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Mucus production and chronic obstructive pulmonary disease, a possible treatment target: zooming in on N-acetylcysteine

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Abstract

Mucus hypersecretion is a trait of chronic obstructive pulmonary disease (COPD) associated with poorer outcomes. As it may be present before airway obstruction, its early treatment may have a preventive role.
This narrative review of the literature presents the role of mucus dysfunction in COPD, its pathophysiology, and the rationale for the use of N-acetylcysteine (NAC).
NAC can modify mucus rheology, improving clearance and reducing damage-induced *MUC5AC* expression. It exerts a direct and indirect (glutathione replenishment) antioxidant mechanism; it interferes with inflammatory molecular pathways, including inhibition of nuclear factor-kB activation in epithelial airway cells and reduction in the expression of cytokine tumor necrosis factor α, interleukin (IL)-6, and IL-10. Some clinical experiences suggest that the adjunctive use of NAC may reduce symptoms and improve outcomes for patients with COPD.
In conclusion, NAC may be a candidate drug for the early treatment of subjects at risk of COPD development.

Key words: COPD, mucus hyperproduction, chronic bronchitis, N-acetylcysteine.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by persistent airflow limitation. It is associated with an excessive chronic inflammatory response to noxious inhaled agents, including particles, gases, and infectious organisms, resulting in a progressive loss of lung function with increased morbidity and mortality [1].

COPD has several clinical phenotypes and components, including the classical expression of emphysema and chronic bronchitis (CB) [2,3]. The latter has been recently objectively assessed, across asthma and/or COPD diagnoses, as frequent productive cough, defined by the two questions from the St. George's Respiratory Questionnaire (SGRQ), and has been found to be an indicator of poor outcomes, including cardiovascular prognosis and decline in forced expiratory volume in the first second [4]. In line with these findings, in patients fulfilling the classical definition of CB (*i.e.*, productive cough of more than 3 months occurring within 2 years [5]), there is evidence of increased severe airway bacterial colonization, frequent and severe exacerbation, reduced lung function, and deterioration in their health status compared to patients without CB. Therefore, its identification should be implemented to detect subjects needing specific management [6].

CB may be present before the development of airway obstruction, as in the case of subjects exhibiting pre-COPD according to the recent definition in the Global Initiative for Chronic Obstructive Lung Disease (GOLD): subjects exposed to noxious agents with respiratory symptoms and/or structural lung lesions and/or physiological abnormalities without airflow obstruction) [7].

This article describes the mechanisms of mucus abnormal production/composition/location, its role in the clinical features and the pathophysiology of COPD, and suggests possible associated treatment targets.

Methods

A free text search was conducted in PubMed until June 2024, using different combinations of pertinent keywords ("COPD"; COPD AND "mucus"; COPD AND "frequent productive cough"; "N-acetylcysteine" AND "COPD") without any time restrictions. Additionally, we considered a recent systematic literature search across the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and ClinicalTrials.gov recently completed for N-acetylcysteine (NAC) [8]. Articles in English were retrieved and selected by the authors based on their relevance to the subject of the article. A narrative review was prepared.

Mucus dysfunction in chronic obstructive pulmonary disease

Physiological role of mucus in the airways

The airway mucus is produced by the epithelium secretory cells, with antimicrobial, immunomodulatory, and protective molecules [9]. It protects the lumen surface and exerts critical functions in host defense, contributing to the barrier activity of the epithelium [10]. The airway luminal surface is coated by a multiphase mucus film with a superficial periciliary layer and an overlying gel layer. The mucus consists of water, ions, lipids, proteins, and mucins. The latter are macromolecules responsible for their viscoelastic and gel-forming properties. The mucus gel layer entraps inhaled particles and pathogens, which are moved proximally by the beating of cilia and then eliminated by coughing or swallowing when the upper airway is reached [11].

MUC5AC and *MUC5B* are the most prominent secreted mucins in the respiratory tract and provide high gel-forming adhesive and space-occupying properties to the mucous gel layer [12]. They are macromolecules composed of multidomain polypeptide chains with thousands of amino acids, large O-glycosylated apoprotein cores, and cysteine-rich N-terminal and C-terminal domains, allowing oligomerization through disulfide bonds [12]. In healthy subjects, *MUC5AC* is mainly produced by proximal airway goblet cells, while *MUC5B* is produced by submucosal glands and secretory cells in all airway levels [13].

