



REVIEW

Mucoactive drugs

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ABSTRACT: Mucus hypersecretion is a clinical feature of severe respiratory diseases such as asthma, cystic fibrosis and chronic obstructive pulmonary disease. Airway mucosal infection and/or inflammation associated with these diseases often gives rise to inflammatory products, including **neutrophil-derived DNA** and filamentous **actin**, in addition to bacteria, apoptotic cells and cellular debris, that may collectively increase mucus production and viscosity. Mucoactive agents have been the medication of choice for the treatment of respiratory diseases in which mucus hypersecretion is a clinical complication. The main purpose of mucoactive drugs is to increase the ability to expectorate sputum and/or decrease mucus hypersecretion. Many mucoactive drugs are currently available and can be classified according to their putative mechanism of action. Mucoactive medications include expectorants, mucoregulators, mucolytics and mucokinetics. By developing our understanding of the specific effects of mucoactive agents, we may result in improved therapeutic use of these drugs. The present review provides a summary of the most clinically relevant mucoactive drugs in addition to their potential mechanism of action.

KEYWORDS: N-Acetylcysteine, carbocysteine, erdosteine, mucoactive, mucus

In healthy individuals, mucus secretion is not excessive and mucus continuously removed by epithelial ciliated cells, then propelled towards the larynx for **swallowing** [1]. However, an increase in airway mucus secretion can be problematic, especially if the rate of secretion exceeds the rate at which it can be removed by normal ciliary action. Increased mucus secretion (hypersecretion) is a clinical feature of severe respiratory diseases, such as asthma, cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). Typically during infection and/or inflammation, the airway mucosa responds by **increasing the volume** of mucus that is secreted. This response is mainly due to hyperplasia and hypertrophy of **goblet** cells and the submucosal gland, a phenomenon recognised as **secretory hyperresponsiveness** [2]. The inflammatory process results in **loss** of cells and **ciliary** function, destruction of the surfactant layer by airway phospholipases and alteration of the biophysical properties of the mucus [3, 4]. In addition, **by-products** accumulated during the inflammatory process include **neutrophil-derived DNA** and filamentous actin (F-actin), **dead/apoptotic cells**, **bacteria** and cell debris. Collectively, these factors contribute to mucus **purulence**, and when expectorated, this mucus is termed **sputum** [5].

Mucus is a highly oligomerised mucin **polymer** composed of **water** and various macromolecular

glycoproteins as part of its **gel structure** [6, 7]. Drugs that affect airway secretion have been produced for many years now, their main use being to cleanse the respiratory tract. Drugs that are designed to specifically **alter** the **viscoelastic** properties of mucus in addition to promoting secretion clearance are characterised as “mucoactive”. Previous attempts have been made to characterise agents that affect mucus, although they sometimes lacked simplicity [8, 9]. The main difficulty involved with characterising mucoactive agents is due to the fact that many drugs exhibit overlapping effects. Regardless, mucoactive drugs can be broadly and simply characterised into several major groups according to their main actions [2]. Mucoactive drugs can be classified as expectorants, mucoregulators, mucolytics or mucokinetics, based on their potential mechanism of action (table 1 and fig. 1).

EXPECTORANTS

An expectorant can be defined as an agent that induces discharge or expulsion of mucus from the respiratory tract. This typically requires a coughing or sneezing action to loosen and bring up the mucus from the lungs or upper respiratory tract. These events can be seen as beneficial if mucus plugs that obstruct large, medium or small airways are dislodged. Effects following

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expectorant medication can improve alveolar aeration and provide relief from neural irritation triggered by mechanical properties of the mucus plugs or effects of their inflammatory components. Together, these may in turn reduce the mechanical effort of breathing and dyspnoea. The precise **mechanism** by which **expectorants** exert their action is still **unclear**, although it is thought that they may act as **irritants** to gastric vagal receptors, and recruit efferent parasympathetic reflexes that induce glandular exocytosis of a **less viscous mucus** mixture [9, 10]. Some frequently used expectorants include aerosol (**hypertonic saline**), iodide-containing compounds, glyceryl guaiacolate (guaifenesin) and ion channel modifiers, such as the P2Y2 purinergic agonists. These agents are addressed in detail below.

