Hydrator Therapies for Chronic Bronchitis

Lessons from Cystic Fibrosis

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Abstract

Patients with the chronic bronchitis form of chronic obstructive pulmonary disease and cystic fibrosis share similar clinical features, including mucus obstruction of airways and the development of chronic/recurrent airways infections that often manifest as disease exacerbations. There is growing evidence that these diseases may have parallels in disease pathogenesis as well, including cystic fibrosis transmembrane conductance regulator dysfunction, mucus dehydration, and defective mucociliary clearance. As progress is made in the development of therapies that target the basic defects that lead to cystic fibrosis lung disease, it is possible that similar approaches could also benefit patients with chronic bronchitis. A deeper understanding of how tobacco smoke and other triggers of chronic bronchitis actually lead to disease, and exploration of the concept that therapies that restore cystic fibrosis transmembrane conductance regulator function, mucus hydration, and/or mucociliary clearance may benefit patients with chronic bronchitis, hold the prospect of significant progress in treating this prevalent disease.

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Cystic fibrosis (CF) is an inherited disease with clearly defined ion transport abnormalities that lead to defective lung host defenses (1). A growing understanding of CF pathogenesis has guided the development of therapeutics that specifically target these basic defects and are having a significant impact on the outcome of this deadly disease. In recent years, parallels between CF and cigarette smoke–induced chronic bronchitis (CB) have been identified (2–4), opening up the possibility that specific treatment approaches used in CF could have similar beneficial effects in this much larger patient population (5). Given that the treatment of chronic obstructive pulmonary disease (COPD) has been constrained largely to a narrow range of therapeutic classes, namely bronchodilators and antiinflammatory agents, the identification of new therapeutic targets is exciting and brings the hope that novel treatment approaches could eventually have an impact on patient outcomes.

In this article, we review shared themes in CF and CB pathogenesis and outline therapeutic approaches that address abnormalities in airway surface liquid (ASL) hydration and mucociliary clearance (MCC).

The Relationship between Airway Surface Liquid Hydration and Mucus Transport

Patients with CF gradually develop bronchiectatic lung disease, manifesting as productive cough with markedly thickened secretions and episodes of clinical deterioration known as pulmonary exacerbations. The evolution of CF lung disease is typically a slowly progressive process that begins early in life, although the lung at birth is essentially normal. Our best understanding of how CF lung disease begins and progresses is based on well-described ion transport defects. Specifically, patients with CF lack cAMP-mediated anion transport because of the absence of a functional cystic fibrosis transmembrane conductance regulator (CFTR) channel. The relative importance of chloride vs, bicarbonate transport continues to be debated and may be tissue specific (e.g., intestine vs. lung vs. sweat gland) (6, 7). In addition, epithelial sodium channel (ENaC)

activity becomes dysregulated because of the loss of CFTR's inhibitory influence over this channel (8, 9). Although abnormalities in ion transport have been shown to cause defects in bacterial killing using *in vitro* and animal model systems (10), it is clear that these specific ion transport defects also lead to mucus dehydration and reduced clearance (10, 11). Indeed, *in vitro* studies have demonstrated that well-differentiated airway epithelial cultures progressively lose the ability to transport mucus as it becomes progressively dehydrated, thus providing a key mechanistic link between mucus dehydration and defective mucus clearance in patients (12). Ultimately, adherent mucus plaques and mucus plugs provide a nidus for the development of chronic infection and inflammation, which, in turn, drives airways destruction.

In vitro and animal model data supporting the mucus dehydration hypothesis are strong, and *in vivo* human data linking mucus dehydration to defective mucus clearance are growing. Sputum samples collected from adults with CF are markedly dehydrated, as demonstrated by an elevation in the percent solids content. Although airway secretions from healthy subjects, collected via bronchoscopy or sputum induction, typically contain ~1.5% solids content (or >98% water), the sputum from a typical adult patient with CF will contain ~6% solids. Mucus samples removed from CF airways at the time of lung transplant are typically even more dehydrated (~12% solids) (13). Direct sampling of mucus overlying the central airways of young patients with CF (<4 yr of age) using bronchoscopic techniques reveals that their secretions are also abnormally dehydrated (i.e., they have an elevated percent solids content) but to a degree that is intermediate between healthy volunteers and adult subjects with CF (our unpublished data). Together, these data suggest that ASL/mucus dehydration is a process that progresses through the lifespan of these patients.