Mucus dysfunction

Mucus dysfunction is a central pathological trait in patients with COPD. The concentration of *MUC5AC* and *MUC5B* in the mucus is higher in patients with frequent exacerbations. The expression of these mucins is further increased during exacerbations and is directly related to viral load, symptom score, and lung function decline [14,15].

Interleukin (IL)-13, signal transducer and activator of transcription 6 (*STAT6*), and SAM pointed domain containing ETS transcription factor (*SPDEF*) are the major factors in inflammatory pathways causing the differentiation of epithelial cells into goblet cells [16]. IL-13 activates Janus kinase 1, which phosphorylates *STAT6* after binding to a receptor containing the IL-4Rα subunit. Although *MUC5AC* lacks a consensus *STAT6*-binding site, *STAT6* activation increases the expression of *SPDEF*, which in turn upregulates genes involved in mucous cell metaplasia and decreases the synthesis of forkhead box protein A2, which negatively regulates *MUC5AC* [13,17].

Abnormal mucus production/composition and or localization is induced by airway inflammation, which may be associated with different cytokine expression profiles depending on the many different triggering stimuli [18]. Airway inflammation induces an increased number of goblet cells in the airway epithelium and an overproduction of mucin [19]. This increase in goblet cell number in the respiratory epithelium during airway inflammation has been described as both mucous cell metaplasia and goblet cell hyperplasia. Metaplasia implies a change in cell phenotype, whereas hyperplasia suggests cell proliferation as a mechanism for the increase in goblet cell numbers [19].

Increased mucus production, hypersecretion, and reduced clearance result in mucus accumulation and possibly plug formation in the airways [20,21]. Mucus hyperproduction can impair mucociliary clearance, reducing the elimination of pathogens and toxic particles. Additionally, it can contribute to airway obstruction, leading to ventilation-perfusion mismatch [19]. These events clinically manifest as coughing and wheezing.

Reappraisal of mucus pathophysiology and plugs

Induced sputum from healthy subjects exposed to oxidizing agents resulted in increased mucus elasticity. Since inflammation, oxidative stress, and irritant exposure are pathogenetic components of COPD development, these mechanisms could favor the production of mucus plugs [22]. Mucus plugs are defined as areas of opacification within the airway lumen, contiguous with the patent airway lumen across sequential transverse computed tomography slices [23]. Their role and prognostic value have been recently investigated.

Mucus plugs were observed in computed tomography (CT) scans of 57% of smokers with COPD, although only 33% of those with high mucus plug scores (the number of pulmonary segments with plugs) had related symptoms [23]. In another study, the prevalence of plugs in CT scans was 25% in smokers with COPD and 10% in smokers without COPD (p=0.001) [24]. Both studies reported that the presence of plugs was associated with more severe airflow obstruction, lower oxygen saturation, more COPD exacerbations, and reduced exercise capacity [23,24]. Persistence of plugs was ascertained after 1 year in 67% of patients and after 5 years in an even larger proportion (73%) of subjects [23,24]. The concordance between the clinical expression of CB and the presence of mucus plugs identified by CT scans has been a matter of discussion. While some of the initial studies reported an association between mucus plug score and CB, particularly when using a high mucus plug score (≥4) and the CB definition from the SGRQ [25], other studies did not confirm this association, with a lack of correlation observed in up to 30% of patients with COPD [24]. Recently, the presence of plugs in CT scans in the absence of mucus-related symptoms of CB [*i.e.*, cough, phlegm (silent mucus plugs)] was also reported by Mettler *et al.* [26] in patients with COPD with a smoking history. Such silent mucus plugs occurred most commonly in the upper and middle lobes. They were related to reduced exercise capacity, lower forced expiratory volume in 1 second, poorer quality of life (QoL), and increased likelihood of severe exacerbations [26]. The authors identified several risk factors associated with silent mucus plugs, including female sex, Black race, and older age. Age may influence the sensitivity of cough receptors, leading to reduced coughing in these patients, which can manifest as silent mucus plugs.