Hypertonic saline

Aerosol using hypertonic solution (saline, urea or ascorbic acid) has been previously thought to induce ciliary motility, proteolysis and mucus liquefaction [8]. This was attributed to intra- and intermolecular binding and **osmotic** hydration of luminal fluid. Studies have shown that long-term use of inhaled hypertonic saline improves pulmonary function in patients with CF, and inhaled mannitol has also been shown to be beneficial in non-CF bronchiectasis [11–13]. However, a meta-analysis of short-term clinical studies suggested that nebulised hypertonic saline improved mucociliary clearance in CF **only**, but was **less effective** than DNase [14]. Regardless, this method (either with saline or mannitol) has been proven to be an **extremely useful** tool for the generation of **sputum** for diagnostic and research purposes [11–13].

Iodide-containing compounds

Iodide-containing agents are considered to be expectorants that are thought to promote the secretion of airway fluid. Although iodides have long been used as expectorants, their clinical use has been debated, due to their potential toxicity [8, 10, 15]. Iodinated glycerol, first introduced in 1915, reduces chest discomfort and offers anti-tussive effects in patients with chronic bronchitis, without affecting dyspnoea or lung function [16]. Domiodol, another iodinated organic compound, has been shown to significantly increase secretion volume in adult subjects with chronic bronchitis [8, 17]. Furthermore, domiodol has been shown to significantly reduce symptoms of acute infectious pulmonary diseases or acute flare-ups of chronic bronchitis effects in children [18].

Guaifenesin (glyceryl guaiacolate)

Guaifenesin has no mucolytic action but may reduce bronchial sputum surface tension. No evidence is available to suggest antiseptic or anti-tussive effects. The main benefit offered by guaifenesin appears to be as an expectorant for the symptomatic treatment of coughs, producing small quantities of thick viscous secretions. Guaifenesin can stimulate the cholinergic pathway and increase mucus secretion from the airway submucosal glands. However, guaifenesin has not been shown to be clinically effective in randomised controlled trials [19, 20].

Ion channel modifiers

Tricyclic nucleotides (uridine triphosphate and adenosine triphosphate) regulate ion transport through P2Y2 purinergic receptors that increase intracellular calcium. Nebulised uridine

TABLE 1 Mucoactive drugs and their potential mechanisms of action

Mucoactive drugs	Potential mechanism of action
Expectorants	
Hypertonic saline	Increases secretion volume and/or hydration
Guaifenesin	Stimulates secretion and reduces mucus viscosity
Mucoregulators	
Carbocysteine	Metabolism of mucus producing cells, antioxidant and anti-inflammatory effects, modulates mucus production
Anticholinergic agents	Decreases secretion volume
Glucocorticoids	Reduces airway inflammation and mucin secretion
Macrolide antibiotics	Reduces airway inflammation and mucin secretion
Mucolytics	
<i>N</i> -Acetylcysteine	Breaks disulphide bonds linking mucin polymers Antioxidant and anti-inflammatory effects
<i>N</i> -Acetylcystein	Increases chloride secretion and breaks disulphide bonds
Erdosteine	Modulates mucus production and increases mucociliary transport
Dornase alfa	Hydrolyses the DNA in mucus and reduces viscosity in the lungs
Gelsolin	Severs actin filament cross-links
Thymosin β_4	Severs actin filament cross-links
Dextran	Breaks hydrogen bonds and increases secretion hydration
Heparin	Breaks both hydrogen and ionic bonds
Mucokinetics[#]	
Bronchodilators	Improves cough clearance by increasing expiratory flow
Surfactants	Decreases sputum/mucus adhesiveness
Ambroxol	Stimulates surfactant production and inhibits neuronal sodium channels

[#]: also referred to as cough clearance promoters.