Potential Mechanisms of Airway Surface Liquid Dehydration in Chronic Bronchitis

Several laboratories have reported that cigarette smoke, in both the acute and chronic settings, may induce CFTR dysfunction (2–4, 14, 15). Both *in vitro* and *in vivo* studies have shown that CFTR-mediated chloride transport is reduced by cigarette smoke, and that these defects may persist in former smokers with COPD. In fact, evidence of systemic CFTR dysfunction, including abnormal sweat chloride values, has also been demonstrated in active and former smokers with COPD (14, 15). Given the clinical and pathological parallels between CF and CB, including mucus retention, infection, and neutrophil-dominated airways inflammation, it has been hypothesized that acquired CFTR dysfunction in COPD may play an important role in disease pathogenesis. Specifically, reduced CFTR function could lead to ASL dehydration through the mechanisms already described, and this may result in defective mucus clearance. To test this hypothesis, patients with symptoms of CB and airways obstruction (mean FEV_1 61.6% of predicted) underwent induced sputum and bronchoscopic procedures to collect lower airway secretions so that their solids content, an index of hydration, could be measured. Furthermore, MCC scans were performed using gamma scintigraphy to characterize the extent and pattern of mucus clearance defects. Interestingly, a moderate degree of mucus dehydration was observed when comparing with nonsmoking control subjects and asymptomatic smokers without airways obstruction, both in induced sputum (3% vs. 1.7–1.9% solids in control subjects) and in filter paper samples obtained via bronchoscopy(4% vs. 1.5–2% solids in control subjects). Furthermore, patients with CB had reduced MCC rates when compared with either smoking or nonsmoking control subjects without symptoms or airways obstruction. In fact, the degree of mucus dehydration, as assessed by filter paper sampling of the lower airways, in fact correlated inversely with the observed rate of MCC and lung function in the same patient (12). Although these data do not provide definitive proof of causality, they clearly demonstrate a connection among progressive dehydration of the airways, defective mucus transport, and disease severity. Closer examination of MCC data in patients with CB reveals a clear slowing in the central airways, cilia-driven clearance, but generally preserved cough-driven clearance. In contrast, the MCC defect described in patients with CF is most apparent in the peripheral lung region, and extremely poor cough clearance is also characteristic (16, 17). How differences in MCC patterns reflect the relevance of shared and dissimilar disease mechanisms in CF and CB is not yet clear but is worthy of further investigation.

Translating Hydrator Therapies from Cystic Fibrosis to Chronic Bronchitis

Hypertonic Saline

The strong weight of evidence linking mucus dehydration to the pathogenesis of CF lung disease has been a major driver for the development of new therapies that target this problem. Perhaps the simplest hydrator therapy to emerge is inhaled hypertonic saline (HS). Clinically, twice-daily HS was shown to dramatically reduce pulmonary exacerbations over the course of a 1-year clinical trial in patients with CF while providing more modest improvements in lung function (18). As a result, HS is now used as a long-term therapy in more than 60% of patients with CF in the United States (19).

Studies that delve into the mechanisms that underlie the benefits of HS in CF are likely to shed light onto potential benefits in CB as well. The inhalation of a hyperosmotic solution, such as 7% sodium chloride, drives the movement of water down its concentration gradient across the water-permeable airway epithelium into the luminal compartment. This added volume of water is expected to reduce the concentration of mucus solids and thereby improve the transportability of airway secretions. HS may have other effects that also improve mucus clearance, including the disruption of ionic bonds and improved rheologic properties (20). Several studies have shown that the acute inhalation of a hyperosmotic aerosol, such as HS or mannitol, does indeed accelerate MCC in multiple disease states (21–25). This effect was predicted not to be durable, however, particularly in CF, in which sodium hyperabsorption may dominate basal ion transport processes. In healthy subjects, it has indeed been shown that HS has a short pharmacodynamic effect on MCC (26). Surprisingly, however, when the pharmacodynamic effect of HS was assessed in subjects with CF after 2 weeks