Mucus plugs appear to be related to poor outcomes, as suggested by a pathology study that examined the lung tissue of patients with advanced-stage COPD undergoing lung volume reduction surgery. It was found that occlusion of small conducting airways (with <2 mm lumen diameter) with mucus plugs was associated with increased death risk [27]. An observational study on 4,363 patients with COPD reported the occlusion of medium- to large-sized airways (*i.e.*, approximately 2-10 mm lumen diameter) by mucus plugs being associated with increased all-cause mortality [adjusted hazard ratio (HR) for mucus plugs affecting 1-2 *vs.* 0 lung segments, 1.15; adjusted HR for mucus plugs affecting ≥3 *vs.* 0 lung segments, 1.24] [18]. In addition, those with mucus plugs had increased hazards of respiratory and cancer deaths compared to patients with COPD without plugs [28].

Mucus, inflammation, and oxidative stress in chronic obstructive pulmonary disease/chronic bronchitis

The abnormally high inflammatory response of the airway epithelium to inhaled noxae is a common feature of many aspects of

COPD and is associated with oxidative stress and mucus dysfunction [1,18]. Many patients have mucus hyperplasia, which results from chronic airway irritation by pollutants and cigarette smoke. Neutrophilic inflammation and oxidative stress may induce increased secretion of transforming growth factor α and activate epithelial growth factor receptor, which acts as a mediator of mucus hyperplasia [29].

It has been known for many years that mucus abnormalities and increased mucin formation in COPD reduce airway mucus clearance [30]. These conditions prompt an increased risk of airway infection, inflammation, and fibrosis. The sputum of 25-50% of patients with COPD contains pathogens, such as *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and other bacteria or bacilli. Airway infection further induces mucus production and hampers cilia activity in a feed-forward mechanism promoting disease progression [13,30].

The most common exogenous factor that stimulates production with structural/functional abnormalities is cigarette smoke [31]. Tobacco smoke is a complex mixture of free radicals and other oxidants, which may cause an imbalance in oxidants *vs.* antioxidants in the airways of patients with COPD [32]. Reactive oxygen species induced by tobacco smoking may interfere with mucin hydration and reduce mucus expulsion [33]. Additionally, reduced antioxidant capacity is a trait of subjects with COPD, leading to an excess of oxidized species in response to triggers. At the same time, the levels of oxidative stress markers have been found to be higher in both patients with COPD and smokers without COPD compared with healthy non-smokers [34].

Chronic smoking causes mucus abnormalities, which have adverse effects on cilia structure and function. The mechanism involved includes the activation of *ErbB* receptors and impairment of the cystic fibrosis transmembrane conductance regulator function. In addition to inducing mucus dysfunction, tobacco smoking also has a direct pro-inflammatory activity. Smoke-induced inflammation increases mucin synthesis and decreases mucus hydration and clearance [35].

Patients with COPD have reduced antioxidant activity in the airways; extracellular and intracellular levels of glutathione (GSH) are frequently abnormal in COPD, and the inability to maintain normal GSH levels may contribute to disease progression [36]. Indeed, GSH is the principal small molecular weight thiol in the lungs and, together with its redox enzymes, provides an important protective antioxidant system [37]. Oxidative stress in response to endogenous and exogenous oxidants, including cigarette smoke and other inhaled oxidants, promotes the chronic inflammation characteristic of COPD [38,39]. A systematic review of studies on the effects of active and passive tobacco smoke confirmed that it induces oxidative stress and inflammatory response in the airways and is a risk factor for COPD [40].

Treatment of chronic obstructive pulmonary disease: a role for N-acetylcysteine?

Besides its ability to break disulfide bonds, NAC can modify mucus rheology, improving clearance and reducing damage-induced *MUC5AC* mucin expression [41,42]. NAC is a pleiotropic molecule and possesses other actions that have the potential to have favorable effects on the pathobiology of COPD. Noteworthy, NAC exerts a direct and indirect (GSH replenishment) antioxidant mechanism [43], which has been linked to the inhibition of the epithelial–mesenchymal transition *in vivo* [44]. The pharmacological effect of NAC is also based on interference with inflammatory molecular pathways, including inhibition of NF-kB activation in epithelial airway cells and reduction in the expression of cytokine tumor necrosis factor α, IL-6, and IL-10 [36,38]. NAC can also lyse sputum DNA, increase airway surface liquid thickness, and promote airway clearance. Moreover, it inhibits mucus secretion and cell hyperplasia. Notably, NAC decreases *MUC5AC* expression [42,43].