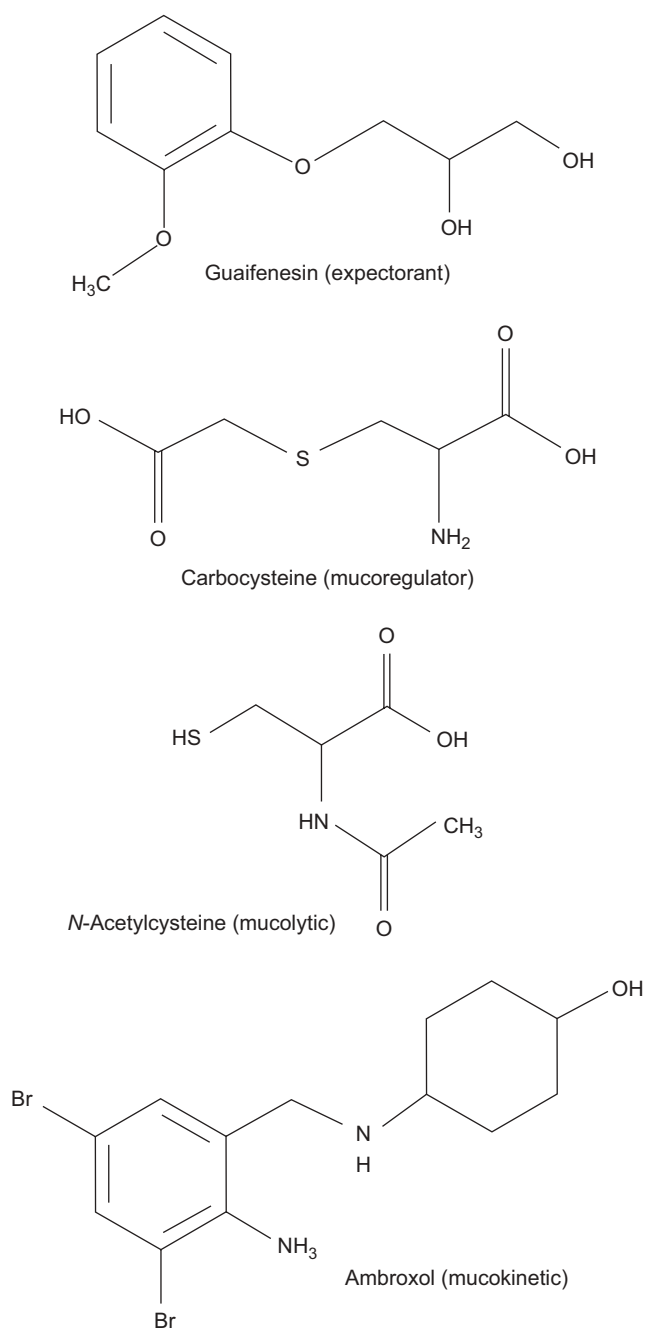


FIGURE 1. Chemical structures of selected expectorant, mucoregulatory, mucolytic and mucokinetic drugs.

triphosphate aerosol in the presence or absence of amiloride has been shown to provide enhanced mucociliary clearance in healthy subjects [21]. P2Y₂ purinergic receptor agonists have been recently developed and phase 3 studies are currently in progress [22].

MUCOREGULATORS

Drugs that regulate mucus secretion or interfere with the DNA/F-actin network can be described as mucoregulatory agents. Among others, they include carbocysteine, anticholinergics, glucocorticoids and macrolide antibiotics. The mechanism of action of these compounds is wide ranging. For example,

carbocysteine, an antioxidant, has the ability to restore viscoelastic properties of mucus and provide anti-inflammatory effects, in addition to providing protective effects on respiratory cells. In contrast, Anticholinergic agents block parasympathetic nerve activity, thereby reducing mucus secretion. Instead, glucocorticoids are potent anti-inflammatory drugs that are purported to improve mucociliary clearance. These mucoregulatory agents are examined in greater detail below.

