most potent tonically active stimulus for glandular exocytosis and mucus secretion in human airways. Muscarinic M3 receptors on submucosal glands mediate the secretory response. Anticholinergic drugs such as atropine, glycopyrrolate, scopolamine, ipratropium, and tiotropium offer a rational approach to block these secretory reflexes and reduce glandular output and, potentially, sputum volume [25,26]. However, if both mucus and serous cells are stimulated, or there is an increase in mucus cells as seen in chronic bronchitis, then the effects on variables such as sputum composition and viscosity may be much more complex [6].

Atropine is the classic anticholinergic agent. However, it has often been administered as atropine methonitrate [26]. Atropine methonitrate blocks mucociliary clearance of the gel, but not the sol phase of mucus. In contrast, ipratropium bromide does not alter mucociliary transport [4•,6]. This difference may be due to the methonitrate. If this moiety inhibits nitric oxide synthase and nitric oxide–mediated ciliary activity, then decreased clearance of the gel phase that is swept along by the cilia would be an expected side effect. Because nitric oxide has so many homeostatic and inflammatory functions in airways [27], it may be prudent to review experiments performed with "atropine" to determine if the counter ion has any confounding effects on glandular secretion, vasodilation, vascular permeability, or bronchial smooth muscle relaxation. To date, most studies of nitric oxide have concentrated on asthma and not mucus hypersecretion.

Glycopyrrolate, a quaternary ammonium derivative of atropine, has been reported to have antisecretory activities without the side effects of atropine [28].

Ipratropium and tiotropium have been used as bronchodilators in asthma, and to decrease glandular secretion in chronic bronchitis [25,26]. They reduce rhinorrhea in dose-dependent fashion in allergic rhinitis, nonallergic rhinitis, and, in higher doses, both experimentally induced and community-acquired rhinovirus 39 common colds [25,29,30]. As expected, anticholinergic drugs have no effect on sneezing or the sensation of nasal blockage [25]. Approximately 10% of the dose is systemically bioavailable, but significant side effects were not demonstrated except for very high doses.

More selective muscarinic receptor antagonists may have a greater benefit, because the M3 receptor on glands and smooth muscle are most responsible for exocytosis and smooth muscle contraction [26]. M2 receptors on nerves are inhibitory autoreceptors. M2 agonists may be beneficial by inhibiting the actions of cholinergic and nociceptive nerves.

Water

Water has long been touted as a valuable mucokinetic. However, scientific data to support these claims are lacking. Drinking 200 mL of cold water had no effect on nasal mucus velocity, whereas hot water and chicken soup increased velocity, a fact attributed to heat and aroma rather than fluid intake [31]. Aerosolized water has been advocated, but appears to be a good agent for inducing cough and bronchospasm in asthma. As noted by Ziment [4•,5], therapeutic humidifiers, including ultrasonic and microsonic mists, have no rational value in treating lung disease and must be condemned. The only value of aerosolized water is to add moisture to dry oxygen or medical gas mixtures. Their harm is to increase fungal, bacterial, and algae growth and allergens in the humidifier and humidified room.

Hypertonic Solutions

Hypertonic solutions of saline, urea, and ascorbic acid were at one time thought to promote ciliary motility, proteolysis, and mucus liquefaction [4•]. This was due to interference with intramolecular and intermolecular binding and osmotic hydration of luminal fluid. A metaanalysis of short-term clinical studies suggested that nebulized hypertonic saline improved mucociliary clearance in cystic fibrosis only, but was less effective than DNase [32]. Inhaled hypertonic solutions can potently induce coughing and bronchospasm in asthma. This method is very useful for sputum generation as a research tool.

Proteolytic Enzymes

Trypsin

Nebulized trypsin degrades mucoproteins and fibrin in sputum [4•]. Uncontrolled studies reported improvement in clinical symptoms, but it was unclear if this was related to digestion of sputum. The recommended dose was 25,000 to 200,000 units aerosolized 1 to 6 times per day for several days. Concerns regarding clinical harm due to α-1-antitrypsin deficiency, allergic reactions, hemoptysis, mucosal metaplasia, and emphysematous degradation of alveolar walls have led to abandonment of trypsin in therapy. Similarly, serratopeptidase, fericase, onoprose, neuraminidase, chymotrypsin, papain, bromelain, ficin, helicidin, leucine amino peptidase, elastase, and ribonuclease have been considered for use to degrade mucus, but have not been considered for clinical development [4•].

Gelsolin

Globular and filamentous actin is released from desquamated cells in airways, and contributes to the viscosity of sputum. Gelsolin caps actin to prevent its polymerization. This may reduce sputum viscosity. Preliminary studies suggested efficacy in cystic fibrosis [33]. Gelsolin may be useful in other disorders where neutrophils and other cells are sloughed into the airways and their actin released.