of regular usage, a sustained improvement in MCC (>8 h) was observed (16). Subsequent studies suggested that even a single dose of HS may have a prolonged impact on MCC in adult patients with CF (26), in marked contrast to that which was observed in healthy subjects (27). The working hypothesis explaining this paradox is that the large burden of dehydrated secretions in the CF airway can serve as a reservoir for water driven into the luminal compartment by HS, akin to a dehydrated sponge. The creation of this volume depot in the critically important mucus layer may prevent it from being rapidly reabsorbed across the epithelial surface. If correct, this hypothesis also suggests that the duration of effect, and perhaps the efficacy, of HS may relate to the severity of a patient's lung disease and mucus burden, with greater effects being expected in patients with more advanced disease.

When considering patients with CB, the critical question that these data raise is whether HS, by reversing mucus dehydration, may effectively stimulate mucus transport, reduce mucus obstruction, and prevent disease exacerbations in this population as well. Not surprisingly, HS has been shown to acutely stimulate MCC in patients with the CB phenotype of COPD (12, 28). Importantly, the delivery of 7% sodium chloride via jet nebulizer also appears to be well tolerated. The key unanswered question, however, is whether long-term use of HS will improve clinical outcomes. Extrapolating from the CF experience, perhaps the most likely benefit may be a reduction in pulmonary exacerbations in patients at high risk of these events. Obviously, demonstration of this type of benefit will require a large study over a relatively long time period. Shorter-term and mechanistic outcome measures that may be of value include routine measures of lung function, patient-reported outcomes, and the assessment of the sustained effect that repeated HS treatments have on MCC. A small, short-term study of this nature is currently underway (www.clinicaltrials.gov identifier [NCT 01792271]).

Other Hydrators

The development of other hydrator therapies for CF has also been pursued aggressively. Dry powder mannitol, sharing an essentially identical mechanism of action with HS, has already been approved in Australia, the European Union, and the United Kingdom. Therapies that block or otherwise inhibit the activity of ENaC are also in active development. ENaC inhibitors reduce the reabsorption of fluid from the ASL compartment and could therefore serve as an adjunct to therapies that increase fluid secretion into the airway. Although inhaled amiloride, the prototypical ENaC inhibitor, failed to show significant clinical benefit in CF studies (29, 30), newer agents with much greater potency, longer duration of action, and improved safety profiles have emerged subsequently and have entered into clinical trials. Finally, small molecule modulators of the defective CFTR protein itself have moved rapidly through clinical development and are now available to approximately 50% of patients with CF (31–35). Although CFTR may have pleotropic effects in the lung, CFTR modulators may certainly be viewed as "hydrators" because they have clearly been shown to improve ASL volume *in vitro*. Ivacaftor, a highly effective CFTR modulator that is approved for patients with CF carrying at least one gating mutation, was shown to dramatically increase MCC in patients with the G551D mutation, highlighting the relationship among ion transport, ASL hydration, and MCC (36).

Given the possibility that HS may prove to be too short acting or otherwise ineffective in the CB population, development of an appropriately designed alternative agent that is potent and long acting is an attractive therapeutic option (Figure 1). Although sodium transport may not be up-regulated in patients with CB (unlike in those with CF), the use of an ENaC blocker to inhibit this rate-limiting step of fluid reabsorption could still prove to be beneficial if mucus dehydration and defective MCC are important parts of CB disease pathogenesis. Agents that reduce ENaC activity via indirect mechanisms, such as the inhibition of surface proteases that are involved in channel activation, may also have potential usefulness. An approach that combines an ENaC blocker with a second agent that stimulates fluid secretion, such as a hyperosmotic agent, may also be very attractive and worthy of investigation. Finally, stimulation of chloride secretion via non-CFTR pathways could be explored, including the use of P2Y2 agonists that stimulate calcium-activated chloride channels (37).