Carbocysteine

S-Carboxymethylcysteine (carbocysteine or SCMC; also available in the lysinate form, SCMC-Lys) is a mucoactive drug (fig. 1), has antioxidant and anti-inflammatory properties, and is commonly used for the treatment of COPD [23]. Pre-clinical and clinical studies on the pharmacological properties of SCMC have demonstrated that this cysteine derivative has the ability to increase the synthesis of sialomucins, important structural components of mucus. In effect, SCMC resets the balance between sialomucins and fucomucins, possibly by intracellular stimulation of sialyl transferase activity [24], restoring the viscoelastic properties of mucus [25]. SCMC is not thought to act directly upon the mucus structure, in contrast to true mucolytic agents, such as N-acetylcysteine (NAC) or N-acetylcysteyn (NAL). Evidence from animal studies suggests that SCMC increases chloride transport across the airway epithelium, which may contribute towards its mucoregulatory action [26]. In addition to the mucoregulatory action exerted by carbocysteine, the mechanism of action by which it provides anti-inflammatory effects has also been investigated. In pre-clinical and clinical studies, carbocysteine has been shown to reduce neutrophil infiltration into the airway lumen [27], decrease levels of interleukin (IL)-8, IL-6 cytokine levels and 8-isoprostane exhaled in chronic obstructive pulmonary disease [28]. Since the chemotactic recruitment of peripheral blood mononuclear cells into the lung by IL-8 plays a crucial role in the development and maintenance of several inflammatory diseases, the inhibition of IL-8 production may contribute towards the therapeutic effect of SCMC-Lys. These anti-inflammatory effects have previously been directly attributed to scavenging effects of the thioether drug group on reactive oxygen species (ROS) [29, 30]. Carbocysteine may also modulate airway inflammation by reducing the production of cytokines in rhinovirus infections [31]. It has also been shown that carbocysteine inhibits the adherence of bacteria and viruses to ciliated epithelial cells *in vitro* [31, 32].

Additional evidence has shown that respiratory cells treated with SCMC-Lys stimulate a CF transmembrane conductance regulator (CFTR)-like channel that results in a significant increase in chloride and glutathione (GSH) membrane flux [33]. Furthermore, it has also been recently demonstrated that SCMC-Lys provides protective effects on human respiratory cells during oxidative stress [34]. In this particular study, cells exposed to oxidative stress and then treated with SCMC-Lys were shown to stimulate both GSH and chloride membrane flux, increase GSH concentration and buffer the increase in ROS in cells expressing the CFTR channel [34]. These findings provide further mechanistic insights on how SCMC-Lys may exert its antioxidative protective effects.

In addition to demonstrating beneficial effects *in vitro*, SCMC is also recognised to provide benefit to patients. SCMC has been

shown to be an effective and safe drug for the treatment of COPD in randomised clinical trials, reducing the incidence of exacerbations and improving patient quality of life [35–38]. However, it should be noted for the PEACE (Preventive Effect on ACute Exacerbation) study that subjects were Chinese (25% nonsmokers) who had limited access to other drugs that target exacerbations (*e.g.* long-acting bronchodilators and inhaled corticosteroids) [35]. No significant toxicity has been reported either in animal models or following prolonged use in humans, and no drug interactions have been identified. Moreover, SMC has been shown to improve oxidative stress and chronic inflammation associated with severe chronic diseases, in particular advanced cancer and cancer-related syndromes, both alone and in combination with other antioxidant drugs [30, 39, 40].