DNase

Purulent nasal and lung secretions contain large amounts of DNA from dead neutrophils. DNA contributes to mucus viscosity. Inhalation of recombinant human DNase (rhDNase) decreases the size (1.3 kbp to 0.4 kbp; $P < 10^{-9}$) and concentration (0.6 mg/mL to 0.3 mg/mL; $P < 0.05$) of DNA fragments in sputum from cystic fibrosis subjects [34]. These cleavage events decreased mucus viscosity and improved mucus transport capacity. Prolonged treatment has been shown to improve FEV_1 by up to 5.80% of predicted (3.99 to 7.61), and age-adjusted risk for respiratory exacerbations by up to 37% ($P < 0.01$) [32]. Hoarseness, laryngitis, and rash, but not anaphylaxis, were more frequent in rhDNase-treated groups.

Glucocorticoids

Because glucocorticoids are potent anti-inflammatory agents, it would be reasonable to expect they would be beneficial in mucus hypersecretion. However, prednisone has no effect on the secretion of mucin into sputum in asthmatic subjects [35], and 1 μM dexamethasone had no effect on the secretion of lysozyme, lactoferrin, or mucins in human nasal mucosal explants in vitro. These findings suggested that the mechanisms of gland cell gene expression and exocytosis were largely resistant to steroid modulation. It is probable that the major effects of glucocorticoids in inflammatory airway diseases are on inflammatory cells, and that changes in glandular exocytosis are the consequence of reduced production of secretagogues, such as leukotrienes, histamine, neutrophil elastase, and cholinergic reflexes. This hypothesis requires confirmation, but suggests roles for specific antagonists in specific situations in which each mediator is present and active.

Macrolides

Erythromycin, azithromycin, clarithromycin, roxithromycin, and other macrolide antibiotics may inhibit immune function and mucus production. Erythromycin inhibits respiratory glycoconjugate secretion from human airways [36] and Cl^- ion transport [37]. Clinically, macrolides have suppressed mucus production in severe bronchorrhea, diffuse panbronchitis, sinobronchial syndrome, and otitis media with effusion [38••]. In sinusitis, erythromycin was a useful adjunctive therapy in subjects with lymphocytic infiltrates, but less so in those with eosinophilic (allergic) infiltrates [39]. The molecular mechanisms are undetermined. Inhibition of neutrophil chemotaxis, lymphocyte and macrophage function, modulation of airway smooth muscle and neural tone, and clinical improvements in severe asthma have been reported [38••].

Purinergic Receptor Agonists

Diquafosol, a purinergic P2Y2 receptor agonist, has been shown to increase lacrimation in the dry-eye syndrome [40]. The mechanism is unknown. It has not been tested in syndromes such as senile rhinitis where drying of the mucosa is a significant finding. Caution must be used, however, because the purinergic agonist adenosine monophosphate (AMP) is a bronchoconstrictor.

Conclusions

Despite intensive interest in mucus hypersecretion, it is essential to define the specific components of mucosal secretions that are "hypersecreted." This requires determining the origin of exocytosed macromolecules, and relative contributions of submucosal gland mucus and serous cells and epithelial goblet and other secretory cells, degree of

vascular permeability, and cellular phenotypes of inflammatory infiltrates. If allergic inflammation is present, as in allergic rhinitis and asthma, glucocorticoids reduce eosinophil, T-lymphocyte, and mast cell infiltration, and, in turn, reduce secretion of mucus. In chronic bronchitis, where a neutrophilic infiltrate predominates, it has been difficult to demonstrate remarkable efficacy with oral or inhaled glucocorticoids. Because parasympathetic reflexes play a role, anticholinergic agents such as ipratropium are useful to decrease glandular mucoglycoconjugate exocytosis. Vasoconstrictors such as α-adrenergic agonists are of value in hyperpermeability states such as common cold. DNase appears to be appropriate for decreasing the viscosity of sputum in cystic fibrosis.

Despite their widespread use, the clinical utility of the mucolytic and expectorant drugs remains in doubt [41••]. A recent metaanalysis of 23 studies suggested a significant reduction of 0.79 exacerbations per chronic obstructive pulmonary disease (COPD) subject per year compared with placebo (29% decrease). Mucolytics as a group reduced the days of illness by nearly 7 days. However, the therapy was estimated to be cost-effective only if there was a reduction of 1.2 exacerbations per COPD patient per year. No changes were found in lung function. Thus, there is a great need to better define the nature of mucus, and to develop better ways to modulate the production of its various components in diseases marked by bronchorrhea and rhinorrhea.

As the biology of mucins and the effects of proinflammatory mediators on mucus products are discovered, it is anticipated that exciting, efficacious, and innovative new therapies will emerge that replace the currently available derivatives of paleolithic empiricism. Reduction of expression of specific mucin or glycosyl transferase genes, improved degradation of intraluminal mucus components, and agents that promote the differentiation of "normal" epithelial cell populations offer great potential benefits for patients with mucus hypersecretion.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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