The evidence that CFTR dysfunction is present in patients with COPD raises the possibility that CFTR modulators could also provide therapeutic benefit. Obviously, these patients are expected to have a normal CFTR gene sequence, and the observed reduction in CFTR activity likely results from a reduced number of channels of the cell surface (2, 38). Ivacaftor is a CFTR modulator that increases channel gating and open probability of not only mutant channels with gating abnormalities (i.e., gating mutations, R117H, and temperature- or chemically corrected delF508), but also wild-type channels. It is conceivable, and there is supporting *in vitro* evidence, that treatment of a patient with CB with reduced CFTR function

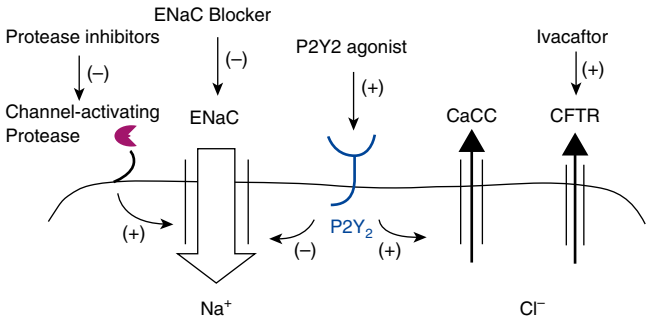

Figure 1. Hydration of airway surfaces is controlled by multiple ion channels. These channels and the regulatory elements that govern their activity provide multiple potential therapeutic targets that could be used to restore mucus hydration and clearance in patients with chronic bronchitis. CaCC = calcium activated chloride channel; CFTR = cystic fibrosis transmembrane conductance regulator; ENaC = epithelial sodium channel.

using an effective CFTR modulator could increase the activity of residual channels, stimulate anion secretion, improve mucus hydration, and accelerate MCC (5). It seems likely, however, that the severity of the baseline CFTR dysfunction may influence whether this strategy is likely to be effective. It is well known that patients with mild CFTR mutations often have normal lung function despite possessing only 5 to 10% of wild-type channel activity. Therefore, the question is whether the reduction of CFTR activity in a patient with CB to 20–40% of normal is sufficient to be a primary driver of disease pathogenesis, or whether such a patient would benefit clinically from a CFTR modulator that reverses this more modest degree of channel dysfunction. Furthermore, ivacaftor may reduce the plasma membrane stability of CFTR, and this could counteract any beneficial effect on channel open probability (39, 40). Therefore, although this hypothesis and treatment avenue remain intriguing, future studies that pursue this novel approach will need to be studied carefully.

Unanswered Questions and a Path Forward

Many questions surround the ASL dehydration hypothesis and the potential use of hydrator therapies for CB. Although CFTR function appears to be reduced in these patients, is the degree of this function severe enough or relevant to disease pathogenesis? Airway secretions sampled from patients with CB are clearly more dehydrated than in those from healthy volunteers, but does this relate to CFTR dysfunction and is the severity of mucus dehydration sufficient to cause a defect in mucociliary transport *in vivo*? MCC is clearly abnormal in patients with CB, but is the pattern of the clearance defect similar to that of CF and reflective of the same underlying disease mechanisms, or perhaps more related to the loss of ciliary function associated with smoking (41)? The answers to all of these important questions may inform us regarding the likelihood of ASL hydrators, as a class, to become a clinically useful treatment approach. Furthermore, these answers may direct us to agents that have the greatest likelihood of success and the identification of patients that are most likely to respond. It will take a significant effort, including the conduct of clinical studies and treatment trials, to answer many of these questions. The use of appropriate outcome measures that are sensitive to and predictive of clinical benefits must also be developed to allow the selection of agents worthy of the investments needed to conduct large-scale clinical trials. Ultimately, this work and these investments are warranted, given the magnitude of harm that this disease inflicts on individuals and society as a whole, and given the current dearth of novel treatment approaches for COPD. The possibility of being able to target a novel element involved in disease pathogenesis and thereby improve patient outcomes is incredibly exciting and brings hope for the future. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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