Anticholinergic agents

Anticholinergic drugs are frequently used as mucoregulators. Cholinergic parasympathetic nerve activity is an active stimulus for mucus secretion in human airways. This secretory response is mediated *via* M3 muscarinic receptor, expressed on submucosal airway cells. Anticholinergic medication, including atropine, ipratropium, scopolamine, glycopyrrolate and tiotropium, block these secretory reflexes, and reduce glandular output and sputum volume [41–43]. Atropine (often administered as atropine methonitrate) has been shown to block mucociliary clearance of the gel, but not the mucus sol phase. In contrast, ipratropium bromide does not appear to affect mucociliary transport [8]. The M1 receptor is not involved with mucus secretion but, in combination with M3, may control water secretion [44, 45].

Glucocorticoids

Glucocorticoids are potent anti-inflammatory agents and widely used in the management of acute exacerbations in patients with asthma or COPD. Glucocorticoids are purported to influence mucociliary clearance. Prednisolone is a glucocorticoid that has been shown to provide improvement in lung clearance in stable asthmatics [46]. However, it is generally accepted that steroids only have limited effects on mucus hypersecretion.

Macrolide antibiotics

Macrolide antibiotics have been successfully used to treat a range of **chronic, inflammatory lung** disorders [47]. Macrolide antibiotics include erythromycin, azithromycin, clarithromycin, roxithromycin. Macrolide therapy using either azithromycin or clarithromycin is now considered **standard** care therapy for **CF**. Clinically, macrolides have been shown to **reduce sputum** production in severe bronchorrhea, diffuse **panbronchitis**, sinobronchial syndrome and **otitis** [48]. The precise **mechanism(s)** of action of macrolide antibiotics still requires further **investigation**, although their specific effects include inhibition of neutrophil chemotaxis, lymphocyte and macrophage function and modulation of airway smooth muscle and neural tone [48]. Data in COPD patients are limited and sometimes contradictory but generally suggest a potential clinical benefit [46, 49]. However, the long-term safety of these antibiotics for the treatment of COPD still needs to be addressed [50].

MUCOLYTICS

Mucolytic can be defined as drugs that **decrease viscosity** and can be categorised into either "**classic**" if they depolymerise mucin glycoproteins or "**peptide**" mucolytics that depolymerise **DNA** and F-actin polymer networks.

Classic mucolytics

NAC is a mucolytic drug (fig. 1), in addition to possessing **antioxidant** and **anti-inflammatory** properties, that is commonly used for the treatment of COPD [23]. **Aerosol** administration of NAC may **dissociate** mucin **disulphide bonds** and other disulphide bond cross-linked gel components to **reduce viscosity**. A number of observations on NAC suggest that it not only exerts mucolytic properties, but **also antioxidant** effects, which may protect against free radical damage [8, 51–54]. NAC has also been shown to **decrease airway inflammation** by reducing lysozyme and lactoferrin concentrations in smokers [55], inhibiting neutrophil and monocyte chemotaxis and oxidative burst responses *in vitro* [56], **reducing** the activation and number of **neutrophils** and **macrophages** in **bronchoalveolar** lavage fluid in smokers [57, 58], and inhibiting the adherence of bacteria to ciliated epithelial cells *in vitro* [59]. Some evidence suggests that oral NAC may reduce exacerbation rates in chronic bronchitis [60, 61]. However, a more recent controlled randomised clinical trial did not demonstrate a reduction in the frequency of exacerbations with NAC in patients with COPD, but only in the subgroup not taking inhaled corticosteroids [62]. Furthermore, NAC treatment of patients with stable, moderate-to-severe COPD has been shown to benefit physical performance, which may be attributed to air trapping [63]. However, like carbocysteine, **little evidence** is currently available in **humans showing that NAC exerts its action by direct effects on mucus**.

The lysine salt alternative to NAC is **NAL**, also a mucolytic and antioxidant thiol compound. The main advantage of NAL over NAC might be that it has a **neutral** pH in solution, whereas **NAC** is **acidic**, and therefore an **irritant** when **inhaled**. Like NAC, NAL also exerts anti-inflammatory effects both *in vitro* and *in vivo* [64], and although large randomised trials have yet to be undertaken, this mucolytic drug could be interesting for the treatment of COPD.