Clinical/*in vivo* evidence

In humans, NAC modulates several inflammatory markers: when administered to smokers for 8 weeks at 600 mg/day, it reduced the plasma concentrations of myeloperoxidase and elastase, decreased the level of lactoferrin and eosinophilic cationic protein in bronchoalveolar lavage fluid, and reduced the chemotactic activity of neutrophils. Chronic oral administration of NAC at 600 mg/day reduced the chemoattractant properties of neutrophils in the sputum of patients with COPD [43].

In a clinical study, systemic oxidative stress, expressed as increased oxidized erythrocyte GSH, decreased thiol proteins, and increased carbonyl proteins in plasma and erythrocytes, was induced by low-flow oxygen administration in stable patients with COPD and was counteracted by the administration of 1200 or 1800 mg/day of NAC [45].

In the randomized, placebo-controlled BRONCUS trial, oral NAC 600 mg/day for 3 years did not reduce the rate of decline in forced expiratory volume in 1 second, but it reduced the number of exacerbations per year in patients not using inhaled corticosteroids (ICS) [46]. In subsequent trials, a higher NAC dose of 1200 mg/day (oral NAC 600 mg, twice daily) was tested. In the 1-year HIACE trial on Chinese patients with stable COPD, high-dose NAC significantly improved lung function and reduced exacerbation frequency compared with placebo [47]. Additionally, a *post-hoc* analysis of the HIACE trial showed that the benefits of high-dose NAC treatment in terms of reduced exacerbation frequency and prolonged time to first exacerbation were significant in the subgroup of patients at high risk of exacerbations but not in those at low risk [48]. The benefits of high-dose NAC in preventing exacerbations were confirmed by a meta-analysis of clinical studies [49].

In the double-blind, placebo-controlled PANTHEON study on patients with moderate-to-severe COPD, NAC 600 mg twice/day or placebo was randomly assigned to 1006 subjects [50]. After 1 year of treatment, the exacerbation incidence was 1.16 per patient/year in the NAC group and 1.49 per patient/year in the placebo group [risk ratio=0.78; 95% confidence interval (CI): 0.67-0.90; p=0.0011]. A *post-hoc* analysis of the PANTHEON study confirmed that NAC reduces the rate of COPD exacerbations defined by conventional criteria, compared with placebo, particularly in patients with a history of smoking or not treated with ICS. Therefore, NAC may represent an alternative to ICS-containing therapies in these subgroups [51].

A recent meta-analysis, including 20 studies on patients with COPD or its potential precursor CB, showed that NAC not only prevented exacerbations but also improved QoL and symptoms [8]. The incidence of exacerbations compared with placebo was significantly reduced by NAC in both COPD [incidence rate ratio (IRR)=0.76; 95% CI: 0.59-0.99] and CB/pre-COPD (IRR=0.81; 95% CI: 0.69-0.95). Although studies assessing QoL in patients with COPD were few, sensitivity analyses showed a significant association of NAC with symptom and/or QoL improvement in patients with CB/pre-COPD and COPD [8].

Based on evidence emerging from recent trials showing that NAC can reduce exacerbations in patients with COPD [50], including those taking ICS, the 2014 GOLD report speculated that NAC could have a role in the treatment of patients with recurrent exacer-

bations; NAC has been listed among available treatments for stable COPD since the 2017 GOLD report [52].

Conclusions

Increased/abnormal mucus production is associated with CB symptoms and an increased risk of exacerbations in patients with COPD in pre-COPD with evidence of poorer prognosis patients with COPD patients. The underlying pathophysiology is related to inflammation and oxidative stress in the airways in response to inhaled irritants and infectious agents. Mucus plugs appear to be associated not only with established CB but also with patients with COPD without mucus-related symptoms. They could be responsible for small airway obstruction resulting in heterogeneous ventilation and higher mortality risk.

Treatments targeting mucus hypersecretion and/or abnormalities, such as NAC, prevent exacerbations and improve symptoms/QoL and might interfere with COPD development in at-risk subjects. NAC is a pleiotropic molecule with mucolytic, anti-inflammatory, and antioxidant effects. As a safe and long-experienced drug, it seems a candidate for adjunctive treatment of many components of COPD [53].

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