More recently, other mucolytics like erdosteine and fudosteine, known as novel thiols, have also been synthesised [65, 66], to overcome problems observed with thiols such as NAC and NAL. Erdosteine is as an antioxidant and has mucolytic properties, in addition to the ability to reduce bacterial adhesiveness. A small randomised control trial showed fewer exacerbations, reduced hospital time and improved quality of life in patients with COPD that were treated with erdosteine when compared with placebo [67]; however, future clinical trials will be needed to confirm these preliminary results. In addition, in COPD patients that smoke, erdosteine has also been observed to reduce levels of ROS and cytokines (IL-6 and -8) in peripheral blood and bronchial secretions, respectively [68]. Fudosteine is a cysteine-donating compound with greater bioavailability than NAC. It reduces hypersecretion by down-regulation of mucin gene expression.

Peptide mucolytics

Unlike classic mucolytics that break down mucin networks, peptide mucolytics are designed to break down the highly polymerised DNA and F-actin network that is characteristic of pus. The proteolytic enzyme dornase alfa cleaves DNA polymers and has been developed for the long-term treatment of mucus hypersecretion in CF [69]. Furthermore, children with CF show improved lung function and outcome following treatment with dornase alfa [70]. Both gelsolin and thymosin β_4 , conversely, are recognised to specifically depolymerise F-actin polymers in CF sputum, therefore reducing its viscosity [71, 72]; however, these agents need to be further evaluated in clinical trials.

Non-destructive mucolytics

Unlike other mucolytics that cleave chemical bonds, non-destructive mucolytics dissociate or disrupt the polyionic oligosaccharide mucin network by a mechanism termed "charge shielding". Examples of these mucolytics include dextran and heparin, and although clinical studies are yet to be undertaken, *in vitro* and pre-clinical studies have demonstrated their efficacy [73–75].

MUCOKINETICS

The majority of mucokinetic agents (sometimes referred to as cough clearance promoters) increase mucociliary clearance by acting on the cilia. Although a wide range of mucokinetics that increase ciliary beat frequency are available, these agents have little effect on mucociliary clearance in patients with pulmonary disease [76]. Mucokinetic medications include broncodilators, tricyclic nucleotides and ambroxol (fig. 1). Surfactants also promote cough clearance of mucus by decreasing the surface adhesion between mucus and airway epithelium [77].

Bronchodilators

There is evidence in favour of the use of β_2 -adrenergic agonists to enhance mucociliary clearance [78, 79]; however, other reports have observed little effect on mucociliary clearance [80]. Interestingly, recent reports have shown that salmeterol could restore secretory functions in CF airway submucosal gland serous cells [81], and that β_2 -adrenergic agonists can enhance mucociliary clearance in patients with airway reversibility [82].

Ambroxol

Ambroxol is thought to stimulate surfactant and mucus secretion, yet promote normalisation of mucus viscosity in viscid secretions. The results of clinical studies of ambroxol are conflicting in that some found clinical benefit [83], whereas others did not [84]. However, a recent systematic review provides evidence of a generalised benefit using ambroxol for a range of parameters, including secretolytic activity (promoting mucus clearance), anti-inflammatory and antioxidant activity and exerts local anaesthetic effect [85].

SUMMARY

The present review provides a summary of the most clinically relevant mucoactive drugs used worldwide in the management of several acute and chronic respiratory diseases, with particular reference to their potential mechanisms of action. Although the

precise mechanism of action of several mucoactive drugs is fairly well established, difficulty still exists regarding how they are sometimes classified, due to overlapping effects that they exhibit. Only by developing our understanding of the mechanism of action and specific effects exerted by mucoactive agents, we may in turn offer improved therapeutic use of these drugs.

STATEMENT OF INTEREST

R. Balsamo and L. Lanata are employees of Dompé SPA, Italy.

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